



**HAL**  
open science

## **Blunting periprocedural myocardial necrosis: Rationale and design of the randomized ALPHEUS study**

Johanne Silvain, Guillaume Cayla, Farzin Beygui, Grégoire Range, Benoît Lattuca, Jean Philippe Collet, Jean Guillaume Dillinger, Ziad Boueri, Philippe Brunel, Christophe Pouillot, et al.

### ► To cite this version:

Johanne Silvain, Guillaume Cayla, Farzin Beygui, Grégoire Range, Benoît Lattuca, et al.. Blunting periprocedural myocardial necrosis: Rationale and design of the randomized ALPHEUS study. *American Heart Journal*, 2020, 225, pp.27-37. 10.1016/j.ahj.2020.04.017 . hal-02844082

**HAL Id: hal-02844082**

**<https://hal.science/hal-02844082>**

Submitted on 15 Jun 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## **Blunting periprocedural myocardial necrosis: rationale and design of the randomized ALPHEUS study**

Johanne SILVAIN MD-PhD<sup>1</sup>, Guillaume CAYLA MD-PhD<sup>2</sup>, Farzin BEYGUI MD-PhD<sup>3</sup>, Grégoire RANGE MD<sup>4</sup>, Benoit LATTUCA MD-PhD<sup>2</sup>, Jean-Philippe COLLET MD-PhD<sup>1</sup>, Jean-Guillaume DILLINGER MD-PhD<sup>5</sup>, Ziad BOUERI MD<sup>6</sup>, Philippe BRUNEL MD<sup>7</sup>, Christophe POUILLOT MD<sup>8</sup>, Franck BOCCARA MD-PhD<sup>9</sup>, Luc CHRISTIAENS MD<sup>10</sup>, Jean-Noël LABEQUE<sup>11</sup> MD, Thibault LHERMUSIER MD-PhD<sup>12</sup>, Jean-Louis GEORGES MD<sup>13</sup>, Anne BELLEMAIN-APPAIX MD<sup>14</sup>, Hervé LE BRETON MD-PhD<sup>15</sup>, Marie HAUGUEL-MOREAU MD<sup>16</sup>, Christophe SAINT-ETIENNE MD<sup>17</sup>, Christophe CAUSSIN MD<sup>18</sup>, François JOURDA MD<sup>19</sup>, Zuzana MOTOVSKA MD<sup>20</sup>, Paul GUEDENEY MD<sup>1</sup>, Mohamad El KASTY MD<sup>21</sup>, Mikael LAREDO MD<sup>1</sup>, Raphaëlle DUMAINE MD<sup>22</sup>, Grégory DUCROCQ MD-PhD<sup>23</sup>, Eric VICAUT MD-PhD<sup>24</sup>, Gilles MONTALESCOT MD-PhD<sup>1‡</sup> for the ALPHEUS study group.

‡Corresponding Author. Professor Gilles Montalescot, ACTION Study Group, [www.action-cœur.org](http://www.action-cœur.org) Sorbonne Université, INSERM UMRS1166, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France. Bureau 1, 2<sup>ème</sup> étage, 47-83 bld de l'Hôpital, 75013 Paris, Telephone: +33 142163007, Fax: +33 142162931. E-mail: [gilles.montalescot@aphp.fr](mailto:gilles.montalescot@aphp.fr)

**Running Title:** Rationale and design of the ALPHEUS study

**Words:** 5020 (without abstract, references and tables)

**Figures:** 2 **Tables:** 4 **References:** 32

**Appendix :** 1

**Authors Affiliations**

- <sup>1</sup> Sorbonne Université, ACTION Study Group, INSERM UMRS1166, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France.
- <sup>2</sup> Cardiology department, Nîmes university Hospital, Montpellier University, ACTION study group, Nîmes, France.
- <sup>3</sup> CHU de Caen – Département de Cardiologie
- <sup>4</sup> CH de Chartres – Département de Cardiologie
- <sup>5</sup> Department of Cardiology, Inserm U942, Lariboisière Hospital, Assistance Publique - Hôpitaux de Paris, University of Paris, Paris, France
- <sup>6</sup> CH de Bastia – Département de Cardiologie
- <sup>7</sup> Hôpital Privé Dijon Bourgogne – Cardiologie Interventionnelle GCIDB VALMY
- <sup>8</sup> Clinique Sainte Clotilde, La Réunion - Département de Cardiologie
- <sup>9</sup> AP-HP, Hôpitaux de l'Est Parisien, Hôpital Saint-Antoine, Department of Cardiology, Sorbonne Université-INSERM UMR S\_938, Centre de Recherche Saint-Antoine, Paris, France
- <sup>10</sup> CHU de Poitiers – Service de Cardiologie
- <sup>11</sup> GCS de Cardiologie de la Côte Basque, CH Bayonne.
- <sup>12</sup> CHU de Toulouse - Département de Cardiologie
- <sup>13</sup> CH de Versailles – Service de Cardiologie, Hôpital A. Mignot, Le Chesnay, France
- <sup>14</sup> CH d'Antibes Juan-Les-Pins - Département de Cardiologie
- <sup>15</sup> Univ Rennes, CHU Rennes, Inserm LTSI U1099, F 35000 Rennes, France
- <sup>16</sup> CHU Ambroise Paré (APHP), Université Versailles-Saint Quentin, ACTION study Group, INSERM-U1018 CESP, Boulogne, France – Service de Cardiologie
- <sup>17</sup> CHU Trousseau, Tours - Département de Cardiologie
- <sup>18</sup> Institut Mutualiste Montsouris- Département de Cardiologie
- <sup>19</sup> CH Auxerre - Département de Cardiologie
- <sup>20</sup> 3rd Faculty of Medicine, Charles University and Cardiocentre Kralovske Vinohrady, Prague, Czech Republic
- <sup>21</sup> Grand Hôpital de l'Est Francilien site Marne-La-Vallée - Département de Cardiologie
- <sup>22</sup> Les Grands Prés Cardiac Rehabilitation center, Villeneuve St Denis.
- <sup>23</sup> FACT (French Alliance for Cardiovascular Trials), DHU FIRE, Hôpital Bichat, AP-HP, Université de Paris, Inserm U-1148, Paris, France
- <sup>24</sup> Unité de Recherche Clinique, ACTION Study Group, Hôpital Fernand Widal (AP-HP), Paris, France. SAMM - Statistique, Analyse et Modélisation Multidisciplinaire EA 4543, Université Paris 1 Panthéon Sorbonne, France.

**Background** Clopidogrel associated with aspirin is the recommended treatment for patients undergoing elective percutaneous coronary intervention (PCI). Although severe PCI-related events are rare, evidence suggest that PCI related myocardial infarction (MI) and myocardial injury are frequent complications that can impact the clinical prognosis of the patients. Antiplatelet therapy with a potent P2Y<sub>12</sub> receptor inhibitor such as ticagrelor, may reduce periprocedural ischemic complications while maintaining a similar safety profile as compared with conventional dual antiplatelet therapy (DAPT) by aspirin and clopidogrel in this setting.

**Methods** ALPHEUS (Assessment of Loading with the P2Y<sub>12</sub> inhibitor ticagrelor or clopidogrel to Halt ischemic Events in patients Undergoing elective coronary Stenting) (NCT02617290) is an international, multicenter, randomized, parallel-group, open label study in patients with stable coronary artery disease who are planned for an elective PCI. In total, 1,900 patients will be randomized before a planned PCI to a loading dose of ticagrelor 180mg or a loading dose of clopidogrel (300 or 600mg) in addition to aspirin. Patients will then receive a DAPT with aspirin and ticagrelor 90 mg twice daily or clopidogrel 75mg once daily for 30 days. The primary ischemic endpoint is PCI-related myocardial infarction (MI type 4a or 4b) or major myocardial injury within 48 hours (or at hospital discharge if earlier) after elective PCI/stent. Safety will be evaluated by major bleeding events (BARC type 3 or 5) at 48 hours (or discharge if it occurs earlier).

**Conclusion** ALPHEUS is the first properly sized trial comparing ticagrelor to clopidogrel in the setting of elective PCI and is especially designed to show a reduction in periprocedural events, a surrogate endpoint for mortality. RCT# NCT02617290

**Keywords:** percutaneous coronary intervention; stent; myocardial infarction; antithrombotic, antiplatelet therapy

**Abbreviations**

ACS	Acute coronary syndrome
ALPHEUS	Assessment of Loading with the P2Y <sub>12</sub> inhibitor ticagrelor or clopidogrel to Halt ischemic Events in patients Undergoing elective coronary Stenting
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass graft
CI	Confidence Interval
CRF	Case report form
hs-Tn	High Sensitivity Cardiac Troponin
LD	Loading dose
OR	Odd ratio
PCI	Percutaneous Coronary Intervention
MI	Myocardial Infarction
STEMI	ST-segment Elevation Myocardial Infarction
cTn	Cardiac Troponin
URL	Upper Reference Limit

## Background

The P2Y<sub>12</sub> inhibitors prasugrel and ticagrelor provide higher level of platelet inhibition than clopidogrel with a faster onset of action<sup>1,2</sup> and better outcome in acute coronary syndrome (ACS) patients<sup>3,4</sup>. The field of elective percutaneous coronary intervention (PCI) for stable patients has not yet been investigated with these two potent drugs and clopidogrel remains the standard of care. PCI is considered as a relatively safe procedure when performed with the latest stents' generation and a standard antithrombotic regimen with parenteral anticoagulation during the procedure and pretreatment with dual antiplatelet therapy of aspirin and clopidogrel. Indeed, hard clinical events such as acute and sub-acute stent thrombosis as well as Q wave myocardial infarction (MI) or stroke remain serious but rare (<0.4%) periprocedural complications while PCI-related myocardial injury or type 4a MI are frequent and can occur in up to 50% of the planned PCI cases, depending on the biomarkers and the definitions used<sup>5,6,7,8</sup>. Such periprocedural complications are most of the time asymptomatic, but they may delay hospitalization discharge, and have been associated with an increased risk of future major adverse cardiovascular events<sup>9,10</sup>. More importantly, recent data have associated type 4a MI and myocardial injury (defined by higher threshold of post PCI biomarker elevation) with all-cause mortality<sup>11</sup>. Atherothrombotic complications (side branch occlusion, flow reduction or coronary embolization) are the most likely mechanisms of procedural myocardial injury and type 4a MI and could be potentially reduced by a more efficient antithrombotic therapy. Obtaining a higher potent platelet inhibition using stronger P2Y<sub>12</sub> inhibitors than clopidogrel (prasugrel or ticagrelor) before and after PCI appears as a relevant strategy to lower periprocedural MI and myocardial injury but is not supported by scientific evidence. To test this hypothesis, we designed the ALPHEUS (Assessment of Loading with the P2Y<sub>12</sub> inhibitor ticagrelor or clopidogrel to Halt

ischemic Events in patients Undergoing elective coronary Stenting) trial to examine the impact of ticagrelor versus clopidogrel in reducing periprocedural events in stable coronary patients undergoing elective high-risk PCI.

## **Methods**

### **Study organization**

The ALPHEUS study (NCT02617290; EUDRACT No: 2015-000850-39) is a phase IIIb, international, multicenter, controlled, randomized open label trial, designed by the ACTION Study Group ([www.action-coeur.org](http://www.action-coeur.org)) at Pitié-Salpêtrière Hospital in Paris, France and funded by the Fonds de Dotation ACTION and a grant by AstraZeneca. The trial is testing the superiority of ticagrelor over clopidogrel to prevent periprocedural myocardial infarction and major myocardial injury in patients undergoing elective high-risk PCI (**Figure 1**). The study is led by Study Chairman (Dr Silvain) and the Study Scientific Director (Dr Montalescot) assisted by the steering committee responsible for the medical, scientific, and operational conduct of the study. ALPHEUS trial uses the Prospective Randomized Open, Blinded Endpoint (PROBE) study design approach<sup>12</sup> where endpoints are evaluated by a blinded central Clinical End-point Committee (CEC)<sup>13</sup>. Members of the Steering Committee, CEC and DSMB are listed in the **Appendix**. Recruitment will take place at 50 high-volume PCI centers in 2 countries (France and Czech Republic) with expertise in clinical research. The study will be performed according to the ethical principles of the declaration of Helsinki, the International Conference on Harmonization /Good Clinical Practice and applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

### **Study Objectives**

The primary efficacy objective of the ALPHEUS study (NCT02617290; EUDRACT No: 2015-000850-39) is to demonstrate the superiority of ticagrelor over clopidogrel to prevent PCI-

related MI (type 4a and type 4b) or major myocardial injury within 48 hours (or at hospital discharge if earlier) in elective PCI. Safety of ticagrelor versus clopidogrel will be evaluated according to the Bleeding Academic Research Consortium (BARC) criteria<sup>14</sup> (BARC type 3 or 5) at 48 hours (or discharge if it occurs earlier).

The secondary efficacy objectives are to demonstrate the superiority of ticagrelor over clopidogrel on: 1) PCI-related MI (type 4a and 4b) or any type of myocardial injury (major or minor) 2) All MI (type 1, type 4 and type 5) 3) Death (any) or all MI 4) Death (any), all MI or major myocardial injury, urgent revascularization or recurrent ischemia requiring catheterization.

The secondary safety objectives are to assess the rates of : 1) major bleeding events as assessed by the BARC criteria (BARC type 3 or 5) at 30day follow-up. 2) nuisance or minor bleeding (BARC type 1 or 2) at 48h and 30 days. 3) any bleeding (BARC 1, 2, 3, 4, 5) at 48h and 30 days. 4) stroke at 48h and 30 days.

### **Study population**

The study will enroll 1,900 stable coronary patients (chronic coronary syndrome) patients of 18 years of age or older undergoing PCI with at least one criterion of high-risk features. Key inclusion and exclusion criteria are listed in **Table 1** and **Table 2**. Stable coronary patients are defined as having a known coronary anatomy with an indication for PCI together with a negative cardiac troponin (cTn) (below the upper reference limit (URL) of the center) or a decreasing level in case of modestly positive high sensitivity cardiac troponin (hs-Tn) prior to intervention. Lack of chest pain within the last 24 hours and no chest pain for more than 15 minutes is requested. A modestly positive hs-Tn corresponds to a value within the grey zone according to local laboratory definitions or a value < 3 times the URL when the grey zone is



not defined. Decreasing cTn is defined as a variation of at least one unit between two consecutive measurements using the same assay.

#### **Enrollment and randomization.**

Patients fulfilling the inclusion criteria and without any exclusion criteria who agree to participate to the protocol and have signed the informed consent form are randomized before PCI to either ticagrelor or clopidogrel. The randomization cannot occur before the coronary status is known. However, the consent form can be signed before the coronary angiogram. Randomization is performed by Interactive Web Response System available via the eCRF and is stratified by center. Treatment allocation is undertaken at a ratio of 1:1. PCI may be staged or immediately performed after the randomization. When PCI is immediate, explanation of the study protocol, signature of the informed consent form is obtained before the coronary angiogram and randomization occurs just after the coronary angiogram. The allocated treatment will be initiated immediately after randomization. A minimum of 60 minutes is recommended between treatment administration and PCI (up to 24 hours). When immediate PCI is the chosen approach, a loading dose of the study drug administered is given immediately after the coronary angiogram and before PCI with a recommended crushed or chewed administration to enhance absorption. All patients will be on aspirin and receiving usual treatments for chronic coronary syndrome. The patients on chronic clopidogrel treatment (maintenance dose for more than 5 days) are eligible and are given either ticagrelor 180 mg loading or clopidogrel loading (300-600 mg according to local practice)<sup>20,21</sup> according to the treatment arm, followed by a 30-day maintenance treatment with the corresponding study drug. The duration of study treatment is 30 days after PCI. Beyond 30 days, the choice of treatment / dose / duration is left to the discretion of the

treating physician. Switch are performed according to local practice and/or international guidelines<sup>15</sup>.

### **Study Endpoints**

**Primary Endpoint.** The primary endpoint of the trial is the rate of PCI-related MI (type 4a or 4b) or major myocardial injury within 48 hours (or at hospital discharge if earlier) of elective PCI/stent. MI related to early stent thrombosis (type 4b) are defined according to the modified Academic Research Consortium definitions (ARC definitions) with a rise and/or fall of cTn values >URL<sup>20</sup>. The definition of PCI related type 4a MI and major myocardial injury are based on the 3<sup>rd</sup> universal definition of MI<sup>5</sup> for patients with normal cardiac troponin at baseline and are based on the 4<sup>th</sup> universal definition of MI<sup>6</sup> for patients with modestly positive troponin at baseline. **Table 3** summarized the definition of type 4a MI and major myocardial injury that needs to be differentiated from minor myocardial injury that is not part of the primary endpoint. Endpoint definitions are detailed in the **appendix**.

**Secondary Endpoints.** The secondary endpoints include the rate of 1/ PCI-related MI (type 4a or 4b) or any type of myocardial injury (major or minor). 2/ All MIs (type 1, 4 and 5) according to the 3<sup>rd</sup> universal definition of MI 3/ Death (any) or all MI 4/ Death (any), MI or major myocardial injury, urgent revascularization or recurrent ischemia requiring catheterization.

**Safety endpoints.** Safety will be evaluated by BARC major bleeding (type 3 or 5). Nuisance or minor bleeding (BARC type 1 or 2) will also be considered. Additional safety assessments will include any bleeding events (BARC 1, 2, 3, 4, 5) and the rate of any stroke.

### **Cardiac biomarkers**

The protocol recommends measuring cTn 6 and 24 hours after PCI or at discharge if earlier for the primary endpoint assessment. All types of cTn assays are considered (classic or high

sensitivity assay) as long as the same assay is used for all measurements. The threshold for cTn is defined as the 99<sup>th</sup> percentile of the URL of a normal reference population. This discriminatory 99<sup>th</sup> percentile is designated as the decision level for the diagnosis of MI or myocardial injury and must be determined for each specific assay with appropriate quality control in each laboratory. Local thresholds with validated 99<sup>th</sup> percentile values are taken into consideration. When multiple measurements are performed  $\leq 48$  h after PCI, the peak values are considered for the analysis.

### **Angiographic Core Laboratory and Clinical Endpoint Committee**

Baseline and procedural coronary angiograms will be digitally recorded and sent to the core laboratory of the ACTION research group. A comprehensive angiographic analysis including coronary lesions and periprocedural complications will be performed by independent experienced observers under the supervision of physicians not involved in the trial all being blinded to treatment allocation. The CEC will review and adjudicate the outcomes using source document, biomarker measurements and the core laboratory analysis. The members of the core laboratory and the CEC are listed in the appendix.

### **Power and sample size calculation**

Power calculations are based on the superiority comparison for the primary objective which is to demonstrate the superiority of ticagrelor over clopidogrel to prevent PCI-related MI (type 4) or major myocardial injury within 48 hours (or at hospital discharge if earlier) of elective PCI/stent. The null hypothesis is the equality of rates and the alternative hypothesis the inequality of rates in the 2 groups. At the time of the design of the ALPHEUS trial (2012), we estimated that the average published rate of MI type 4a or myocardial injury present in the literature and evaluated by classic cTn in non-urgent PCI was 30% , concordant with the latest clinical trial of our group at that time<sup>16</sup> (table 4). It was suggested taking 30%, as the

most conservative approach for the primary endpoint of MI type 4 and major myocardial injury knowing that this rate could be higher when hs-Tn was used. Type 4b MI rate in elective PCI is low (<0.4%) and will come in addition. We hypothesized a 20 % relative risk reduction of the primary endpoint with ticagrelor based on the magnitude of MI reduction obtained in previous ACS trials<sup>3,4</sup>. This rate is also in line with the 19% risk reduction observed in the first 3 days of the TRITON study<sup>17</sup>, mostly related to peri-procedural MI and the 20% risk reduction for MI in the PLATO-PCI analysis also in line with our hypothesis<sup>18</sup>. Considering a total event rate (for the primary endpoint) of 30% at 48 hours in the clopidogrel arm, we calculated that 856 patients/group was required to have 80% power to detect a 20% reduction of the primary endpoint rate at a two-sided alpha level of 5%. Considering a dropout rate close to 10% for the whole study, we planned to randomize 950 patients/group (N=1,900 patients total). An intermediate analysis was planned and performed after the inclusion of the first 950 patients (50% of the calculated sample size of 1,900 patients) and the sample size did not need to be adjusted to preserve the power at 80%-level based on rate of the primary endpoint recorded during this analysis.

### **Statistical aspect**

All tests will be two-sided at a 5% significance level. No adjustment is necessary in this study. The main efficacy analysis will be based on all events that occurred in the intention to treat population defined as all randomized patients who have signed an informed consent form. In case of consent withdrawal only data collected before withdrawal will be used. In addition, an explanatory analysis (per protocol) of all patients randomized and treated without major protocol violations/deviations will be carried out. Pre-defined major protocol violations/deviations are: 1/ Missing data for the primary efficacy endpoints. 2/ Randomized treatment assignment not followed. 3/Inclusion in another clinical study. 4/Other major

violations defined during the blinded data review. Continuous variables will be summarized using number of observations, mean, standard deviation, minimum, maximum, 25%, 50%, 75% quantiles and the two-sided 95% confidence intervals. Means, medians, minimum, maximum and standard deviations will be presented to one further decimal place. There will be counting of the absolute and relative frequencies (percentages) for categorical variables. Percentages will be rounded to one decimal place and there may be occasions where the total of the percentages does not equal 100% exactly. The primary endpoint will be compared by Chi-square test. Sensitivity analysis will be carried out using multivariate logistic regression including baseline factors that are known to affect patient disease introduced as covariates. The 95% confidence interval of the crude and adjusted odds-ratio will be presented. The primary endpoint will be compared by Chi-square test or Fisher's exact test when asymptotic methods are not valid. Sensitivity analysis will be carried out using multivariate logistic regression including baseline factors that are known to affect patient disease introduced as covariates. The 95% confidence interval of the crude and adjusted ratio will be presented (exact CI will be calculated when necessary). For the main criterion, presence of missing data is very unlikely. If necessary, multiple imputation technique will be used for imputation of missing values (SAS PROC MI). The number (%) of patients with severe adverse events (SAEs) will be summarized by body system. For all subjects of the safety analysis set, two-sided 5% confidence intervals will be calculated for the incidence of adverse events. The secondary endpoints will be analyzed in a hierarchical order with the proper statistical adjustment. All statistical analyses will be performed using SAS 9.3 software.

**Pre-defined subgroups of patients**

Elderly, women, body weight categories (<60kg; 60-90kg; >90kg), diabetics, multivessel disease, multistenting ( $\geq 3$  stents), complex PCI, patient on clopidogrel at the time of randomization, renal insufficiency (creatinine clearance  $\leq 60$  ml/min), low ejection fraction (< 40%), delay drug-to-stent, patients with negative versus modestly positive cTn at baseline, staged versus immediate PCI and pretreatment time .

**Substudy**

The BIO-ALPHEUS study is an ancillary study that is performed in selected centers and compare the level of platelet inhibition measured by a centralized platelet function testing (Elisa VASP) and a local crypted measurement (Verify Now P2Y<sub>12</sub>) before the loading dose of anti-platelet treatment targeting the P2Y<sub>12</sub> receptor (baseline), 4 to 6h after the loading dose (post-loading dose) and the next day or before discharge (maintenance dose) in the population included in the ALPHEUS trial. Additionally, a genetic profiling to evaluate the metabolizer status will be performed and the BIO-ALPHEUS pharmacodynamic results will be analyzed in 3 groups: ticagrelor, clopidogrel with a good metabolizing genetic profile, clopidogrel with a bad metabolizing genetic profile. This ancillary study planned to enroll 300 patients in total. This study is conducted using standardized approaches and definitions described in the consensus document on antiplatelet monitoring<sup>19</sup>.

**Data and Safety Monitoring Board**

The organization include a Data and Safety Monitoring Board (DSMB) role is to advise the Study Chairman, the Study Scientific Director and the Sponsor (Assistance-Publique des Hôpitaux de Paris - APHP) regarding the safety of current participants and those yet to be recruited, as well as the integrity of the trial. A fundamental consideration is the safety

(adverse events) of the patients who would be at potential risk due to their participation in the trial. A dedicated DSMB charter was approved during a first meeting of the DSMB prior to the trial initiation.

### **Funding and responsibilities**

The ALPHEUS and the Bio-ALPHEUS studies are funded by the Fond de dotation ACTION ([www.action-fonds.org](http://www.action-fonds.org)) and a grant from AstraZeneca. The Bio-ALPHEUS study is also funded by the Institute of Cardio-metabolism And Nutrition (ICAN). The first draft of the paper was developed by Dr Silvain and Dr Montalescot, and all authors subsequently contributed to its development and final content and are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. AstraZeneca reviewed the manuscript and was allowed to make suggestions, but final content was determined by the authors.

### **Discussion**

#### **Primary Hypothesis**

The primary hypothesis of the ALPHEUS trial is that ticagrelor administered before PCI will significantly reduce periprocedural complications compared with clopidogrel in stable coronary artery disease patients (chronic coronary syndrome) undergoing an elective PCI, without significant excess major bleeding. Although the protocol inclusion criteria excluded patients without high-risk features (patients demographic or lesion/procedural characteristics of a complex PCI), our population correspond to 90% of the elective cases performed in a standard catheterization laboratory and is considered at a low risk for major cardiovascular events related to the procedure. Therefore, a trial based on hard clinical endpoints was excluded as it would necessitate a much larger clinical trial, and we decided

to examine a more frequent and relevant endpoint that is the rate of periprocedural complication (type 4a MI, type 4b MI and major myocardial injury) to be able to demonstrate a difference between ticagrelor and clopidogrel. Although the prognosis value of acute stent thrombosis (type 4b MI) is not debated, we do not expect that such events would weight much in the primary endpoint of the ALPHEUS trial. On the other hand, both prognosis value of type 4a MI and especially myocardial injury are debated as there is several definitions of both endpoints, with varying cut-off thresholds of post-PCI cardiac biomarkers elevation arbitrarily selected and debate about the high sensitivity cardiac troponin that is being now used in the majority of PCI centers.

#### **Periprocedural type 4b and type 4a MI**

In the ALPHEUS trial we used the ARC universal definition<sup>20</sup> for type 4b MI (stent thrombosis) and the 3rd Universal definition of MI<sup>5</sup> to define type 4a MI which is similar to the updated 4<sup>th</sup> Universal definition. Both definitions are using this combination of a post PCI cardiac troponin increase > 5x URL associated with one ischemic criterion. The only difference of the updated 4<sup>th</sup> universal definition lies in the exclusion of ischemic symptoms from the items constituting an ischemic criterion. A contemporary registry on elective PCI<sup>21</sup>, (n=1,390) with negative hs-Tn at baseline, recently assessed the rate of type 4a MI according to post-PCI hs-Tn release using the 3<sup>rd</sup> universal definition of MI. Using this definition and a high sensitive assay, the rates of type 4a and 4b MI (acute stent thrombosis) were 7.0% and 0.14% respectively within the first 48 hours of PCI. More importantly, periprocedural type 4 MI both events were associated with increased cardiovascular events at 30 days and 1 year.

#### **Added value of the Centralized Core Laboratory**



Characterizing type 4a MI is challenging, as it needs a careful review patient's medical data to identify an ischemic criterion. The post PCI electrocardiogram modifications and the loss of myocardial viability on cardiac imaging only occur in major PCI related type 4 a or b MI and are rare events that would be easily notified by site investigators and review by the CEC. Therefore, the most frequent ischemic criteria, apart from the subjective post PCI chest pain, is the presence of an angiographic complications which need a close review of the angiogram, often absent from PCI registry. The need for a centralized review of such events has been demonstrated in previous trial<sup>22</sup> and we planned to use the ACTION core laboratory to review all angiograms of the ALPHEUS trial in a blinded fashion in order to precisely detect this criterion. Our core laboratory has recently showed its expertise in the CULPRIT SCHOCK trial<sup>23</sup> by confirming the importance of a blinded core laboratory to provide independent evaluations in trials testing treatment strategies in an open-label fashion as demonstrated before. The results of the blinded evaluation and the site investigators description of potential angiographic complication will be both provided to the independent CEC for adjudication.

### **Periprocedural myocardial injury**

The best definition of periprocedural myocardial injury is still a matter of intense debate due the paucity of data of the prognosis value of such events on hard endpoints or mortality. First it has to be noted that this is an event relying solely on the measurement of post-PCI cardiac biomarkers which is not subject to bias and was therefore not centralized in our trial. Then that the actual debate is centered on the arbitration between a very sensitive definition such as the low threshold proposed by the recent 4<sup>th</sup> Universal definition of the MI<sup>6</sup> (>URL) with a very high rate of events (40-80% according to the assay) and unknown prognosis value and very high threshold (>70xURL) as proposed by the Academic Research

Consortium 2 (ARC-2)<sup>8</sup> or the Society for Cardiovascular Angiography and Interventions (SCAI)<sup>7</sup> definition that are more restrictive and have strong prognosis value, but lack of sensitivity with less than 1% of events. A summarized representation of the ALPHEUS endpoints and the different existing definitions is presented in **figure 2**. While cardiac imaging studies demonstrated cardiac tissue loss even for minor procedural myocardial injury, such a large criteria still requires validation, especially as previous studies have demonstrated the efficacy of prior more restrictive definitions to predict events, including long-term mortality<sup>9,11,24,25</sup>. In a recent pooled analysis using individual data of 14,443 patients undergoing elective PCI<sup>26</sup>, the accuracy of the different definitions of procedural myocardial injury to predict one-year mortality were compared. This study found that the 4<sup>th</sup> universal definition was too sensitive with more than 50% of patients having periprocedural myocardial injury and was not associated with mortality. More importantly, the study identified that the optimal threshold characterizing major myocardial injury was the 5-fold increase in post-PCI cTn, which corresponded to an 18.3% rate of event and a two-fold increase in all-cause mortality at one year after adjustment for all confounding factors. The afore mentioned registry using this threshold<sup>21</sup> (post PCI hs-Tn >5xURL without any ischemic criteria) and a high sensitivity troponin assay reported a 21.6% rate of major myocardial injury associated with increased cardiovascular events at 30 days and one year. In the ALPHEUS trial periprocedural myocardial injury was also defined by the 3<sup>rd</sup> Universal definition of MI as an increase of cTn >5xURL without ischemic criteria and was renamed “Major” myocardial injury by protocol modification to introduced the criteria of “Minor” myocardial injury defined by an increase above the URL (similarly as the 4th universal definition) but below the 5xURL.

Finally, regarding safety, in this multicenter trial, we expect to perform PCI with a high rate of radial access therefore limiting the bleeding risk. Access bleedings should be infrequent as well as spontaneous organ bleedings that rarely occur in the first 48 hours. In addition, this population will be at lower risk of bleeding than an ACS population.

### **Rationale for the use of ticagrelor**

Ticagrelor inhibits the P2Y<sub>12</sub> receptor in a reversible fashion and is indicated for the prevention of thrombotic events (periprocedural complication of PCI, stent thrombosis, recurrent MI or stroke) in ACS patients in combination with aspirin. In contrast to thienopyridines, ticagrelor has a binding site different from adenosine diphosphate, making it an allosteric antagonist with a reversible binding. Ticagrelor has the advantage of a mortality reduction demonstrated in the PLATO trial<sup>4</sup> with a fast onset and offset of action<sup>2</sup>. Moreover, off-label use of ticagrelor is common in high-risk elective PCI such as left main stenting, stenting in diabetics, multiple stenting, high risk of stent thrombosis and lack of clopidogrel pretreatment<sup>21</sup>. However, this off-label use is not supported by any data. Ticagrelor validated loading dose in PCI for ACS is 180 mg with oral administration (2 tablets of 90 mg) or with crushed or orodispersible tablets<sup>27,28</sup> followed by 90 mg twice daily maintenance dose (MD) was chosen at the time of design of the ALPHEUS trial. Beside the ISAR-REACT 5 trial<sup>29</sup> recently published and conducted in an ACS population, there is no trial that compared ticagrelor to prasugrel in the setting of elective PCI. Ticagrelor was compared to clopidogrel in a small randomized trial of low risk ACS undergoing ad hoc PCI, finding that the 180mg loading dose provided faster and more potent platelet inhibition than clopidogrel LD<sup>30</sup>. Prasugrel was compared to clopidogrel in elective PCI in the SASSICAIA trial<sup>31</sup>, however the study was ended prematurely after the inclusion of 781 patients due to slow enrolment and lack of funding. The similar design would allow a pooled analysis on

individual data and such post hoc analysis is already planned in collaboration with the lead PI of the trial.

### **Limitations**

This trial has limitation by design. First, it is an open labeled trial without a placebo control, and the results of the post PCI troponin are known to the investigators that are in charge of their patients. However, we believe that the PROBE design associating a blinded adjudication of the endpoints based on non-subjective post troponin value and ischemic complication that are provided by the independent core laboratory will compensate for this limitation. Second, the trial does not pretend to evaluate hard clinical endpoint but choose a universally validated surrogate endpoint that has shown to be related to patient prognosis. Third, all troponin assays were authorized in this trial to reflect real-life in a PCI centers. Fourth, we allowed by protocol modification the inclusion of patients with modestly positive baseline high sensitive troponin, with diagnosis criteria following the 4<sup>th</sup> Universal definition of MI for these patients. Fifth, the loading dose of the study drugs was suggested to be administrated one to 24 hours in advance before the PCI, however we authorized the administration of loading dose on table just before PCI in centers performing ad hoc PCI. Such short delay could favor ticagrelor effect as its pharmacodynamic is faster than clopidogrel, but here again reflects real life practice in PCI center. Finally, although the protocol authorized a loading dose of clopidogrel of 300 to 600mg, the intermediate analysis showed that in the vast majority of the cases, the 600mg loading dose was chosen and will therefore reflect contemporary practice in PCI centers.

### **Summary and expected results**

In conclusion, ALPHEUS is being conducted in order to determine whether pre-PCI administration of a loading dose of ticagrelor will result in a lower rate of cardiac

periprocedural complications (type 4 MI and myocardial injury) in elective PCI for stable obstructive coronary artery disease (or chronic coronary syndrome in the new terminology) than clopidogrel. If the study hypothesis is proven, finding from this trial may have a major implication in the possibilities of lowering procedural complications and could lead to an improvement of the long-term prognosis of the patients undergoing elective PCI cases.

### **Current status**

Enrollment started in January 2017 and is expected to conclude in May 2020. At the time of writing on February 21<sup>th</sup>, 1732 patients have been enrolled. Final results are expected in July 2020.

### **Acknowledgements**

We thank all the principal investigators involved in the ALPHEUS trial (**list in the appendix**). The authors would like to thank Karine Brochard, Martine Tanke, Pauline Cavelier and Damien Vanhoye for their help in managing the ALPHEUS study.

### **Relationship with industry**

Dr Silvain reports receiving consulting and lecture or Travel Support from AstraZeneca, Bayer HealthCare SAS, Biotronik, BPI France, Boehringer Ingelheim France, CSL Behring SA, Gilead Science, Sanofi-Aventis France, Terumo France SAS, Abbott Medical France SAS and Zoll. Stockholder of Pharmaseeds. Dr Cayla reports speaker or congress fees has received research grants/consultant fees/lectures fees from Amgen, AstraZeneca, Abbott, Bayer, Biotronik, Bristol-Myers Squibb, Pfizer, Sanofi-Aventis. Dr Beygui reports receiving consulting and lecture from AstraZeneca, Bristol-Myers Squibb, Medtronic, Biosensors, Boston Scientific. Institutional research grants: Medtronic, Biosensors, Acist, Boston Scientific. Dr Rangé reports receiving speaker's and/or consulting fees from Abbott. Dr

Lattuca has received research grants from Biotronik, Boston Scientific, Daiichi-Sankyo, Fédération Française de Cardiologie and Institute of CardioMetabolism and Nutrition; consultant fees from Daiichi-Sankyo and Eli Lilly; and lecture fees from AstraZeneca, Medtronic and Novartis. Dr Collet reports receiving consulting and lecture from AstraZeneca, Bayer, Bristol-Myers Squibb, Fédération Française de Cardiologie, Lead-Up, Medtronic, MSD, Sanofi-Aventis, WebMD. Dr Dillinger reports receiving consulting and lecture fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, Sanofi, and grants from Bayer, Bristol-Myers Squibb/Pfizer and Biosensors. Dr Boueri reports receiving consulting and lecture fees from Novartis, Astra Zeneca. Dr Boccara reports consulting or speaker fees from Amgen, Gilead, ViiV Healthcare, Amgen, Sanofi, MSD, and Servier outside the submitted work. Dr Christiaens reports consulting or speaker fees from Astra Zeneca. Dr Lhermusier reports consulting or speaker fees from Astra Zeneca, Boston Scientifics, Abbott. Research grant from Astra Zeneca. Dr Georges reports consulting or speaker fees from AstraZeneca France, Sanofi-Aventis, Amgen, and Merck Sharpe and Dohme. Dr Bellemain-Appaix reports consulting or speaker fees from Astra Zeneca, Novartis, Pfizer. Dr Saint-Etienne reports consulting or speaker fees from Abbott, Medtronic, Edwards, Biotronik, Abbott. Dr Motovska reports consulting or speaker fees Astrazeneca. Dr Laredo reports fellowship grant from Medtronic, Biotronik, Boston Scientific. Dr Ducrocq reports consulting or speaker fees Amgen, Astra Zeneca, Bayer, BMS, Janssen, Sanofi, Terumo, Proctoring: Boston scientific, CEC: Novo Nordisk, Travel Fees: Astra Zeneca, Bayer, BMS. Dr Vicaut reports consulting or speaker fees from Abbott, Bristol Myers Squibb, Celgene, Edwards, Pfizer, Sanofi And Novartis. Dr Montalescot reports consulting or speaker fees from Abbott, AIM group, Amgen, Actelion, American College of Cardiology Foundation, Astrazeneca, Axis-Santé, Bayer, Boston-Scientific, Bristol-Myers Squibb, Beth Israel

Deaconess Medical, Brigham Women's Hospital, Fréquence Médicale, ICOM, Idorsia, Elsevier, Fédération Française de Cardiologie, Fréquence Médicale, ICAN, Lead-Up, Menarini, Medtronic, MSD, Novo-Nordisk, Pfizer, Quantum Genomics, Sanofi-Aventis, SCOR global life, Servier, WebMD. Other authors have no conflict of interest to report.

Journal Pre-proof

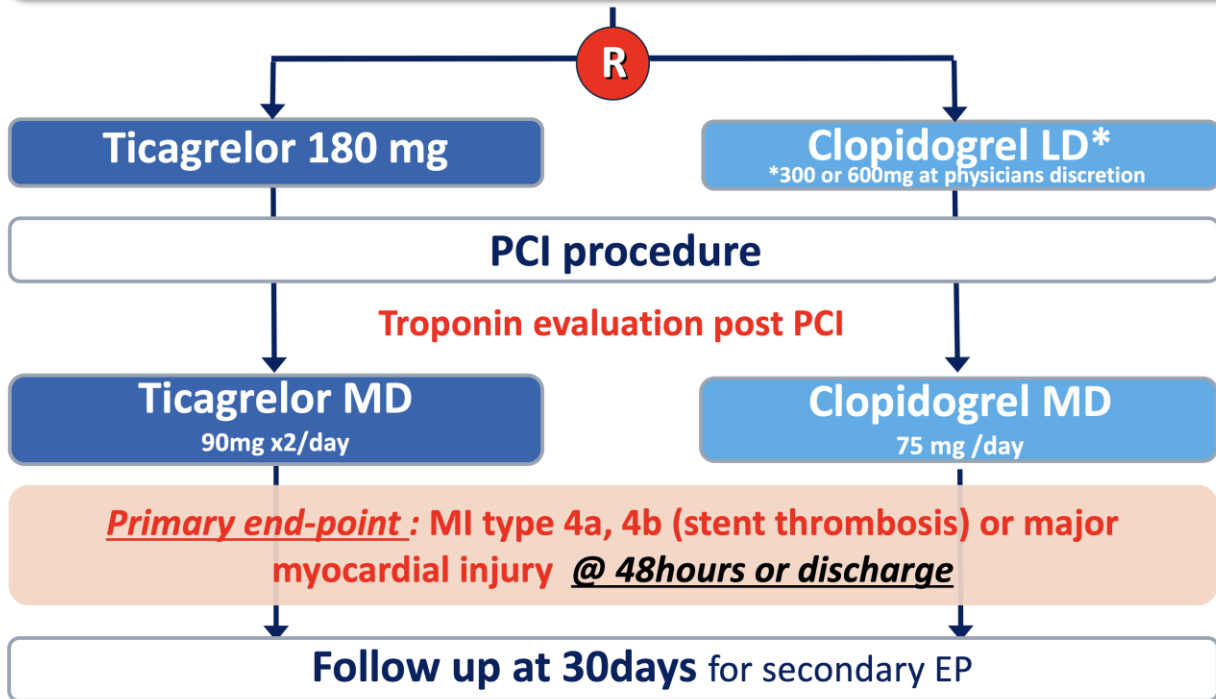
**Figure 1.** ALPHEUS study design (LD : Loading Dose , MD: Maintenance Dose)



# ALPHEUS Trial



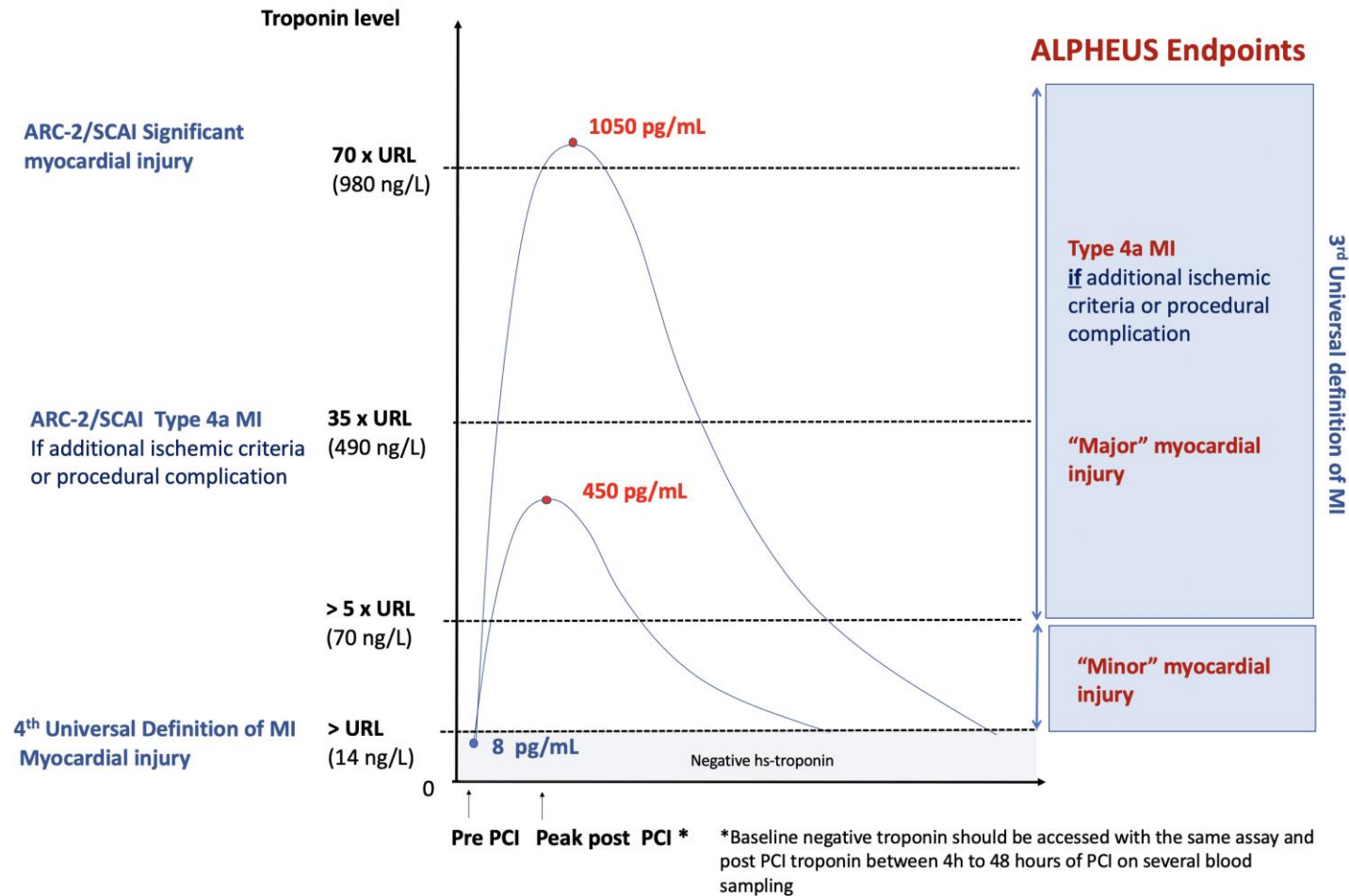
**N= 1900 troponin negative\*** patients scheduled for elective non urgent PCI \* or modestly positive and decreasing



Journal



**Figure 2.** Representation of the ALPHEUS Endpoints definition of periprocedural type 4a MI and myocardial injury definition in red compared to the 3<sup>rd</sup> and 4<sup>th</sup> Universal definition of MI and ARC-2 / SCAI definition in blue.



**Table 1.** ALPHEUS key inclusion criteria

---

**Inclusion criteria**

---

1. Male or female patients aged  $\geq 18$  years (females of non-childbearing potential:  $\geq 1$  year post-menopausal, or surgically sterile)
  2. Undergoing non-emergent single or multiple sites/vessels PCI during the same procedure
  3. Negative cTn before enrolment (according to local measurement – hsTn preferably) during hospitalization for coronary angiogram or PCI  
**Or**  
a modestly positive hs-Tn at baseline within the grey zone of the laboratory (or  $< 3x$  the URL if the grey zone is not defined) **AND** decreasing levels on the last measurement performed.
  4. Having at least one high-risk feature as described below
    - Age  $> 75$
    - Renal insufficiency (Clearance below 60ml/min calculated with Cockcroft-Gault formula)
    - Diabetes Mellitus
    - Overweight (B  $> 30$ )
    - History of ACS (in the past 12 months) including Unstable Angina /Non-STEMI and STEMI
    - Left ventricular ejection fraction  $< 40\%$  and/or prior episode of heart failure
    - Multivessel disease (2 or 3 V)
    - Multiple stents needed defined as i) more than one stent implanted in one vessel or ii) more than 2 stents in 2 or more vessels, or iii) total stent length envisioned  $> 30\text{mm}$
    - Left main stenting
    - Bifurcation stenting (whatever the technique)
    - ACC/AHA type B2 or, C lesion
    - Stenting of venous or arterial coronary graft
  4. Written informed consent obtained at enrolment into the study
-

**Table 2.** ALPHEUS key exclusion criteria

- 
- 1- Women of child-bearing potential (ie, those who are not chemically or surgically sterilized or who are not post-menopause) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator OR women who have a positive pregnancy test at randomization OR women who are breast-feeding
  - 2- Thrombolytic therapy within the previous 24 hours
  - 3- Undergoing primary PCI for ongoing STEMI
  - 4- Undergoing rescue PCI after failed thrombolysis
  - 5- Any other elective PCI scheduled within the following 30 days after the index PCI
  - 6- History of intracranial hemorrhage at any time
  - 7- Increased bleeding risk: intracranial tumor or aneurysm; recent trauma or major surgery (< 1 month) (including bypass surgery); active gastrointestinal bleed, active bleeding
  - 8- Uncontrolled arterial hypertension (defined as a systolic BP  $\geq$ 180 mmHg and/or diastolic BP  $\geq$ 100 mmHg)
  - 9- Recent (<48 hours) or planned spinal/epidural anesthesia or puncture
  - 10- Impaired hemostasis such as known International Normalized Ratio (INR) >1.5; past or present bleeding disorder (including congenital bleeding disorders such as von Willebrand's disease or hemophilia, acquired bleeding disorders, and unexplained clinically significant bleeding disorders), thrombocytopenia (platelet count <100,000/ $\mu$ L)
  - 11- Known severe and moderated hepatic impairment
  - 12- Treatment with oral anticoagulant therapy within 72 hours prior to inclusion or current need for oral anticoagulant therapy in the next month.
  - 13- Use of abciximab within the previous 7 days or, tirofiban or eptifibatide within the past 12 hours of index PCI
  - 14- Prohibited treatments (**see appendix**)
  - 15- Inability to give informed consent or high likelihood of being unavailable for follow-up
  - 16- Participation in another clinical research protocol with other investigational agents or devices within the previous 30 days, planned use of investigational drugs or devices, or previous enrolment in this trial (participation in a trial of routine care is authorized at the same time)
  - 17- Known intolerance to clopidogrel or ticagrelor
  - 18- Hypersensitivity to ticagrelor or its excipients
  - 19- Hypersensitivity to clopidogrel or its excipients
  - 20- Patient on prasugrel or ticagrelor before the procedure
-

**Table 3.** Table description of the definition of in the ALPHEUS trial MI type 4a and major and minor myocardial Injury in baseline cTn negative patients (A) and modestly hs-Tn positive patients (B)

**A**

	BASELINE TROPONIN NEGATIVE	
	cTn > URL and $\leq 5 \times \text{URL}$	cTn > $5 \times \text{URL}$
No additional evidence of prolonged ischemia or procedural complication	Minor Myocardial Injury	Major myocardial Injury
Additional evidence of prolonged ischemia or procedural complication	Major myocardial Injury	Myocardial Infarction Type 4a

**B**

	BASELINE TROPONIN MODESTLY POSITIVE	
	cTn increase by $\geq 20\%$ from baseline value and value $\leq 5 \times \text{URL}$	cTn increase by $\geq 20\%$ from baseline value and above $> 5 \times \text{URL}$
No additional evidence of prolonged ischemia or procedural complication	Minor Myocardial Injury	Major myocardial Injury
Additional evidence of prolonged ischemia or procedural complication	Major myocardial Injury	Myocardial Infarction Type 4a

**Table 4:** Expected event rates at 48 hours calculated on studies available during the design of the trial (MA indicate Metaanalysis).

Authors	Journal	Years	n	MI Type 4a or myocardial injury (>3X URL)
Collet al	New Engl J Med	2012	2,440	29%
Novacket al	Arch Intern Med	2012	4,930	24%
Pervaizet al	Circulation CI	2012	3,687	19%
Porto et al	Circulation CI	2012	50	42%
Feldman et al	Catheter Cardiovasc Inter	2011	22,253 (MA)	26%/34%
Lee et al	Circ CVI	2011	131	24%
Kim et al	Int J Cardiol	2011	213	14%
Mangiacapra et al	JACC CardiovascInterv	2010	338	31%
Locca et al	JACC CardiovascInterv	2010	45	58%
Hoole et al	Coron Artery Dis	2010	243	27%
Nienhuis et al	Catheter Cardiovasc Inter	2008	15,581 (MA)	33%
			<b>Average</b>	<b>30%</b>

## REFERENCES

- <sup>1</sup> Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;116:2923-32.
- <sup>2</sup> Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120:2577-85.
- <sup>3</sup> 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.
- <sup>4</sup> Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361:1045-1057.
- <sup>5</sup> Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:1581-98.
- <sup>6</sup> Thygesen K, Alpert JS, Jaffe AS et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237–269.
- <sup>7</sup> Moussa ID, Klein LW, Shah B et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 2013;62:1563–1570.
- <sup>8</sup> Garcia-Garcia HM, McFadden EP, Farb A, et al. Academic Research Consortium. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Circulation* 2018;137:2635–2650.
- <sup>9</sup> Ndrepepa G, Collieran R, Braun S et al. High-Sensitivity Troponin T and Mortality After Elective Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2016 Nov 2016, 68 (21) 2259-2268; DOI: 10.1016/j.jacc.2016.08.059
- <sup>10</sup> Prasad A, Singh M, Lerman A et al. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *J Am Coll Cardiol* 2006 Nov 7;48(9):1765-70.
- <sup>11</sup> Li Y, Pei H, Bulluck H et al. Periprocedural elevated myocardial biomarkers and clinical outcomes following elective percutaneous coronary intervention: a comprehensive dose-response meta-analysis of 44,972 patients from 24 prospective studies. *EuroIntervention*. 2020 Mar 20;15(16):1444-1450.

- <sup>12</sup> Hansson L, Hedner T, Dahlöf B et al. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Prospective Randomized Open Blinded End-Point*. *Blood Press*. 1992;1:113-9.
- <sup>13</sup> Smith DH, Neutel JM, Lacourcière Y et al. Prospective, randomized, open-label, blinded-endpoint (PROBE) designed trials yield the same results as double-blind, placebo-controlled trials with respect to ABPM measurements. *Journal of Hypertension* 2003;21:1291-1298
- <sup>14</sup> 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.
- <sup>15</sup> Angiolillo DJ, Rollini F, Storey RF et al. International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies. *Circulation*. 2017 Nov 14;136(20):1955-1975.
- <sup>16</sup> Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;367:2100-9.
- <sup>17</sup> Bonaca MP, Wiviott SD, Braunwald E, et al. American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation universal definition of myocardial infarction classification system and the risk of cardiovascular death: observations from the TRITON-TIMI 38 trial. *Circulation* 2012;125:577-83.
- <sup>18</sup> Cannon CP, Harrington RA, James S et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010;375:283-93.
- <sup>19</sup> Sibbing D, Aradi D, Alexopoulos D et al. Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y12 Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. 2019 Aug 26;12(16):1521-1537.
- <sup>20</sup> Cutlip DE, Windecker S, Mehran R et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007 May 1;115(17):2344-51.
- <sup>21</sup> Zeitouni M, Silvain J, Guedeney P et al. Periprocedural myocardial infarction and injury in elective coronary stenting. *Eur Heart J* 2018;39:1100–1109.
- <sup>22</sup> Brener SJ, Cristea E, Lansky AJ et al. Operator versus core laboratory assessment of angiographic reperfusion markers in patients undergoing primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv*.2012;5:563–569.

- 
- <sup>23</sup> Zeitouni M, Barthélémy O, Hauguel-Moreau M et al. Investigator Versus Core Laboratory Evaluation of Coronary Flow and Related Mortality in the CULPRIT-SHOCK Trial. *Circ Cardiovasc Interv.* 2019 Oct;12(10):e008296.
- <sup>24</sup> Christensen MK, Huang H, Torp-Pedersen C et al. Incidence and impact on prognosis of peri-procedural myocardial infarction in 2760 elective patients with stable angina pectoris in a historical prospective follow-up study. *BMC Cardiovasc Disord* 2016 Jun 16;16:140.
- <sup>25</sup> Park DW, Kim YH, Yun SC et al. Frequency, causes, predictors, and clinical significance of peri-procedural myocardial infarction following percutaneous coronary intervention. *Eur Heart J* 2013 Jun ;34(22):1662-9.
- <sup>26</sup> Silvain J, Zeitouni M, Paradies V et al. Peri-procedural myocardial injury, infarction and mortality in patients undergoing elective PCI: a pooled analysis of individual-level data. (Under review to *Eur Heart J*)
- <sup>27</sup> Parodi G, Xanthopoulou I, Bellandi B et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. *J Am Coll Cardiol.* 2015;65:511-2.
- <sup>28</sup> Teng R, Hammarberg M, Carlson GF et al. Pharmacokinetic Profiles of Ticagrelor Orodispersible Tablets in Healthy Western and Japanese Subjects. *Clin Drug Investig.* 2017;37:1035-1045.
- <sup>29</sup> Schüpke S, Neumann FJ, Menichelli M et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med.* 2019 Oct 17;381(16):1524-1534.
- <sup>30</sup> Angiolillo DJ, Franchi F, Waksman R et al. Effects of Ticagrelor Versus Clopidogrel in Troponin-Negative Patients With Low-Risk ACS Undergoing Ad Hoc PCI. *J Am Coll Cardiol.* 2016 Feb 16;67(6):603-613.
- <sup>31</sup> Mehilli J. Comparison of Loading Strategies With Antiplatelet Drugs in Patients Undergoing Elective Coronary Intervention. Oral presentation ESC 2019 (not published).



# ALPHEUS Trial



N= 1900 **troponin negative\*** patients scheduled for elective non urgent PCI \* or modestly positive and decreasing

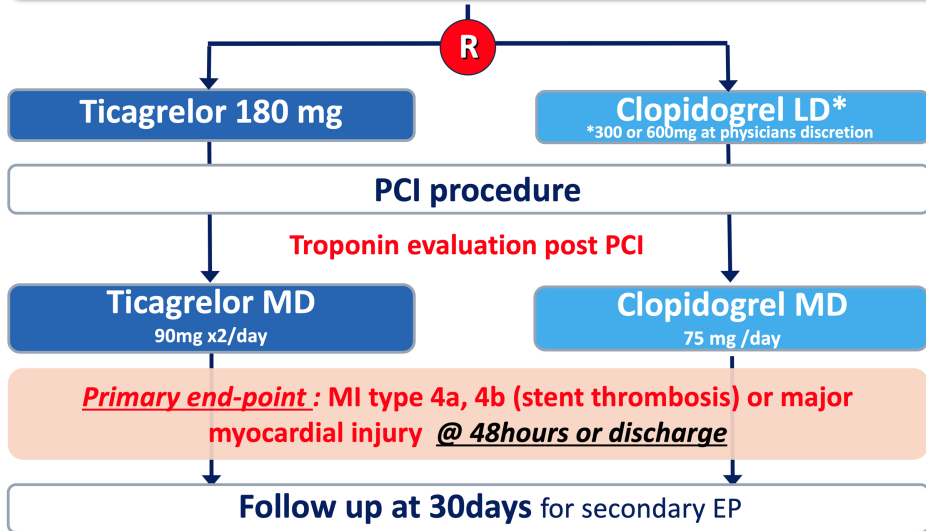


Figure 1

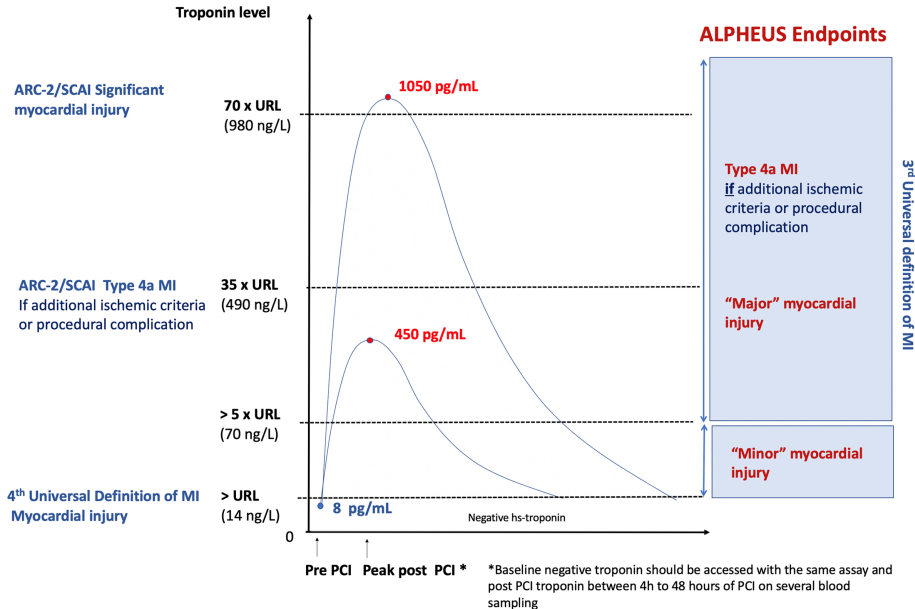


Figure 2