DUBIUS
RANDOMIZED CONTROLLED TRIAL

Downstream versus Upstream strategy for the administration of P2Y12 receptor Blockers In non ST elevated acUte coronary Syndromes with initial invasive indication.

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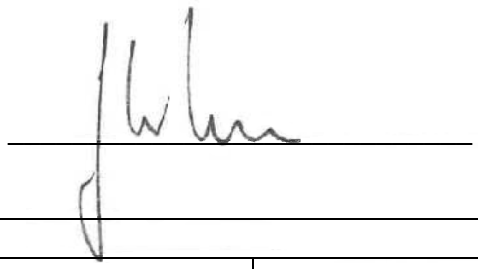
Contact List

Sponsor	Azienda Ospedaliera di Padova Via Giustianiani, 1 35128 Padova PD
Coordinating Investigator and Person authorized to sign the protocol and the protocol amendment for the sponsor	Prof. Giuseppe Tarantini, MD
Co-Investigator	Dr. Giuseppe Musumeci, MD
Writing Committee	Sergio Berti, Francesco Bedogni, Francesco Saia, Alfredo Marchese, Ciro Mauro, Marco Mojoli, Luca Favero, Plinio Cirillo, Alberto Menozzi, Ugo Limbruno, Massimo Napodano, Paolo Calabrò, Sabino Iliceto, Dominick J. Angiolillo.
Steering Committee	Sergio Berti, Rino Sardella, Francesco Bedogni, Ferdinando Varbella, Alfredo Marchese, Fabio Tarantino, Daniela Trabattoni, Nicola Signore, Leonardo De Luca, Luigi Oltrona Visconti, Salvatore Ierna, Paola Colombo, Antonio Montinaro, Zoran Olivari, Carlo Cernetti, Giampaolo Pasquetto, Dominick J. Angiolillo.
Clinical Events Committee	Serafina Valente, Emanuela Piccaluga, Claudio Cavallini, Battistina Castiglioni, Alessio La Manna.
Data Safety Monitoring Board (DSMB)	Prof. Giuseppe Tarantini, MD Prof. Dario Gregori, MA, PhD Dr. Matteo Martinato, RN, MSc, PhD Dr. Gennaro De Crescenzo, MA
Data Management/Analysis	Prof. Giuseppe Tarantini, MD Prof. Dario Gregori, MA, PhD
Data Monitoring	Prof. Giuseppe Tarantini, MD Prof. Dario Gregori, MA, PhD Dr. Gennaro De Crescenzo, MA Email: dubius.sctb.dctv@unipd.it
Sponsor'sRPPV (Responsible Person for PharmacoVigilance)	Dr. Matteo Martinato, RN, MSc, PhD matteo.martinato@sanita.padova.it nucleoricercaclinica@sanita.padova.it eudra.vigilance@sanita.padova.it Tel. 0498218314/4439 Fax 0498217490
Name, title, address, and telephone number of the sponsor's medical expert for the trial	Prof. Giuseppe Tarantini, MD UOC Cardiologia - Azienda Ospedaliera di Padova Via Giustiniani, 1 35128 Padova PD Tel. 0498211844/2322 e-mail giuseppe.tarantini.1@gmail.com

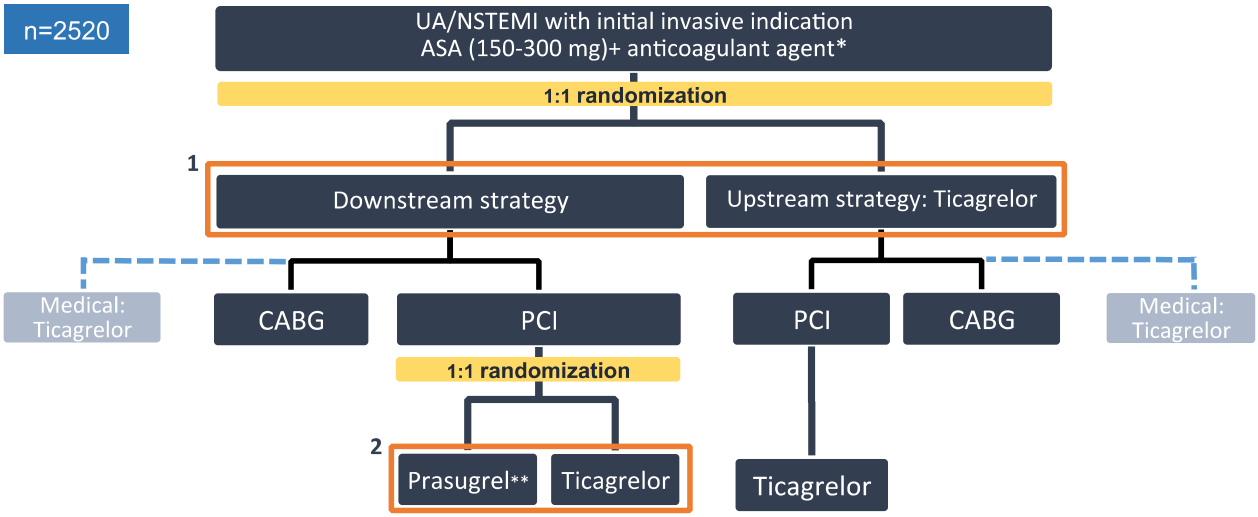
Signatures confirm that this protocol has been carefully read and fully understood, and that there is agreement to comply with the conduct and terms of the trial specified herein in compliance with Good Clinical Practice and all other regulatory requirements.

Role	**Name and title**
Coordinating Investigator	**Prof. Giuseppe Tarantini**
Signature:  10 . 11 . 2015 **Date (DD MM YYYY)**	

Role	**Name and title**	**Site**
Principal Investigator (the investigator who is responsible for conducting the trial at the present site)		
Signature: _____ **Date (DD MM YYYY)**		

Trial site name	**Address**	**Telephone number**

DUBIUS TRIAL



Primary powered hypotheses:

1. Superiority of a downstream administration strategy for P2Y12 receptor blockers (prasugrel or ticagrelor) over the upstream administration strategy (ticagrelor only) in terms of the primary endpoint.
2. Non inferiority of Prasugrel vs Ticagrelor in the PCI group of the downstream strategy arm in terms of the primary endpoint.

Primary endpoint: NACE (Net Adverse Cardiac Events) at 30 days. NACE defined as a composite of: death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), non fatal MI, or non fatal stroke, BARC type 2, 3, 4 and 5 bleeding.

All randomizations are blocked for age > 75 yr

****Allowed anticoagulants are: unfractioned heparin, fondaparinux, enoxaparin, bivalirudin.***

***** 60 mg oral bolus then 5 mg/die if >75 yrs or < 60 kg***

TABLE OF CONTENTS

PROTOCOL SUMMARY

Title	**Downstream versus upstream strategy for the administration of P2Y12 receptor blockers in non ST elevated acute coronary syndromes with initial invasive indication.**
Acronym	**DUBIUS**
Main purposes	To evaluate the impact on outcomes of the currently accepted antithrombotic strategies based on the administration of newer P2Y12 receptor blockers (prasugrel and ticagrelor) in a population of non ST elevated ACS (NSTEACS) patients with an initial invasive indication. Furthermore, to evaluate the effects of bivalirudin administration in comparison to standard therapy with unfractioned heparin (plus provisional anti-GPIIbIIIa) in NSTEACS patients who undergo PCI and will thus receive these potent antiplatelet agents which may theoretically favor the occurrence of bleedings. A combined measure of efficacy and safety endpoints, the so-called net clinical benefit (NACE), will be considered at early (30 days) and mid term (12 months) follow-up.
Duration of enrollment	Study start date: 2015 Estimated end of enrollment: 2016
Study population	2520 patients with NSTEACS (unstable angina [UA] or non ST elevated myocardial infarction [NSTEMI]), with an initial invasive indication and who meet inclusion criteria.
Study design	Prospective, double randomized (1:1 upstream vs. downstream administration of P2Y12 receptor blockers; 1:1 downstream prasugrel vs. downstream ticagrelor) active control, parallel arms, multi-center adaptive clinical investigation in a population of NSTEACSpatients with an initial invasive indication.
Studysites and geography	More than 40 cardiology clinics with or without on-site cath lab in Italy will be involved.
Primary (powered) hypothesis	1. Superiority of the downstream administration strategy for P2Y12 receptor blockers (prasugrel or ticagrelor) over the upstream administration strategy (ticagrelor only) in terms of the primary endpoint. 2. Non inferiority of Prasugrel vs Ticagrelor in the PCI group of the downstream strategy arm in terms of the primary endpoint.
Secondary exploratory (unpowered, non-randomized) hypothesis	Superiority of Bivalirudin over UFH (plus provisional antiGPIIbIIIa based upon clinical judgement) in the PCI group
Primary Endpoint	• Incidence at 30 days and 12 months of NACE (Net Adverse Cardiac Events), defined as a composite of: death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), non fatal MI, or non fatal stroke, BARC type 3, 4 and 5 bleeding. [Time Frame: 30 days and 12 months] [Designated as safety issue: Yes]
Secondary Endpoints	• Single digit and composite of death from vascular causes, MI, stroke, TIA, severe recurrent ischemia, recurrent ischemia, or other arterial thrombotic event. [Time Frame: 30 days, 12 months]

	[Designated as safety issue: No]. • Death from any cause. [Time Frame: 30 days, 12 months] [Designated as safety issue: No] • Any stent thrombosis according to the ARC criteria (possible, probable, or definite). [Time Frame: 30 days, 12 months] [Designated as safety issue: No] • Target vessel revascularization (TVR). [Time Frame: 30 days, 12 months] [Designated as safety issue: No] • Target lesion revascularization (TLR). [Time Frame: 30 days, 12 months] [Designated as safety issue: No] • NACE (Net Adverse Cardiac Events) occurred in the period between admission and coronary revascularization defined as a composite of: death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), non fatal MI, or non fatal stroke, BARC type 2 3, 4 and 5 bleeding, [Time Frame: 30 days, 12 months] [Designated as safety issue: Yes] • Compliance to mandated antiplatelet therapy [Time Frame: 30 days, 12 months] [Designated as safety issue: No] • BARC type 2, 3, 4 and 5 bleeding (single digit and composite). [Time Frame: 30 days, 12 months] [Designated as safety issue: No] • All TIMI major, major-life-threatening, and minor bleeding [Time Frame: 30 days, 12 months] [Designated as safety issue: No] • All CABG surgery-related TIMI major, minor, and composite of TIMI major or minor bleeding [Time Frame: 30 days, 12 months] [Designated as safety issue: No]Non-CABG surgery-related TIMI major, minor, and composite of TIMI major or minor bleeding [Time Frame: 30 days, 12 months][Designated as safety issue: No]
Statistical analysis	Primary powered hypotheses 1. Superiority of a downstream administration strategy for P2Y12 receptor blockers (prasugrel or ticagrelor) over the upstream administration strategy (ticagrelor only) 2. Non inferiority of Prasugrel vs Ticagrelor in the PCI group of the downstream strategy arm (where $\delta > 0.01$) Secondary unpowered non-randomized exploratory hypothesis 3. Superiority of Bivalirudin over UFH (plus provisional antiGPIIbIIIa based upon clinical judgement) in the PCI group The sample size calculation is based on the primary endpoint at 30 days of incidence of NACE (Net Adverse Cardiac Events), defined as a composite of: death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), non fatal MI, or non fatal stroke, BARC type 3, 4 and 5 bleeding. The study has been first targeted for the first group of randomization, aimed at showing superiority of a downstream administration strategy for

	P2Y12 receptor blockers (prasugrel or ticagrelor) over the upstream administration strategy (ticagrelor only). The sample size has been computed using an adaptive approach in three study stages. After each stage a sample size reassessment is performed. Assuming a drop-out rate of about 10%, the total sample size (rounded up) is of 2520 patients (1260 upstream + 1260 downstream). As a second target, non inferiority of Prasugrel vs Ticagrelor in the PCI group of the downstream strategy. Analyses will be performed at the study completion, so no ad-interim evaluations are assumed for this study group. Assuming that at least 80% of the patients will have an indication for PCI in the downstream group, based on the above calculations, a sample of about 1000 should be available for randomization in this group. As a third unpowered non-randomized target, superiority of a Bivalirudin over UFH (plus provisional antiGPIIbIIIa based upon clinical judgement) in the overall PCI group (without distinguishing between upstream and downstream randomized patients) will be studied.
Inclusion criteria	• Age ≥ 18 and < 85 • Non ST elevated acute coronary syndrome (unstable angina, non ST elevated myocardial infarction), with an onset of symptoms during the previous 24 hours. • An initial invasive strategy is chosen (the patient is expected to undergo coronary angiography within 72 h from admission). • Subject is able to start therapy with a new P2Y12 inhibitor (prasugrel or ticagrelor) OR is on a maintenance dose of clopidogrel or ticlopidine and is able to switch to a new P2Y12 inhibitor (prasugrel or ticagrelor). • Subject is able to verbally confirm understanding of risks and benefits of dual antiplatelet therapy in coronary acute syndromes and he/she or his/her legally authorized representative provides written informed consent prior to any Clinical Investigation related procedure, as approved by the appropriate Ethics Committee. • Patient agrees to comply with follow-up evaluations.
Exclusion criteria	**General Exclusion criteria** • Known hypersensitivity/contraindication to aspirin, clopidogrel, prasugrel, ticagrelor, heparin or bivalirudin, or sensitivity to contrast media, which can't be adequately pre-medicated. • Platelet count <100,000 cells/mm³ or >700,000 cells/mm³, or a white blood cell (WBC) count <3,000 cells/mm³ within 7 days prior to index procedure. • Shock. • Have severe hepatic impairment defined as Child Pugh Class C. • Pregnant or nursing subjects and those who plan pregnancy in the period up to 3 years following screening. (Female subjects of child-bearing potential must have a negative pregnancy test done within 28 days prior to enrollment).

	• Other medical illness (e.g., cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin etc.) as per physician judgment that may cause non-compliance with the protocol or confound the data interpretation or is associated with a limited life expectancy. • Subject is belonging to a vulnerable population (per investigator's judgment, e.g., subordinate hospital staff or sponsor staff) or subject unable to read or write. • Currently participating in investigational drug or device trial that has not completed the primary endpoint or that clinically interferes with current trial endpoints. Subject must agree not to participate in any other clinical investigation for a period of three years following the index procedure, including clinical trials of medication and invasive procedures. Questionnaire-based studies, or other studies that are non-invasive and do not require medication are allowed. **Bleeding Risk Exclusion Criteria** • Prior history of hemorrhagic or ischemic stroke, a transient ischemic attack (TIA), or sub-arachnoid hemorrhage. • History of intracranial neoplasm, arterovenous malformation, or aneurysm. • Have received fibrinolytic therapy within 48 hours of entry or randomization into the study. • Have active pathological bleeding or history of bleeding diathesis. • Have clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding. • Have had recent surgery (within 4 weeks of entry into the study) or are scheduled to undergo surgery within the next 2 months. **Prior/Concomitant Therapy Exclusion Criteria** • Have received a loading dose of a thienopyridine (ticlopidine, clopidogrel or prasugrel) or a maintenance dose of prasugrel or Ticlopidine or Ticagrelor within 7 days of entry into the study. • Are receiving a GPIIb/IIIa inhibitor (eptifibatide, tirofiban, or abciximab). • Are receiving warfarin or other coumarin derivatives. • Are receiving or will receive oral anticoagulation or other oral antiplatelet therapy (except aspirin [ASA]) that cannot be safely discontinued within the next 3 months. • Are receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued or are anticipated to require >2 weeks of daily treatment with NSAID or COX2 inhibitors during the study. • Concomitant therapy with a strong cytochrome P-4503A inhibitor or inducer.
Follow-up	Office visit at 30 days and 12 months.

1 *INTRODUCTION*

1.1 Background

The term acute coronary syndrome (ACS) is applied to patients in whom there is a suspicion of myocardial ischemia and comprises three types clinical manifestations: ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). The first two are characterized by a typical rise in biomarkers of myocardial injury.

Current pharmacological treatments for acute coronary syndromes focus on an efficient inhibition of platelet function and of the coagulation cascade. Additionally, in patients at high risk for future events (i.e., re- infarction or recurrent ischemia), an early invasive strategy of cardiac catheterization and revascularization is recommended. Since percutaneous coronary intervention (PCI) may be associated to further plaque trauma, platelet-dependent thrombosis, and embolization into the coronary microcirculation, it is best practice to treat patients who undergo PCI with agents that inhibit platelet activation to prevent recurrent ischemia. As a consequence, current guidelines recommend dual antiplatelet therapy with aspirin plus another agent in patients with ACS who are undergoing PCI. The advent of aggressive, multidrug antithrombotic therapy during ACS has led to significant reductions in short- and long-term ischemic outcomes.

Current evidence supports the use of newer antiplatelet therapy (ticagrelor and prasugrel) over clopidogrel in patients with ACS. Recommendations on prasugrel administration are largely based on results from the TRITON-TIMI 38 study, which showed that prasugrel treatment resulted in a significantly greater reduction in the primary composite efficacy end point (death from CV causes, non-fatal MI, or non-fatal stroke) than the approved clopidogrel dosing regimen in clopidogrel-naive patients with ACSs scheduled to undergo PCI. The reduction in ischemic events with prasugrel as compared with clopidogrel was, as expected, associated with a significant increase in the rate of bleeding. Exploratory analyses identified 3 subgroups as having increased risk of bleeding, including patients with a history of stroke or transient ischemic attack, patients >75 years old, or patients with a body weight <60 kg. Recommendations on ticagrelor administration come mostly from PLATO study, which showed that at 12 months, the primary end point -a composite of death from vascular causes, myocardial infarction, or stroke -had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (P<0.001), without significant difference in the rates of major bleeding (11.6% and 11.2%, respectively; P=0.43). However, ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting, including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types.

Optimal timing for initiation of therapy with P2Y12 receptor blockers (upstream versus downstream administration) in ACS patients with an initial invasive indication remains unclear. Theoretically, the advantage of early administration of P2Y12 receptor blockers for patients with unknown coronary artery anatomy prior to diagnostic coronary angiography is to achieve higher inhibition of platelet aggregation and thus prevent recurrent atherothrombotic events in patients likely to undergo PCI. However, remarkable differences in P2Y12 receptor blockers administration timing exist in available studies. In one pivotal

trial, patients were treated with P2Y12 blockers for several days to weeks before revascularization (Lancet 2001;358:527-33.), whereas other trials involved treatment around the time of cardiac catheterization. (N Engl J Med 2007;357:2001-15, N Engl J Med 2009;361:1045-57).

Guidelines recommend clopidogrel administration to be performed soon after hospital admission, but this recommendation has never been tested directly in a randomized trial. (DOI: 10.1056/NEJMe1308820). Furthermore, a recent systematic meta-analysis evaluating the association of clopidogrel pretreatment vs no pretreatment with mortality and major bleeding after PCI in 37814 patients showed that among patients scheduled for PCI, clopidogrel pretreatment was not associated with a lower risk of mortality, and that there was no significant association between pretreatment with clopidogrel and major bleeding (JAMA. 2013 Apr 10;309(14):1461).

Pretreatment of ACS patients with prasugrel has been recently challenged by the ACCOAST Trial. In this study, 4033 NSTEMI patients were randomly assigned to receive prasugrel as pretreatment (2 to 48 hours before cardiac catheterization) or to receive prasugrel after catheterization if PCI was planned. The pretreatment strategy as compared with the late-administration strategy had no significant effect on the rate of major ischemic events over the course of the 30-day study period, and the trial was terminated because prasugrel pretreatment produced an excess of major or life-threatening bleeding events. Notably, pretreatment with prasugrel led to maximal platelet inhibition at the time of vascular access, which explains why excess procedure related bleeding was observed. Overall, these results indicate that patients with NSTEMI with and indication to early invasive strategy will take advantage of a downstream administration of prasugrel only after angiographic definition of their coronary anatomy.

It remains to be investigated whether a similar strategy could be applied to ticagrelor, the other high-potency P2Y antagonist currently available. The recent ATLANTIC trial has showed that prehospital administration of ticagrelor in patients with acute STEMI appeares to be safe even if it does not improve pre-PCI coronary reperfusion (N EnglJ Med. 2014 Sep 11;371:1016-27.). On the contrary, the role of pretreatment with ticagrelor in NSTEACS patients has not been properly investigated by a dedicated RCT.

Notably, up to 16% of patients with NSTEMI ultimately undergo coronary-artery bypass grafting (CABG). (N Engl J Med 2001;345:494-502 [Errata, N Engl J Med 2001;345:1506, 1716.]) Because current guidelines recommend P2Y12 inhibition soon after hospital admission, many patients with NSTEMI who need CABG will have received P2Y antagonists before the catheterization. Administration of P2Y12 inhibitors within 5 days before CABG has been linked to excess bleeding and prolonged hospitalization, prompting recommendations that CABG be delayed until 5 to 7 days after discontinuation of P2Y antagonists.

Rationales for the present study are: first, it is unclear whether in NSTEACS patients a strategy of downstream administration of newer P2Y12 receptor blockers (prasugrel or ticagrelor) might be superior to upstream administration of ticagrelor due to possible reduction of bleeding rates; second, there are no published studies that directly compare the efficacy and the rates of bleeding between downstream administration of ticagrelor and prasugrel. Third, the interaction in terms of ischemic outcomes and bleedings between newer P2Y12 receptor blockers and different anticoagulants is unclear. Bivalirudin, a direct

thrombin inhibitor, appears to have a better safety profile compared to heparin and thus reasonably seems to be particularly indicated when using these new antiplatelet agents.

2 *STUDY OBJECTIVES*

The primary objective of this clinical study is to evaluate the impact on outcomes of the currently accepted antithrombotic strategies based on the administration of newer P2Y12 receptor blockers (prasugrel and ticagrelor) in a population of NSTEACS patients with an early invasive indication. As an exploratory target, this study will also investigate the effects of bivalirudin administration in comparison to standard therapy with unfractioned heparin in NSTEACS patients who undergo PCI and will thus receive these potent antiplatelet agents which may theoretically favor the occurrence of bleedings. A combined measure of efficacy and safety endpoints, the so-called NACE (Net Adverse Cardiac Events), will be considered at early (30 days) and mid term (12 months) follow up. Main analyses will take into account the following:

1. The net clinical benefit of downstream strategy for the administration of newer antiplatelet agents (prasugrel or ticagrelor) versus the upstream strategy (ticagrelor only) in NSTEACS patients with early invasive indication.

2. The net clinical benefit of prasugrel versus ticagrelor administration, within the PCI group of the downstream strategy arm.

3. The net clinical benefit of unfractioned heparin versus bivalirudin within in the PCI group within both downstream and upstream strategy arms (exploratory analysis).

3 STUDY DESIGN

Prospective, multicenter, randomized, controlled study designed to enrol approximately 2520 subjects with NSTEACS who will be randomized in a 1:1 fashion to a downstream administration strategy of P2Y12 receptor blockers (prasugrel or ticagrelor) vs. an upstream administration strategy (ticagrelor only). The patients of the downstream strategy arm who will undergo PCI will be also randomized in a 1:1 fashion to downstream prasugrel vs. downstream ticagrelor. For all the patients undergoing PCI both the use of unfractioned heparin (plus anti GPIIbIIIa based upon clinical judgement) and of bivalirudin will be allowed at the time of PCI; the choice of the anticoagulant at the time of PCI will be based upon clinical judgement. All randomizations will be blocked for age (>75 or ≤ 75 years).

4 *HYPOTHESES AND ENDPOINTS*

4.1 Study hypotheses

Primary (powered) hypotheses:

1. Superiority of the downstream administration strategy for P2Y12 receptor blockers (prasugrel or ticagrelor) over the upstream administration strategy (ticagrelor only) in terms of the primary endpoint.
2. Non inferiority of Prasugrel vs Ticagrelor in the PCI group of the downstream strategy arm in terms of the primary endpoint.

Secondary exploratory (unpowered, non-randomized) hypothesis:

Superiority of Bivalirudin over UFH (plus provisional antiGPIIbIIIa based upon clinical judgement) in the PCI group in terms of the primary endpoint.

4.2 Endpoints

Primary endpoint:

Incidence at 30 days and 12 months of NACE (Net Adverse Cardiac Events), defined as a composite of: death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), non fatal MI, or non fatal stroke, BARC type 3, 4 and 5 bleeding.

The rationale for choosing these composite endpoint was to use the most unbiased estimate of the effect regarding irreversible organ damage, that is, MI, ischemic and hemorrhagic stroke, plus an estimate of life threatening and fatal bleedings.

Secondary Endpoints:

1) Single digit and composite of death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), MI, stroke, TIA, severe recurrent ischemia, recurrent ischemia, or other arterial thrombotic event
2) Death from any cause
3) Any stent thrombosis according to the ARC criteria
4) Target vessel revascularization (TVR)
5) Target lesion revascularization (TLR)
6) NACE (Net Adverse Cardiac Events) occurred in the period between admission and coronary revascularization defined as a composite of: death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), non fatal MI, or non fatal stroke, BARC type 2, 3, 4 and 5 bleeding
7) Compliance to mandated antiplatelet therapy
8) BARC type 2, 3, 4 and 5 bleeding (single digit and composite)
9) All TIMI major, major-life-threatening, and minor bleeding
10) All CABG surgery-related TIMI major, minor, and composite of TIMI major or minor bleeding
11) Non-CABG surgery-related TIMI major, minor, and composite of TIMI major or minor bleeding

4.3 Measures Taken to Avoid/Minimize Bias

In order to minimize bias, the study design includes randomization. Study site personnel who are present during the initial procedure will not be involved in the follow-up evaluations.

4.4 Randomization

The 2520 subjects with an acute coronary syndrome will be randomized in a 1:1 fashion to a downstream administration strategy of P2Y12 receptor blockers (prasugrel or ticagrelor) vs. an upstream administration strategy (ticagrelor only). The patients of the downstream strategy arm who will undergo PCI, will be randomized in a 1:1 fashion to downstream prasugrel vs. downstream ticagrelor. The first randomization will occur as soon as possible after admission. The second randomizations will occur before PCI procedure (only for patients who require PCI, based upon clinical judgment).
All randomizations will be stratified by age (>75 years or <75 years). A centralized online system will be used for randomization. Once randomized, the subjects are considered enrolled in the study and analyzed as the intent-to-treat (ITT) population.

5 *SELECTION AND WITHDRAWAL OF SUBJECTS*

5.1 Study Population

Patients who present with NSTEACS (UA/NSTEMI), with an onset of symptoms during the previous 24 hours and for whom an initial invasive strategy is chosen.

5.2 Patient Screening

Patients who present with an acute coronary syndrome should be screened for study eligibility by a member of the study team previously trained to the study protocol. Patients who meet general eligibility criteria will be asked to sign an informed consent.

5.3 Informed Consent

The Principal Investigator, Subinvestigator, or designee, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subjects. All subjects or legally authorized subjects' representatives must sign and personally date the Ethics Committee (EC) approved informed consent prior to any study-specific procedures. The signed informed consent will be kept in the subject's medical records and a copy will be given to the subject or the legally authorized representative.

5.4 Eligibility Criteria

5.4.1 Inclusion Criteria

Patients must meet ALL of the following criteria:

- Age ≥ 18 and < 85
- Non ST elevated acute coronary syndrome (unstable angina, non ST elevated myocardial infarction), with an onset of symptoms during the previous 24 hours.
- An initial invasive strategy is chosen (the patient is expected to undergo coronary angiography within 72 h from admission).
- Subject is able to start therapy with a new P2Y12 inhibitor (prasugrel or ticagrelor) OR is on a maintenance dose of clopidogrel or ticlopidine and is able to switch to a new P2Y12 inhibitor (prasugrel or ticagrelor).

- Subject is able to verbally confirm understanding of risks and benefits of dual antiplatelet therapy in coronary acute syndromes and he/she or his/her legally authorized representative provides written informed consent prior to any Clinical Investigation related procedure, as approved by the appropriate Ethics Committee.
- Patient agrees to comply with follow-up evaluations.

5.4.2 Exclusion Criteria

Patients will be excluded if **ANY** of the following conditions apply:

General Exclusion criteria

- Known hypersensitivity/contraindication to aspirin, clopidogrel, prasugrel, ticagrelor, heparin or bivalirudin, or sensitivity to contrast media, which can't be adequately pre-medicated.
- Platelet count <100,000 cells/mm³ or >700,000 cells/mm³, or a white blood cell (WBC) count <3,000 cells/mm³ within 7 days prior to index procedure.
- Shock.
- Have severe hepatic impairment defined as Child Pugh Class C.
- Pregnant or nursing subjects and those who plan pregnancy in the period up to 3 years following screening. (Female subjects of child-bearing potential must have a negative pregnancy test done within 28 days prior to enrollment).
- Other medical illness (e.g., cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin etc.) as per physician judgment that may cause non-compliance with the protocol or confound the data interpretation or is associated with a limited life expectancy.
- Subject is belonging to a vulnerable population (per investigator's judgment, e.g., subordinate hospital staff or sponsor staff) or subject unable to read or write.
- Currently participating in investigational drug or device trial that has not completed the primary endpoint or that clinically interferes with current trial endpoints. Subject must agree not to participate in any other clinical investigation for a period of three years following the index procedure, including clinical trials of medication and invasive procedures. Questionnaire-based studies, or other studies that are non-invasive and do not require medication are allowed.

Bleeding Risk Exclusion Criteria

- Prior history of hemorrhagic or ischemic stroke, a transient ischemic attack (TIA), or sub-arachnoid hemorrhage.
- History of intracranial neoplasm, arteriovenous malformation, or aneurysm.
- Have received fibrinolytic therapy within 48 hours of entry or randomization into the study.
- Have active pathological bleeding or history of bleeding diathesis.
- Have clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding.
- Have had recent surgery (within 4 weeks of entry into the study) or are scheduled to undergo surgery within the next 2 months.

Prior/Concomitant Therapy Exclusion Criteria

- Have received a loading dose of a thienopyridine (ticlopidine, clopidogrel or prasugrel) or a maintenance dose of prasugrel or Ticlopidine or Ticagrelor within 7 days of entry into the study.
- Are receiving a GPIIb/IIIa inhibitor (eptifibatide, tirofiban, or abciximab).

- Are receiving warfarin or other coumarin derivatives.
- Are receiving or will receive oral anticoagulation or other oral antiplatelet therapy (except aspirin [ASA]) that cannot be safely discontinued within the next 3 months.
- Are receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued or are anticipated to require >2 weeks of daily treatment with NSAID or COX2 inhibitors during the study.
  Concomitant therapy with a strong cytochrome P-4503A inhibitor or inducer.

5.5 Subject Enrolment

2520 subjects will be enrolled in approximately 40 investigational sites in Italy. Each site will enrol a maximum of 252 subjects (10% of the total). All subjects enrolled will be randomized to a downstream administration strategy of P2Y12 receptor blockers (prasugrel or ticagrelor) vs. an upstream administration strategy (ticagrelor only).
The patients of the downstream strategy arm who will undergo PCI, will be randomized in a 1:1 fashion to downstream prasugrel vs. downstream ticagrelor at the time of PCI.
For all the patients undergoing PCI both the use of unfractioned heparin (plus anti GPIIbIIIa based upon clinical judgement) and of bivalirudin will be allowed at the time of PCI; the choice of the anticoagulant at the time of PCI will be based upon clinical judgement.
The first randomization will occur as soon as possible after admission. The second randomization will occur before PCI procedure (only for patients who require PCI, based upon clinical judgement). All randomizations will be blocked by age (>75 years or <75 years). A centralized online system will be used for randomization. Once randomized, the subjects are considered enrolled in the study and analyzed as the intent-to-treat (ITT) population.

5.6 Subject Follow-up Duration

Each subject will be followed with office follow-up visit at 30 days and 1 year. All subjects will be required to the assigned anti-platelet therapy for a minimum of 12 months post procedure. Follow-up visit/contact will be conducted by any qualified Investigator or site coordinator who has been trained on the protocol and Case Report Forms (CRF). Subject follow-up schedule is detailed below:

- 30 ± 7 days (office visit)
- 1 year ± 30 days (office visit)

5.7 Subject Discontinuation

Each enrolled subject will remain in the study until completion of the required follow-up period, however, a subject's participation in any clinical study is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:
- Subject death
- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically indicated
- Subject lost-to follow-up

The reason for subject discontinuation must be documented on the eCRF and source documents.

The Principal Investigators must also report all subject discontinuations to their EC as defined by their Institution's procedure.

5.8 Study Completion

A study completion form must be completed when:
- The subject is considered lost to follow-up
- If the subject misses two consecutive scheduled follow up time points, and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost to follow-up.
- Site personnel shall make all reasonable efforts to locate and communicate with the subject at each contact time point.
- The subject voluntarily withdraws from the study
- The Investigator withdraws the subject from the study
- Upon study completion

5.9 Additional Subject Enrollment

Discontinued subjects will not be replaced.

5.10 Early Termination of the Study

Possible reasons for early study termination include:
-Unanticipated adverse effects of therapies present an unreasonable risk to subjects.
-The Executive Steering Committee makes a decision for the early termination of the study per recommendation

6 *TREATMENT OF SUBJECTS*

6.1 Baseline

Subject in-hospital care will occur in accordance with standard hospital policy for the care of subjects with acute coronary syndromes.

6.1.1 Subject Information

Subject information will include demographics (e.g., age, gender), risk factors (dyslipidemia, hypertension, family history of premature coronary disease, tobacco use and diabetes), and cardiac history (previous MI, intervention history and past/current angina (CCS and Braunwald Classification).

6.2 Laboratory Assessments

The following laboratory assessments are to be performed after admission.
Required as soon as possible after admission:
-Complete Blood Cell Count (CBC)
-Creatinine, BUN, blood chemistry
-Pregnancy test (if applicable)

-Troponin (I or T) or CPK-MB
-Electrocardiogram (ECG)

Strongly recommended after admission:
Lipid profile (total cholesterol, LDL, HDL, triglycerides)

6.3 Treatment

6.3.1 Invasive Treatment

Despite all enrolled subjects must have an initial indication to coronary angiography, subjects may or may not undergo coronary angiography and possible PCI, based upon clinician's judgement. Coronary angiography and PCI will occur in accordance with standard hospital policy for the care of subjects with acute coronary syndromes. The patients of the downstream strategy arm who will undergo PCI will be randomized in a 1:1 fashion to downstream prasugrel vs. downstream ticagrelor at the time of PCI. For all the patients undergoing PCI, both the use of unfractioned heparin (plus anti GPIIbIIIa based upon clinical judgement) and of bivalirudin will be allowed at the time of PCI; the choice of the anticoagulant at the time of PCI will be based upon clinical judgement. Randomization at the time of PCI will occur after clinician's decision to perform PCI and before PCI is performed. Deferred PCI (not during diagnostic coronary angiography) is allowed.

6.3.2 Treatment of Subjects

1. At the time of diagnosis:

- Anticoagulants: All enrolled subjects should receive an anticoagulant agent as soon as possible after subject is diagnosed with an ACS. The required anticoagulant agents are: unfractioned heparin OR fondaparinux OR enoxaparin OR bivalirudin (dosing according to latest ESC guidelines).

- Antiplatelets:

- **Patients randomized to upstream strategy:** subjects randomized to the upstream strategy arm must receive a loading dose of aspirin and ticagrelor at admission as soon as possible after subject is diagnosed with a NSTEACS. The loading dose of aspirin may be omitted for those subjects on chronic therapy for ≥7 days prior to the index procedure, however, it is recommended that the loading dose be re-administered based on clinician's judgement. The following loading doses are required: Aspirin: 150-300 mg, Ticagrelor 180 mg.

- **Patients randomized to downstream strategy:** Subjects randomized to downstream strategy arm must receive a loading dose of aspirin as soon as possible after subject is diagnosed with a NSTEACS. The loading dose may be omitted of aspirin for those subjects on chronic therapy for ≥ 7 days prior to the index procedure, however, it is recommended that the loading dose be readministered based on clinician's judgement. The following loading dose is required: Aspirin: 150-300 mg. Administration of clopidogrel is allowed for patients already receiving chronic therapy with clopidogrel, but clopidogrel loading doses should be omitted. Clopidogrel should not be administered to patients who are not already receiving chronic therapy with clopidogrel.

2. Pre-procedure:

- Anticoagulants:

- The pre-procedure anticoagulation regimen will be based upon clinician's judgement (open label). Acceptable anticoagulant medications in this case are: UFH, Enoxaparin, Fondaparinux, Bivalirudin (preferred anticoagulant agents and dosage according to latest guidelines on UA/NSTEMI).

- Antiplatelets:

- **Patients randomized to upstream strategy:** All subjects randomized to the upstream strategy arm will be maintained at a minimum of 90 mg of ticagrelor b.i.d. and a minimum of 75 mg of aspirin, until coronary angiography is performed. If medically indicated, the protocol mandated medication may be interrupted or altered. The start of anti-platelet medication, any changes to, and termination of, will be documented in the eCRF.

- **Patients randomized to downstream strategy:** All subjects randomized to the downstream strategy arm will be maintained at a minimum of 75 mg of aspirin until coronary angiography is performed. Subjects already receiving chronic therapy with clopidogrel may be maintained at a minimum of 75 mg of clopidogrel until coronary angiography is performed. If medically indicated, the protocol mandated medication may be interrupted or altered. The start of anti-platelet medication, any changes to, and termination of, will be documented in the eCRF.

3. Peri- and post-procedure:

- Anticoagulants:

For all the patients undergoing PCI, the choice of the anticoagulant at the time of PCI will be based upon clinical judgement.

- Antiplatelets:

- **Patients randomized to upstream strategy:** All subjects randomized to the upstream strategy arm will be maintained at a minimum of 90 mg of ticagrelor b.i.d. and a minimum of 75 mg of aspirin, for at least 12 months. If medically indicated, the protocol mandated medication may be interrupted or altered (e.g. subject has an indication to CABG; bleeding). The start of anti-platelet medication, any changes to, and termination of, will be documented in the eCRF. If the subject develops hypersensitivity or intolerance to ticagrelor, clopidogrel may be used as a substitute at a dose in accordance with standard hospital practice (to be documented in the eCRF).

- **Patients randomized to downstream strategy:** If subject has an indication to PCI, subject will be randomized in a 1:1 fashion to downstream prasugrel vs. downstream ticagrelor (randomization will occur after clinician's decision to perform PCI and before PCI is performed). At the time of PCI, the following loading doses are required (according to randomization): Prasugrel 60 mg*, ticagrelor 180 mg.All subjects of the

downstream strategy arm who undergo PCI will be then maintained at a minimum of 75 mg of aspirin for at least 12 months plus 10 mg of prasugrel* daily for at least 12 months OR ticagrelor 90 mg b.i.d. for at least 12 months according to randomization. If medically indicated, the protocol mandated medication may be interrupted or altered (e.g. subject has an indication to CABG; bleeding). The start of anti-platelet medication, any changes to, and termination of, will be documented in the eCRF. If the subject develops hypersensitivity or intolerance to ticagrelor or to prasugrel, clopidogrel may be used as a substitute at a dose in accordance with standard hospital practice (to be documented in the eCRF).

***If subject is >75 years old or with a body weight < 60 kg, loading dose of prasugrel should be 60 mg and daily dose of prasugrel should be 5 mg.**

4. Patients with indication to Medical treatment/Conservative strategy:

- **Anticoagulants:** If the patient has an indication to medical treatment based on coronary angiography OR if the patient has an initial invasive indication but coronary angiography is not performed (e.g. switch from invasive to conservative strategy is chosen), anticoagulation can be continued based upon clinician's judgement (open label) and according to latest guidelines on UA/NSTEMI).

- **Antiplatelets:** If the patient has an indication to medical treatment based on coronary angiography OR if the patient has an initial invasive indication but coronary angiography is not performed (e.g. switch from invasive to conservative strategy is chosen), subject should continue on ticagrelor(upstream arm) or start ticagrelor before discharge (downstream arm).

In the case of medical treatment and in the case of conservative strategy after angiography, the patient will be not part of the per-treatment-evaluable population but will be part of the intention-to-treat population.

5. Patients with indication to CABG

- **Anticoagulants:** Anticoagulant medications should be continued based on clinician's judgement, local standard of care and latest guidelines on UA/NSTEMI. If PCI is performed and subject has still an indication to CABG, administration of per protocol mandated anticoagulation PCI should be based on clinician's judgement and on local standard of care (details to be documented in the eCRF).

- Antiplatelets: If the patient has an indication to CABG, antiplatelet therapy should be managed according to latest ESC recommendations (including: Sousa-Uva M et al, Expert position paper on the management of antiplatelet therapy in patients undergoing coronary artery bypass graft surgery. European Heart Journal (2014) 35, 1510–1514).
Aspirin administration should be maintained before CABG. If aspirin is discontinued at the time of CABG, aspirin should be restarted within the first 24 h and preferably within 6 h after CABG.
Upstream strategy arm: if ticagrelor is discontinued prior to CABG, resumption of a P2Y12 should be considered as soon as bleeding is controlled.
Downstream strategy arm: a P2Y12 inhibitor should be started before discharge. If CABG is not performed during the same hospital admission, the P2Y12 may be discontinued before CABG, and resumption of a P2Y12 should be considered as soon as bleeding is controlled.

Patients with an indication to CABG after angiography will be not part of the per-treatment-evaluable population but will be part of the intention-to-treat population.

6.3.3 Concomitant Medications

Glycoprotein IIb/IIIa receptor inhibitors
The use of GPIIb/IIIa inhibitors prior to randomization is not permitted and is an exclusion criterion. Planned or unplanned use of a GPIIb/IIIa inhibitor according to local policies (while waiting for PCI or during PCI) is allowed.

Other medications
As noted in the ACC/AHA guidelines, lipid management is strongly recommended. All chronic concomitant cardiac medications must be properly recorded on the CRF.

6.3.4 Treatment Compliance

The loading doses of P2Y12 receptor blockers will be administered by clinic personnel, thus ensuring treatment compliance. Subject compliance with maintenance therapy with P2Y12 receptor blockers will be assessed at day 30 and at 1-year follow-up. Compliance will be assessed by drug count, and is defined as taking from 90% to 110% of the prescribed antiplatelet for that time period. Subjects will not be discontinued from the study for noncompliance with maintenance therapy, as the primary analysis is designated as ITT.

6.3.5 Temporary Discontinuation of Mandated P2Y12

There may be situations in which mandated P2Y12 receptor blocker is temporarily discontinued during the maintenance phase, such as for adverse events or elective surgical procedures. Administration of P2Y12 receptor blocker may be temporarily discontinued for ≤7 days without contacting the PI or designee. If the P2Y12 receptor blocker was discontinued for a procedure, it should be restarted when the investigator decides it is safe to do so. For periods of discontinuation that would be expected to last >7 days, the investigator could contact the PI or designee to discuss whether the subject should restart the P2Y12 receptor blocker.
It is important to note that the P2Y12 receptor blocker should not be discontinued if the subject experiences one of the following efficacy endpoints of the study: MI, UR, GPIIb/IIIa bailout, or stent thrombosis.
If an antiplatet effect is not desired, treatment with the P2Y12 receptor blocker should be discontinued at least 7 days prior to surgery.

6.3.6 Temporary Discontinuation Due to a Bleeding Event

The investigator can temporarily discontinue the P2Y12 receptor blocker if a subject experiences a bleeding event. The bleeding event, the treatment of the event, and any concomitant therapy provided to the subject because of the bleeding event should be documented in CRFs. The P2Y12 receptor blocker may be restarted once the event has abated and when, in the investigator's opinion, it is safe to do so. The dates that the P2Y12 receptor blocker was discontinued and then restarted should be documented.

6.3.7 Permanent Discontinuation of the P2Y12 receptor blocker

It may be necessary for a subject to permanently discontinue the P2Y12 receptor blocker. In keeping with the ITT analysis, the subject will be observed for endpoints and adverse events

until the completion of the study. Investigators should contact the PI or designee prior to permanent P2Y12 receptor blocker discontinuation. When the decision to stop the P2Y12 receptor blocker permanently is made after consultation with the PI or designee, the reason for permanent discontinuation of the P2Y12 receptor blocker will be recorded. The subject will continue to be observed for endpoints and adverse events and should continue to have scheduled follow-up visits. Electrocardiograms and local laboratory tests associated with evaluation of endpoints or adverse events in these subjects may be performed as deemed appropriate by the investigator. If the P2Y12 receptor blocker is discontinued, the decision to start open-label thienopyridine is left to the investigator's discretion. If discontinuation is due to an adverse event, the event is to be followed and documented in the CRF. Some possible reasons that may lead to permanent early P2Y12 receptor blocker discontinuation include:

• The subject was inadvertently randomized and, in the opinion of the investigator after consultation with the PI or designee, continuation of the P2Y12 receptor blocker is not advisable.

• In the opinion of the investigator, a bleeding episode or any other adverse event or a significant change in a laboratory value warrants permanent discontinuation of the subject's prasugrel therapy. Investigators are advised to contact the PI or designee prior to making such a decision.

• The subject requests to stop prasugrel permanently.

• The subject has a stroke or TIA during the study.

7 EVALUATION OF SAFETY AND EFFECTIVENESS

Safety and effectiveness will be evaluated at the time points (listed below) throughout the study.

- In-hospital (from time of randomization and until discharge)
- 30 ± 7 days (office visit)
- 1 year ± 30 days (office visit)

If a subject has a clinic visit outside of the protocol required follow-up visit windows, additional information shall be obtained from the subject's source documents. All efforts must be made to obtain all follow-up information on subjects who underwent procedures or were treated for adverse events in a non-study-related hospital(s).

7.1 Tests and Measurements at Each Follow-up

Laboratory test, additional tests and data will be obtained periodically on all subjects as follows:

- **Baseline (as soon as possible after admission):**
  - 12 lead ECG
  - ACS type (UA or NSTEMI)
  - Cardiac markers: Troponin (I or T) or CK and CK-MB
    Serial measurements of cardiac markers (Troponin (I or T) or CK and CK-MB) must be performed until a decline is noted in minimum of two samples 8 hours apart in total.
  - Complete Blood Cell Count (CBC)
  - Creatinine, BUN, blood chemistry
  - Pregnancy test (if applicable)

- **Before discharge**
  - Adverse events (with related laboratory tests results, ECGs, details of the index procedure and any subsequent repeat coronary angiography and results of such, if applicable).
  - Cardiac markers: Troponin (I or T) or CK and CK-MB.
    Serial measurements of cardiac markers (Troponin (I or T) or CK and CK-MB) must be performed until a decline is noted in minimum of two samples 8 hours apart in total.

- **30 ± 7 days follow-up (office visit)**
  - Adverse events (with related laboratory tests results, ECGs, details of any subsequent repeat coronary angiography and results of such, if applicable).
  - Compliance to protocol required anti-platelet medications
  - Use and changes in chronic anti-platelet medications

- **12 months ± 30 days follow-up (office visit)**
  - Adverse events (with related laboratory tests results, ECGs, details of any subsequent repeat coronary angiography and results of such, if applicable).
  - Compliance to protocol required anti-platelet medications
  - Use and changes in chronic anti-platelet medications

Additional (Unscheduled) Follow-up visits
- Additional subject visits may occur as clinically warranted. The following information will be collected at such visits:
- Data regarding adverse events with related laboratory tests results, ECG, details of any subsequent repeat coronary angiography and results of such, if applicable.
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG)
- Compliance to protocol required anti-platelet medications.
- Use and changes in chronic anti-platelet medications.

7.2 Adverse Events

7.2.1 Adverse Event Definition

7.2.1.1 Adverse Event and Adverse Reactions

An adverse event is any untoward medical occurrence in a subject administered a study treatment and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational treatment whether or not related to the study product. Elective procedures for a pre-existing condition are not considered AEs. Abnormal laboratory values will not be considered AEs unless: 1) the PI determined that the value is clinically significant, 2) the abnormal lab value required intervention, or 3) the abnormal lab value required subject termination from the study.An adverse reaction (AR)is any untoward and unintended responses to a drug being tested, regardless of the dose administered.

7.2.1.2 Serious Adverse Event and Serious Adverse Reaction

If the adverse event/reaction meets any of the criteria below, it is regarded as serious adverse event.

- Results in death

- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Involves a congenital anomaly or birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

7.2.1.3Unexpected adverse reaction/event

An unexpected adverse reaction/event is an adverse reaction/event if the nature or severity is not consistent with the applicable product reference safety information.

7.2.1.4 Adverse Event Associated With the Use of the Drugs

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below.

Not Related: An adverse event that is not related to the use of the drug.

Doubtful: An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible: An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s),concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable: An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely: An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

7.2.1.5 Severity Criteria

An assessment of severity grade will be made using the NCI-CTCAE (version 4.03). The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

7.2.2 Adverse Event Reporting

7.2.2.1 Adverse Event Monitoring

The Investigator will monitor the occurrence of adverse events for each subject, during the course of the study. All adverse events (AEs) reported by the subject, observed by the Investigator, or documented in medical records will be recorded on the adverse event CRF, whether believed by the Investigator to be related or unrelated to the investigational treatment. Starting with the study enrolment, any new event/experience that was not present at baseline, or worsening of an event present at baseline, is considered an adverse event. All adverse events will be monitored until they are adequately resolved or stabilized. Serious adverse events and unanticipated adverse effects will be collected and monitored throughout the entire course of the study (up to 12 months follow-up). Unchanged, chronic conditions are not adverse events and should not be recorded on the adverse event CRF.

7.2.2.2 Serious Adverse Event reporting to EC

Each adverse event or complication meeting the definition for serious adverse event will be reported immediately by the Principal Investigator or designee. A CIOMS form(appendix II) will be completed and the event will be reported to the sponsor by the site immediately and within 24 hours of the Investigators' knowledge of the event to the following e-mail address which is monitored 7/7 24/24:

eudra.vigilance@sanita.padova.it

In case of need please refer to the Sponsor's RPPV(Responsible Person for PharmacoVigilance) contacts in the contact list.

When completing the form, the investigator will be asked to define the causality and the severity of the AE. The form should be completed in English.

The Investigator will further report the event to the EC according to the institution's EC reporting requirements. The subject's course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

7.2.2.3 Reporting to Regulatory Authorities

In the case of occurrence of a SAE, the Principal Investigator or designee must immediately enter the information related to the SAE in the appropriate form (CIOMS form) and send a notification to the sponsor immediately (as soon as possible and no later than 24 hours after the investigator first becoming aware of the event) as detailed above. In addition, every effort should be made tofurther document any SAE that is fatal or life threatening within a week (7 calendar days) of the initial notification. Any SAE brought to the attention of the investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team. Refer to the "Contact List" provided on page 2.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor must report these events to the appropriate Independent Ethics Committee(IEC) that approved the protocol unless otherwise required and documented by the IEC.

7.2.2.4 Suspected Unexpected Serious Adverse Reactions

The sponsor will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to EudraVigilance in accordance with current regulations i.e. within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported by the mechanism described above within 15 days.

7.2.2.5 DSUR

The sponsor will include details of all SAEs, SARs (including SUSARs) in a DSUR (or Annual Safety Report) produced annually from the date of the first Clinical Trial Authorisation received for the trial to the submission of the End of Trial Declaration. The sponsor will be responsible for forwarding this report to the Competent Authority and involved Ethics Committees following the time frame established in the legislation currently in force.

The Competent Authority and Ethics Committees will be notified immediately if a significant safety issue is identified during the course of the trial.

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators of all participating sites. A copy of any such correspondence should be filed in the ISF.

7.3 Safety Monitoring by Data Safety Monitoring Board (DSMB)

All adverse events will be reported to the DSMB and reviewed on an on-going basis throughout the subject enrollment and follow-up period as specified in the charter to ensure the safety of subjects enrolled in this study. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend that the Executive Steering Committee modify or discontinue the study. All final decisions, regarding study modifications, however, rest with the Executive Steering Committee.

8*STATISTICAL DESIGN AND ANALYSIS*

8. 1 Statistical overview

DUBIUS is a prospective, double randomized (1:1 upstream vs. downstream administration of P2Y12 receptor blockers; 1:1 downstream prasugrel vs. downstream ticagrelor) active control, parallel arms, multi-center adaptive clinical investigation in a population an all-comers population of NSTEACS patients with an initial invasive indication.

A total of 2520 patients will be randomized in approximately 40 centers in Italy.

The study is powered based on the primary endpoint of incidence at 30 days of NACE (Net Adverse Cardiac Events), defined as a composite of: death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), non fatal MI, or non fatal stroke, BARC type 3, 4 and 5 bleeding.

The hypotheses under study are hierarchically organized as follows:

Primary powered hypotheses

1. Superiority of a downstream administration strategy for P2Y12 receptor blockers (prasugrel or ticagrelor) over the upstream administration strategy (ticagrelor only)
   H0 : Endpoint Downstream – Endpoint Upstream = 0
   H1 : Endpoint Downstream - Endpoint Upstream ≠ 0

2. Non inferiority of Prasugrel vs Ticagrelor in the PCI group of the downstream strategy arm (where $\delta > 0.01$)
   H0 : Endpoint Prasugrel – Endpoint Ticagrerol $\geq \delta$
   H1 : Endpoint Prasugrel - Endpoint Ticagrerol$< \delta$

Secondary unpowered non-randomized exploratory hypothesis

3. Superiority of Bivalirudin over UFH (plus provisional antiGPIIb-IIIa based upon clinical judgement) in the PCI group
   H0 : Endpoint Bivalirudin – Endpoint UFH = 0
   H1 : Endpoint Bivalirudin - Endpoint UFH < 0

8.2 Analysis population

For the upstream vs. downstream analysis, the intent-to-treat population (ITT) will consist of all subjects randomized in each of the two randomization groups, regardless of the treatment actually received. Subjects will be analysed in the treatment group to which they were randomized. Deregistered subjects will not be included in the Intent-to-Treat Population.

In particular, the following will hold:

1. In the upstream vs. downstream group, all randomized patients with NSTEACS and an initial invasive indication.

For the non-inferiority evaluation (NI) of Ticagrelor vs. Prasugrel group, a per-protocol (PP) population will be used for patients following the downstream strategy after PCI, being more conservative for NI evalutations.

As a secondary analysis, in the Bivalirudin vs. UFH group, all patients undergoing PCI.

8.3 Per-treatment evaluable population

The per-treatment evaluable population will consist of subjects who have been randomized in their corresponding randomization group/arm who have no procedural protocol deviations which would be considered major, other than those relating to treatment group (randomized versus actually received).
Analyses based on the per-treatment evaluable population will be “as treated”. Subjects will be included in the treatment group corresponding to the study treatment/strategy actually received/followed. Deregistered subjects will not be included in the Per-Treatment Evaluable Population.

8.4 Sample size calculation and assumptions

The sample size calculation is based on the primary endpoint at 30 days of incidence of NACE (Net Adverse Cardiac Events), defined as a composite of: death from vascular causes (death from cardiovascular causes or cerebrovascular causes and any death without another known cause), non fatal MI, or non fatal stroke, BARC type 3, 4 and 5 bleeding. Incidence data for sample size calculation were extrapolated from the following studies: N Engl J Med. 2013 Sep 12;369(11):999-1010; N Engl J Med. 2009 Sep 10;361(11):1045-57; N Engl J Med. 2007 Nov 15;357(20):2001-15.The sample size has been computed using an adaptive approach in three study stages in order to compensate for discrepancies between expected and observed incidence of the primary endpoint. After each stage a sample size reassessment is performed.

This study has been first targeted for the first group of randomization, aimed at showing superiority of a downstream administration strategy for P2Y12 receptor blockers (prasugrel or ticagrelor) over the upstream administration strategy (ticagrelor only).

The following assumptions were considered:

- Two-sided superiority Chi-square test without continuity correction for rejecting the hypothesis H0: $\pi_2 - \pi_1 = 0$
- $\alpha = 0.05$ for hierarchical comparison
- Power 0.80

- The critical values and the test characteristics of the group sequential test design were calculated for the O'Brien and Fleming design.
- An incidence rate of π 1 = 0.08 in downstream arm and π 2 = 0.115 in upstream arm (odds ratio of 1.494)
- An allocation rate of 1:1

Based on the above assumptions, this yields 1146 + 1146 = 2292 observations.
For comparison, the sample size in a fixed sample size design is $n_1 = 1126.4$, $n_2 = 1126.4$.
Thus, the maximum sample size in the group sequential test design is 1.017 times the sample size in a fixed sample size design.
The expected (average) total sample size under the alternative hypothesis is 1928.9, under a value midway between H_0 and H_1 it is 2214.6, and under the null hypothesis it is 2280.7.

Table 1

Information rate	bounds accept H_0	bounds reject H_0	sign.level one-sided	α spent	β spent	power achieved	stage n_1	sizes n_2
0.333	-	3.471	0.0003	0.0005	-	0.0329	382.0	382.0
0.667	-	2.454	0.0071	0.0143	-	0.4424	382.0	382.0
1.0	2.004	2.004	0.0225	0.0500	-	0.8000	382.0	382.0

Assuming a drop-out rate of about 10%, the total sample size (rounded up) is of 2520 patients (1260 upstream + 1260 downstream).

As a second target, non inferiority of Prasugrel vs Ticagrelor in the PCI group of the downstream strategy. Analyses will be performed at the study completion, so no ad-interim evaluations are assumed for this study group.
Assuming that at least 80% of the patients will have an indication for PCI in the downstream group, based on the above calculations, a sample of about 1000 should be available for randomization in this group.

The following assumptions were considered:

- Two-sided non-inferiority test for rejecting the hypothesis H_0: $\pi_2 - \pi_1 > 0.01$ (i.e.: Prasugrel and Ticagrelor will not differ for more than 1% in terms of NACE)
- $\alpha = 0.025$ to keep overall confidence bounds in non-inferiority testing at 0.95 level [1]
- Overall sample size of 1000 patients (500 Prasugrel + 500 Ticagrelor)
- The critical values and the test characteristics of the design were calculated using the Farrington and Manning (Statistics in Medicine, 1990, 1447-1454), maximum likelihood method
- An incidence rate of $\pi 1 = 0.05$ in Ticagrelor and $\pi 2 = 0.085$ in Prasugrel (odds ratio of 1.765)
- An allocation rate of 1:1

Based on the above assumptions, the power (1 - β) is 0.805.

As a third unpowered non-randomized target, superiority of a Bivalirudin over UFH (plus provisional antiGPIIb-IIIa based upon clinical judgement) in the overall PCI group (without distinguishing between upstream and downstream randomized patients) will be studied.

The power calculations were performed using ADDPLAN MC 6.0.8.

8.5 Statistical Analyses

8.5.1 Primary Endpoint Analysis

The primary endpoint will be analysed for the Intent-to-Treat (ITT) population for group 1 (downstream vs. upstream) in terms of NACE.
After having reached the sample size foreseen for each of the three stages (1426 per stage), an evaluation using a 95% repeated confidence interval will be used. If the value 0 will be contained in the interval, a sample size reassessment will be performed based on actually observed incidence rates of NACE. Otherwise, data will be passed to the Executive Steering Committee to decide if continue in randomizing patients for the other two analyses or to stop the study.

At the study completion, if no early stops will be decided, the primary endpoint will be analysed for the Intent-to-Treat (ITT) population for group 2 (Ticagrelor vs. Prasugrel) and group 3 (Bivalirudin vs. UFH) in terms of NACE.

In addition, as a secondary analysis, the primary endpoints will be analysed on the PTE population.

8.5.2 Secondary Endpoint Analyses

Analyses of other secondary endpoints will be descriptive in nature and will be performed on both the ITT and PTE populations.
For binary variables such as NACE at 12 months, and clinical procedure success, counts, percentages, and exact 95% confidence intervals using Clopper-Pearson's method will be calculated.
For continuous variables such as diameter stenosis, means, standard deviations, and 95% confidence intervals for the mean using the Bootstrap (1000 replicates) approach.

8.5.3 Additional Analyses

For time-to-event variables, survival curves will be constructed using Kaplan-Meier estimates, and log rank test results will be displayed for descriptive purposes only.

Demographics, procedural, imaging, laboratory, exercise testing, quality of life, diary related data that are not part of the list of endpoints will be displayed for descriptive purposes only.

Unless specified, analyses will be performed with pooled data across all study sites.

8.6 Handling of Multiplicity Issues

Since the study is a multi-armed hierarchical double randomized design, multiplicity will not occur provided that hypotheses will be tested in the following order:

1. An $\alpha=0.05$ has been given for testing superiority of a downstream administration strategy for P2Y12 receptor blockers (prasugrel or ticagrelor) over the upstream administration strategy (ticagrelor only)

2. An α=0.025 (one-sided) has been given for testing non inferiority of Prasugrel vs Ticagrelor in the PCI group of the downstream strategy arm (where δ > 0.01)

8.7 Randomization

All randomizations will be blocked for age (age ≤ 75 or age >75).

8.8 Labeling Claim

Not applicable.

8.9 Procedures for Accounting for Missing, Unused or Spurious Data

All analyses will be based on available data with missing data excluded. Any unused or spurious data will be noted as appropriate in the final report. Analyses will be compared with a multiple imputation approach to detect potential important influences in the study design due to missing values.

8.10 Deviations from the original statistical plan

Any major changes to the statistical plan described above will be documented in an amendment to the clinical investigation plan. Less significant changes to the planned analyses will be documented in the final report.

9 *DIRECT ACCESS TO SOURCE DATA/DOCUMENTS*

The Investigator and the associated institution will permit direct access to source data/documents for study-related monitoring, audits, and EC review and regulatory inspections. Subjects providing informed consent agree to allow Principal Investigator (or designees) access and copying rights to pertinent information in their medical records concerning their participation in this study. The Investigator will obtain, as part of the informed consent, permission for study monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this study. This information may be shared with regulatory agencies; however, the Sponsor undertakes to make every effort to protect the subject's privacy by eliminating any information permitting identification of the subject.

10 *QUALITY CONTROL AND QUALITY ASSURANCE*

10.1 Selection of Clinical Sites and Investigators

The Coordinating Investigator will select Investigators who are qualified by training and experience and are legally entitled to perform clinical research and to participate in the study. Sites will be selected based upon review of a recent site assessment and the qualifications of the

Principal Investigator at the site. All Investigators must be trained to the protocol and study procedures prior to enrolling subjects.

10.2 Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the protocol in full compliance with all established procedures of the EC. The Investigator will not deviate from the protocol for any reason except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject. All deviations must be reported to the Coordinating Investigator (or designees). In subject specific deviations from the protocol, a protocol deviation CRF will be completed. The occurrence of protocol deviations will be monitored by the Coordinating Investigator (or designees). Investigators will inform their EC of all protocol deviations in accordance with their specific EC reporting policies and procedures.

10.3 Monitoring

Coordinating Investigator (or designees) will monitor the study over its duration according to the pre-specified monitoring plan. The study monitor will visit each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the protocol. The study monitor may inspect all documents and required records that are maintained by the Investigator/site, including medical records (office, clinic or hospital) for the subjects in this study. The Investigator/site will permit access to such records. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information. A monitoring visit sign-in log will be maintained at the site. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the study monitor with a suitable working environment for review of study-related documents.

10.4 Regulatory Agency Inspection

In the event that an Investigator is contacted by a Regulatory Agency in relation to this study, the Investigator will notify the Coordinating Investigator (or designees) immediately. The Investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study. The Sponsor will provide any needed assistance in response to regulatory inspections.

11 *DATA HANDLING AND RECORD KEEPING*

For the duration of the study, the Investigator will maintain complete and accurate documentation including but not limited to medical records, study progress records, laboratory reports, case report forms, signed informed consent forms, device accountability records, and correspondence with the EC and Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the study.

11.1 Source Documentation

Source documents are defined as original documents, data and records. Regulations require that the Investigator maintain source documents in the subject's medical records, which confirm the data entered on the case report forms.

11.2 Electronic Case Report Form (eCRF) Completion

Data collection based on source-documented hospital and/or clinic chart reviews will be performed accurately on the eCRFs by site personnel trained to the protocol and eCRF completion. Coordinating Investigator (or designees) will provide monitoring of eCRF completion.

11.3 Record Retention

The Investigator/Site will maintain all records pertaining to this study for three years following study completion or as otherwise instructed by the Coordinating Investigator (or designees) or per local regulations if longer.

12 *ETHICAL CONSIDERATION*

All subjects must provide written informed consent in accordance with the site's EC, using an EC-approved informed consent form. Study-specific procedures must not be performed until a signed informed consent has been obtained. The Investigator/designee, who have been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subject. If the subject agrees to participate, the informed consent form must be signed and personally dated by the subject or legally authorized representative. The Investigator/designee must also sign the informed consent form, prior to subject enrollment. Any additional persons required by the site's EC to sign the informed consent form must also comply. All subjects are to be fully informed and study conduct must be in accordance to the World
Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects..

13 *PUBLICATION POLICY*

At the conclusion of the study, a multicenter abstract reporting the primary results will be prepared by the Coordinating Investigator (in collaboration with the Executive Steering Committee and Principal Investigators from high enrolling sites) and presented at an annual scientific meeting. A multicenter publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the study is not allowed until both the preparation and publication of the multicenter results. Following analysis and presentation of the primary endpoint results, active participation of all Executive Steering Committee members and Investigators from high enrolling sites will be enthusiastically solicited for data analysis and abstract and manuscript preparation.

Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the study requires approval by the Coordinating Investigator after review by the Executive Steering Committee.

APPENDIX I: DEFINITIONS

- **ADVERSE EVENT (AE)**

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a study product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign
(including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the study product

- **BARC DEFINITION FOR BLEEDING:**

This study pre-specified endpoints will take into account type 2, 3, 4 and 5 BARC bleeding.

Type 2: Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:
1) requiring nonsurgical, medical intervention by a healthcare professional,
2) leading to hospitalization or increased level of care, or
3) prompting evaluation

Type 3

Type 3a

Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
Any transfusion with overt bleeding

Type 3b

Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 h
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period
Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

- **CORONARY ARTERY BYPASS GRAFT SURGERY (CABG)**

Emergent CABG is defined as immediate transfer from the cath lab to the operative room for emergent bypass surgery during the initial treatment phase.

CABG during follow-up is only considered as a clinical-indicated Target Lesion Revascularization if coronary angiography indicates a diameter of stenosis greater than 50% of the stented coronary segment associated with one of the following conditions:
- A positive history of recurrent angina pectoris presumably related to the target vessel.
- Objective signs of ischemia (exercise test or equivalent) presumably related to the target vessel,
- Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve).

- **DEATH (Per protocol)**

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

Vascular death:

Death from vascular causes includes cardiovascular deaths, cerebrovascular deaths, and any other death for which there was no clearly documented nonvascular cause.

Non-vascular death:

Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

- **MAJOR PROTOCOL DEVIATIONS**

Major protocol deviations include, but are not limited to, enrollment of a subject:
-whose informed consent was not properly obtained
-in whom antiplatelet medication was not per protocol.
-in whom anticoagulant medication was not per protocol.

- **MYOCARDIAL INFARCTION:**

MI will be adjudicated based on the third universal definition of myocardial infarction (*Thygesen et al*, 2012):

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

- **PERCUTANEOUS CORONARY INTERVENTION (PCI)**

Refers to all interventional cardiology methods for treatment of coronary artery disease.

- **PRINCIPAL INVESTIGATOR**

A physician responsible for conducting the clinical study at each investigational site.

- **COORDINATING INVESTIGATOR**

A physician-specialist, related to the study, who is responsible for the overall conduct of the study at all sites and compliance with protocol and relevant regulations.

- **STENT THROMBOSIS**

Stent thrombosis is defined and discussed by the Academic Research Consortium as follows:

Timing

- Acute scaffold/stent thrombosis* 0-24 hours post stent implantation
- Subacute scaffold/stent thrombosis* > 24 hours-30 days post stent implantation
- Late scaffold/stent thrombosis† > 30 days-1 year post stent implantation
- Very late scaffold/stent thrombosis† > 1 year post stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early scaffold/stent thrombosis (0-30 days) – this definition is currently used in the community.

Stent Thrombosis Categories: a) Definite b) Probable, and c) Possible

a) Definite stent thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

Angiographic confirmation of stent thrombosis*

The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
- Nonocclusive thrombus: intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
- Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

*The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
†Intracoronary thrombus.

Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via

examination of tissue retrieved following thrombectomy.

b) Probable stent thrombosis
Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days‡
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

‡ For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

- **REVASCULARIZATION (Per ARC Circulation 2007; 115: 2344-2351)**

Ischemia-Driven Target Lesion Failure (IDTLF)
IDTLF is defined as the composite endpoint of
- cardiac death,
- myocardial infarction (Q wave and Non-Q wave),
- ischemia-driven target lesion revascularization by CABG or PCI.

Ischemia-Driven Target Lesion Revascularization (IDTLR)
IDTLR is defined as revascularization at the target lesion associated with any of the following:
- positive functional ischemia study
- ischemic symptoms and angiographic minimal lumen diameter stenosis > 50% by core laboratory quantitative coronary angiography (QCA)
- revascularization of a target lesion with diameter stenosis > 70% by core laboratory QCA without either ischemic symptoms or a positive functional study

Ischemia-Driven Target Vessel Failure (IDTVF)
IDTVF is defined as the composite endpoint of
- cardiac death,
- myocardial infarction (Q wave and Non-Q wave),
- ischemia-driven target lesion revascularization by CABG or PCI,
- ischemia-driven target vessel revascularization by CABG or PCI.

Ischemia-Driven Target Vessel Revascularization (IDTVR)
IDTVR is defined as revascularization at the target vessel associated with any of the following:
- positive functional ischemia study
- ischemic symptoms and angiographic minimal lumen diameter stenosis > 50% by core laboratory quantitative coronary angiography (QCA)
- revascularization of a target vessel with diameter stenosis > 70% by core laboratory QCA without either ischemic symptoms or a positive functional study

Target Vessel Failure (TVF)
TVF is defined as the composite endpoint of
- cardiac death,
- target-vessel myocardial infarction (Q wave or non-Q wave), and
- target vessel revascularization (main branch or side branch)

Target Lesion Revascularization (TLR)

TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLR should be classified prospectively as clinically indicated (CI) or not clinically indicated by the Investigator prior to repeat angiography. An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where Investigator reports are not in agreement. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

Target Vessel Revascularization (TVR)
TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel (main branch or side branch). The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches, and the target lesion itself

Non Target LesionRevascularization (Non-TLR)
Any revascularization in the target vessel for a lesion other than the target lesion isconsidered a non-TLR.

Non Target Vessel Revascularization (Non-TVR)
Any revascularization in a vessel other than the target vessel is considered a non-TVR. A revascularization is considered clinically driven if angiography at follow-up shows a percent diameter stenosis ≥ 50% (Angiographic Core Laboratory QCA assessment) and if one of the following occurs:
(1) A positive history of recurrent angina pectoris, presumably related to the target vessel;
(2) Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel;
(3) Abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve, fractional flow reserve);
(4) A TLR or TVR with a diameter stenosis ≥ 70% even in the absence of the abovementioned ischemic signs or symptoms.

TIMI Bleeding
- Non-CABG Related Bleeding:
    1. Major
        Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
        Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit
        Fatal bleeding (bleeding that directly results in death within 7 d)
    2. Minor
        Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit
        No observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit
        Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
        Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
        Leading to or prolonging hospitalization

Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

3. Minimal

Any overt bleeding event that does not meet the criteria above

- Bleeding in the Setting of CABG:

  Any clinically overt sign of haemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in haematocrit

  Bleeding in the Setting of CABG:

  Fatal bleeding (bleeding that directly results in death)

  Perioperative intracranial bleeding

  Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding

  Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.

  Chest tube output >2 L within a 24-h period

APPENDIX II: CIOMS FORM

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	