GLOBAL LEADERS (ECRI-1)

COMPARATIVE EFFECTIVENESS OF 1 MONTH OF TICAGRELOR PLUS ASPIRIN FOLLOWED BY TICAGRELOR MONOTHERAPY VERSUS A CURRENT-DAY INTENSIVE DUAL ANTIPLATELET THERAPY IN ALL-COMERS PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION WITH BIVALIRUDIN AND BIOMATRIX FAMILY DRUG-ELUTING STENT USE.

PROTOCOL No. ECRI-12-001, 02EU11

Status: Final Version 1.4 (Date: 10 September 2013)

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Sponsor:

European Cardiovascular Research Institute (ECRI)

Westblaak 92

3012 KM Rotterdam

The Netherlands

CRO:

Cardialysis

Westblaak 92

3012 KM Rotterdam

The Netherlands

Protocol approval page

Study title: Comparative effectiveness of 1 month of ticagrelor plus aspirin followed by ticagrelor monotherapy versus a current-day intensive dual antiplatelet therapy in all-comers patients undergoing percutaneous coronary intervention with bivalirudin and BioMatrix family drug-eluting stent use.

Protocol version: 1.4, dated 10 Sep. 2013
We, the undersigned, have read and approved the protocol specified above, and agree upon the contents:

P.W. Serruys, Erasmus Medical Centre Steering Committee Member, Principal Investigator	Date
S. Windecker, Insel Hospital Bern Steering Committee Member, Principal Investigator	Date
M. Valgimigli, University Hospital Ferrara Steering Committee Member, Principal Investigator	Date
P. Vranckx, Virga Jesse Hospital Steering Committee Member, Principal Investigator	Date
G.A. van Es Managing Director, ECRI-Trials B.V.	Date

CHANGE HISTORY RECORD – After final version 1.0

Protocol version	***Protocol date***	***Description and reason for change***	***Effects on other documents***
1.0	*21 Dec. 2012*	*Biosensors will release an enhanced delivery system for the BioMatrix Flex™ stent. This will result in a change of the stent name (BioMatrix NeoFlex™). As both stents will probably be used in the Global Leaders study, BioMatrix Flex™ has been changed into BioMatrix family drug-eluting stent thoughout the protocol.*	*All documents containing BioMatrix Flex™ stent will be modified*
1.0	*21 Dec. 2012*	*Administration of bivalirudin was added to the trial title.*	*All documents containing the trial title will be modified*
1.0	*21 Dec. 2012*	*Instruction For Use BioMatrix FlexTM stent (appendix V) has been removed, as both the BioMatrix Flex™ stent and the BioMatrix NeoFlex™ can be used. The instruction for both stents will be provided outside the protocol.*	*None*
1.0	*21 Dec. 2012*	*Page 41:* ***anti-coagulation:*** *Text concerning bivalirudin has been modified after review of the manufacturer.*	*None*
1.0	*21 Dec. 2012*	*Exclusion criterion 7: 'Known history of intracranial haemorrhage, stroke or intra-cranial aneurysm', was changed into 'Known history of intracranial haemorrhagic stroke or intra-cranial anuerysm'.Administrative correction.*	*All documents containing the exclusion criteria will be modified.*
1.1	*14 Jan. 2013*	*Page 41: 'In Europe, the use of bivalirudin is contraindicated for patients with severe renal impairment (GFR <30ml/min) and in patients with moderate renal impairment (GFR 30-59 ml/min) the infusion dose should be reduced to 1.4 mg/kg/hour, while in Canada an infusion dose of 1.0 mg/kg/hour should be considered in patients with severe renal impairment (GFR<30 ml/min).* *For more detailed instructions on the preparation, administration and approved dosing of bivalirudin please refer to the Package Insert or Summary of Product Characteristics (SPC), the Package Information Leaflet (PIL) and the dosing cards.' was added to the protocol.*	*None*
1.2	*15 Feb.*	*Page 40 added: 'Known pregnancy is an exclusion*	*None*

	2013	*criterion in this trial, not an exclusion from treatment (e.g. STEMI). All drugs mandated in the Global Leaders trial have been used in the trial's treatment scenarios and should be used according to their labelling. The investigator should weigh risks and benefits of treatment given the subject's specific pathology, and take all necessary precautions. If required by local regulations a pregnancy test is needed before randomisation in elective patients who are not using effective contraceptives to verify that they are not pregnant; such a test is considered impractical in the context of STEMI. Effective contraceptives should be discussed with females of childbearing potential'.*	
1.2	*15 Feb. 2013*	*Page 66, table 'Site responsibilities for submitting data and reports': Unanticipated Adverse Events changed into Suspected Unexpected Serious Adverse Reactions*	*None*
1.2	*15 Feb. 2013*	*Page 10: Due to a typo 'phase IV' was changed into 'phase III'.*	*All documents containing Phase IV will be modified.*
1.2	*15 Feb. 2013*	*In the title of section 9.6.1 (page 46) and 9.6.2 (page 47) the time windows of the follow-up visits were changed to match the eCRF.*	*None*
1.2	*15 Feb. 2013*	*Page 94: post-staged ECG was removed.*	*None*
1.2	*15 Feb. 2013*	*Page 55: Reference to section 4.3 was changed to section 4.2.2.3*	*None*
1.2	*15 Feb. 2013*	*Page 57: Site initiation WebEx meetings, was changed to Site initiation meetings.* *Deleted: The monitoring organisation and ECRI will participate in these teleconferences as well as the Country Leaders who play a prominent role in explaining the scientific purpose and study protocol.* *Administrative change to the following sentence: A baseline monitoring visit will be scheduled when the first patient has been enrolled. The visit must be performed within 2 to 3 weeks after inclusion of the first patient and data of all enrolled patients have been entered into the eCRF.*	*None*

1.2	*15 Feb. 2013*	*Page 85 added: 'If you are a female of childbearing potential your physician will ask you to do a pregnancy test before the study starts in case required by local regulations. Also, your physician will discuss with you the use of effective contraceptives for the duration of the study'..*	*Will be added to the Patient Information and Informed Consent Form V1.3.*
1.2	*15 Feb. 2013*	*Page 36: post-randomisation was changed into post-procedure*	*None*
1.2	*15 Feb. 2013*	*Page 53, administrative change: for ticagrelor are described in the Investigator Brochure and for clopidogrel in the Summary of Product Characteristics.*	*None*
1.2	*15 Feb. 2013*	*Page 54:* 'and the Summary of Product Characteristics of' was added	*None*
1.2	*15 Feb. 2013*	*Page 13: Pregnancy test was added to the table and column diagnostic was added for the angiogram.*	*None*
1.3	*17 Apr. 2013*	*Page 13 added: Exclusion criterion 10. Female who is breastfeeding at time of randomisation;*	*All documents containing exclusion criteria will be modified.*
1.3	*17 Apr. 2013*	*Page 36/37 added: In case a surgery reguires discontinuation of ticagrelor, the anti-coagulation regimen is left at the discretion of the investigator. However the following is advised:* *For surgery within 1 month of index procedure: keep the patient on aspirin (75-100 mg qd) and stop ticagrelor at least 72 hours before the surgery. Ticagrelor treatment should be resumed as soon as possible in the post-operative period.* *For surgery more than 1 month after index procedure: restart 30-day aspirin treatment (75-100 mg qd) and stop ticagrelor at least 72 hours before the surgery. Ticagrelor treatment should be resumed as soon as possible*	*None*

		in the post-operative period.	
1.3	*17 Apr. 2013*	*Page 40 added:Exclusion criterion 10.Female who is breastfeeding at time of randomisation;*	*All documents containing exclusion criteria will be modified.*
1.3	*17 Apr. 2013*	*Page 44 added: for 72 hours prior to the surgery.*	*None*
1.3	*17 Apr. 2013*	*Page 45 added: In case of severe renal impairment (GFR <30ml/min) bivalirudin is contra-indicated, however the patient can be included in the trial under the use of heparin under standard clinical practice.*	*None*
1.3	*17 Apr. 2013*	*Page 54-55: Reference to IB of ticagrelor has been changed into reference SmPC of ticagrelor*	*All safety reported related documents will be adjusted*
1.3	*17 Apr. 2013*	*Page 55 added: All-cause mortality cases that are unexpected and suspected to be related to ticagrelor, clopidogrel and/or ASA will not be excluded from expedited reporting.* *In addition to SAEs that are endpoints, myocardial ischemia related events other than new Q-wave MI (e.g. non Q-wave MI, unstable angina pectoris, stable angina pectoris and silent ischemia) are also considered disease related and therefore will not be subject to expedited reporting*	*All safety reported related documents will be adjusted*

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1. PROTOCOL SUMMARY

Study Name and Number	Global Leaders ECRI-12-001, 02EU11
Title	Comparative effectiveness of 1 month of ticagrelor plus aspirin followed by ticagrelor monotherapy versus a current-day intensive dual antiplatelet therapy in all-comers patients undergoing percutaneous coronary intervention with bivalirudin and BioMatrix family drug-eluting stent use.
Clinical Study Phase	Phase III
Objectives	To determine in all-comers patients undergoing PCI under standardised treatment (including the BioMatrix family of drug-eluting stents and bivalirudin), whether treatment with 1 month of ticagrelor and aspirin followed by 23 months of ticagrelor monotherapy is superior with respect to the composite of all-cause mortality or non-fatal new Q-wave MI compared to treatment with 12 months of standard dual anti platelet therapy (DAPT) followed by aspirin monotherapy.
Study Design	Investigator-initiated, prospective randomised, multi-centre, multi-national, open-label trial to be conducted in approximately 60-80 interventional cardiology centres in Europe, North America, South America and Asia-Pacific. Patients will be randomised at a 1:1 ratio to study or reference treatment strategy. Randomisation will occur at the time of the index procedure prior to PCI. Subjects will be stratified according to centre and according to the clinical presentation (Stable Coronary Artery Disease (CAD) vs. Acute Coronary Syndrome (ACS)). All patients will be followed for a period of 2 years.
Treatments	**Experimental treatment strategy** All patients in the treatment group will receive acetylsalicylic acid (ASA) and ticagrelor for 1 month followed by 23 months of ticagrelor monotherapy. **Reference treatment strategy** ACS patients incl. unstable angina (UA) patients: ASA and ticagrelor for 12 months followed by 12 months of ASA monotherapy. Stable CAD patients*: ASA and clopidogrel for 12 months followed by 12 months of ASA monotherapy. * Biomarker negative, no clinical signs and/or symptoms of ongoing myocardial ischemia. All patients will receive a BioMatrix family drug-eluting stent during the index PCI.

	All patients will receive bivalirudin during the index procedure in countries where it is available. **Note**: After 2 years, the medical treatment is left to the discretion of the physician.
Primary Endpoint	The composite of all-cause mortality or non-fatal new Q-wave MI up to 2 years post randomisation.
Secondary Endpoints	The composite of investigator-reported BARC3 or BARC5 bleeding according to BARC definitions up to 2 years post randomisation.
Patient Enrolment	A total of 16,000 patients will be enrolled. Subjects will be randomised at a 1:1 ratio to the DAPT treatment strategies (experimental or reference treatment strategy).
Additional Endpoints	<u>Components of the primary composite endpoint up to 2 years:</u> - All-cause mortality - Non-fatal new Q-wave MI <u>Investigator reported endpoints up to 2 years:</u> - Ischemic stroke, including stroke of undetermined cause - Haemorrhagic stroke - Composite of all-cause mortality, stroke and non-fatal new Q-wave MI - Coronary revascularisation - Definite Stent Thrombosis according to the Academic Research Consortium
(Follow-up) Assessments	- Screening - Day 0 / Index procedure - Post-procedure up to discharge - Clinical follow-up visits at 1 month, 3 months, 6 months, 1 year, 1.5 years and 2 years.
Key Inclusion Criteria	"All comer" patients 1. Age ≥18 years; 2. Presence of one or more coronary artery stenoses of 50% or more in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation. The vessel should have a reference vessel diameter of at least 2.25 mm (no limitation on the number of treated lesions, vessels, or lesion length); 3. Able to provide informed consent and willing to participate in 2 year follow-up period.

Key Exclusion Criteria	1. Known intolerance to aspirin, P2Y12 inhibitors, bivalirudin, stainless steel or biolimus; 2. Known intake of a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor; 3. Known moderate to severe hepatic impairment (alanine-aminotransferase ≥ 3 x ULN); 4. Planned surgery, including CABG as a staged procedure (hybrid) within 12 months of the index procedure, unless dual antiplatelet therapy is maintained throughout the peri-surgical period; 5. Need for chronic oral anti-coagulation therapy; 6. Active major bleeding or major surgery within the last 30 days; 7. Known history of intracranial haemorrhagic stroke or intra-cranial aneurysm; 8. Known stroke (any type) within the last 30 days; 9. Known pregnancy at time of randomisation; 10. Female who is breastfeeding at time of randomisation; 11. Currently participating in another trial and not yet at its primary endpoint.
Primary Analysis	Intention-to-treat.
Steering Committee	A separate Steering Committee Charter is maintained by ECRI with names, roles and responsibilities of the Steering Committee members.
Data Safety Monitoring Board (DSMB)	A separate DSMB Charter is maintained by ECRI with names, roles and responsibilities of the DSMB members.

2. TIME SCHEDULE

Trial periods	Screening/index procedure			Post-PCI to Hospital Discharge	Follow-up hospital visits					
Timing	**Diagnostic**	**Pre-PCI**	**PCI**	**Discharge**	**1 Month**	**3 Months**	**6 Months**	**1 Year**	**1.5 Years**	**2 Ye**
In-/exclusion Criteria		X								
Informed consent		X								
Angiogram (Syntax Score)[1]	X									
Randomisation		X								
Physical examination		X								
Medical and cardiac history		X								
Pregnancy test [3]		X								
12-lead ECG [2]				X		X				X
Concomitant medication		X	X	X	X	X	X	X	X	X
Treatments										
Medication regimen		X	X	X	X	X	X	X	X	X
Safety										
Serious Adverse Event (SAE)			X	X	X	X	X	X	X	X

[1]In angiograms for Syntax Score assessment both the right coronary artery (RCA) and left coronary artery (LCA, incl. LAD and LCX) must be imaged and sent to Core Lab.
[2]ECGs: recorded and sent to Core Laboratory. [3] If required by local regulations.

3. PRINCIPAL CONTACTS

Steering Committee Chairman:
Prof. P.W. Serruys
Tel: +31-10-240-2424

Sponsor:
ECRI-Trials B.V.
PO Box 2125, 3000 CC, Rotterdam
The Netherlands
Tel: +31-10-206-2850

Project management:
ECRI-Trials B.V.
Janette Symons
E-mail: J.Symons@ecri-trials.com
Tel: +31-10-206-2856

Site management and monitoring:
Europe:
Cardialysis B.V.
PO Box 2125, 3000 CC, Rotterdam
The Netherlands
Tel: +31-10-206-2828

Outside of Europe:
Theorem Clinical Research
1016 West Ninth Ave.
King of Prussia PA, 19406
U.S.A.

Packaging, labelling and drug distribution:
Fisher Clinical Services UK Ltd.
Langhurstwood Road, Horsham
West Sussex RH12 4QD
U.K.

4. INTRODUCTION

4.1 Background

4.1.1 Coronary stenting

Atherosclerosis and coronary artery thrombosis are a major cause of premature death worldwide, and are an important source of loss of disability-adjusted life years.[1,2,3] Treatment goals for patients with coronary artery disease (CAD) are improvement in survival and a reduction in the risk of myocardial infarction (MI) and symptoms of coronary disease.[4]

Percutaneous coronary intervention (PCI) with stent implantation to treat obstructive coronary lesions that cause ischemia can improve a patient's functional status and outcome.[5,6,7] The expanding use of PCI, coupled with refinements in technology including the introduction of drug-eluting stents (DES) and more intensive adjunctive pharmacological treatment, resulted in treatment of increasingly complex lesions and patients with a history of clinically significant cardiovascular disease, coexisting conditions, and/or complex coronary anatomy.[8] DES have markedly improved outcomes of PCI owing to their pronounced ability to reduce restenosis compared with bare-metal stents (BMS) especially when focusing specific subgroups with diabetes mellitus, small coronary vessels, and long lesions. DES greatly reduced the need for repeated procedures for in-stent restenosis compared with BMS; however, they also extended the period during which patients are at risk for stent thrombosis. Different classes of drugs mounted in a polymer layer on the surface of the stent have been shown to be very effective in preventing neointimal hyperplasia. Currently, there are 22 DES stents CE marked [9] and commercially available on the market.

PCI is an important mechanical treatment of stable and unstable CAD. However, balloon inflation and stent placement can potentiate an existing pro-thrombotic state around lesion areas and lead to attendant ischemic complications. The magnitude of the thrombotic process triggered upon plaque disruption is modulated by different elements that determine plaque and blood thrombogenicity. Exposure of tissue factor in the atherosclerotic plaque to flowing blood leads to increased thrombin generation, resulting in platelet- and fibrin-rich thrombus formation.[10] Such platelet aggregates can occur in response to spontaneous disruption of a vulnerable plaque, but they can also develop during PCI in response to balloon inflations and deployment of coronary stents.[11,12]

In view of the central role of the platelet in coronary thrombosis, and heightened platelet activation after PCI, the choice of the concomitant pharmacological environment (dual or even triple antiplatelet therapy and/or anticoagulants) has become critical, as has the dosage of the drugs.[13,14] The value of a periprocedural antithrombotic regimen depends on the balance between prevention of ischemic complications and bleeding complications.[15] Post-PCI bleeding has been strongly associated with subsequent mortality.[16] Non-access site bleeding after PCI is common, representing approximately two-thirds of all TIMI bleeding events, and is associated with a 4-fold increase in 1-year mortality.[17,18]

4.1.2 All-comers patient population

Cardiovascular disease knows no geographic boundaries and represents a global pandemic. With this, the clinical development marketplace has become truly global. Currently, a substantial number of PCI procedures are elective and performed in stable patients; however, increasing numbers of procedures are being performed in patients with acute coronary syndromes (ACS). Initial evidence with DES was based on patients with single, "simple" lesions and without serious co-morbidities. Over time, their use has expanded to patients with more complex lesion and clinical characteristics.

In line with the above, the unstable patients were excluded from the initial coronary stent studies. However, more recently, large "all-comers" investigations of stents have been performed enrolling unrestricted patient populations. [19,20,21,22] These studies most closely reflect the routine clinical practice of PCI.

A large, adequately powered, global, randomised controlled trial in an unrestricted population provides a unique opportunity to compare clinical outcomes amongst different patient subgroups nestled within a single trial, including their clinical and/or angiographic characteristics.

4.1.3 DAPT in contemporary coronary stent trials

PCI may be complicated by adverse cardiac events including death, MI and a need for urgent revascularisation regardless of whether bare-metal or drug eluting stents are used, some of which may be explained by acute, sub-acute, or late stent thrombosis.[23] Modulation of thrombotic and coagulation potential is a key factor in improving early (<30 days) clinical outcomes and in preventing complications in patients undergoing PCI.[24] Platelet adhesion, activation, and aggregation play key roles in both normal haemostasis and in pathological intracoronary thromboses that cause ACS and the ischemic complications following coronary artery interventions, including recurrent MI.[25,26]

For more than a decade, the mainstay of antiplatelet therapy has been the combination of the cyclo-oxygenase inhibitor aspirin, and the ADP-receptor antagonist clopidogrel. Evidence has emerged, however, regarding the inherent limitations of clopidogrel. The pharmacokinetic and pharmacodynamic effects of clopidogrel are highly variable and may be influenced by genetic polymorphisms, which translate into differential pharmacodynamic and therapeutic responses, leading to the notion of clopidogrel "non-responders."[27,28,29,30] Furthermore, high on-treatment platelet reactivity is an emerging risk factor in patients undergoing PCI, and increased doses of clopidogrel only partially ameliorate this difficulty.[31]

Two newer oral adenosine diphosphate (ADP) blockers, prasugrel and ticagrelor, have been associated with less inter-patient variability and more potent inhibition of platelet-aggregation.[32,33,34,35] Both prasugrel and ticagrelor have proven to be superior to clopidogrel in patients with ACS who were undergoing PCI. As of today, these drugs have not been tested in patients undergoing elective PCI for stable, obstructive CAD. However, in daily PCI practice, a large group of elective patients can be

identified that provide an even higher risk of adverse ischemic events as compared to those with ACS (*data on file, Cardialysis Rotterdam*).

4.1.4 Antithrombotic drugs during PCI with a specific focus on the use of bivalirudin as preferred anti-coagulant agent in the setting of an all-comers study

There is clear evidence that anticoagulation in addition to platelet inhibition is effective and that the combination of the two therapies is more effective than either treatment alone. To minimise the risk of ischemic complications during and shortly after PCI, many adjunctive antithrombotic regimens targeting thrombin generation and/or activity have been investigated and are currently in use.[36,37] Unfractionated heparin (UFH) has been widely used as the standard anticoagulant during PCI for more than two decades.[38] Heparin exerts its anticoagulant effect indirectly by binding to antithrombin, thereby dramatically enhancing the ability of antithrombin to inhibit coagulation system enzymes, particularly thrombin and factor Xa. Yet, there are several important disadvantages associated with the use of UFH.[39,40] Due to its unpredictable, nonlinear pharmacokinetics, UFH exhibits a variable anticoagulant effect, variable binding to blood proteins and the vessel wall, and sensitivity to the inhibitory effects of platelet factor-4. Further, the heparin–antithrombin complex is not very effective in neutralizing clot-bound thrombin and, in some patients, heparin causes an immunologic thrombocytopenia (i.e. heparin-induced thrombocytopenia [HIT]), which can result in immune-mediated thrombosis. These limitations of heparin have spurred the development of anticoagulants with different mechanisms of action, with the goal of improving outcomes and safety for patients undergoing PCI. A valuable alternative to heparin is the group of direct thrombin inhibitors (DTI). These comprise a class of anticoagulants that bind directly to thrombin and block its interaction with its substrates.[41,42] Potential advantages associated with the use of DTIs compared with UFH include increased efficacy via the ability to bind to and inhibit fibrin-bound thrombin.[41,42,43] Bivalirudin (Angiox® or Angiomax®, The Medicines Company) is currently the most widely investigated DTI in the span of patients undergoing PCI.[43,44] When used in place of heparin plus planned glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, it has consistently demonstrated a reduction in protocol-defined major and minor bleeding.[17,44] In patients with ST-segment elevation MI (STEMI) undergoing primary PCI, the use of this drug has resulted in a significant mortality reduction.

Bivalirudin is currently indicated in Europe for "the treatment of adult patients with acute coronary syndromes (unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)) planned for urgent or early intervention and as an intravenous (IV) anticoagulant in patients undergoing percutaneous coronary intervention (PCI) including patients with ST segment elevation myocardial infarction (STEMI) undergoing primary PCI." [Summary of product characteristics, March 2010].

Therefore, bivalirudin is currently the only anticoagulant strategy, that is approved for use in elective, urgent or emergent PCI, and as such it should be considered the ideal anticoagulant drug to be implemented in all-comers PCI patients.

Being a direct thrombin inhibitor and unlike heparins (unfractionated or low molecular weight), bivalirudin is able to inhibit both soluble and fibrin bound thrombin with similar potency, providing a distinct pharmacological advantage particularly in ACS patients. Furthermore, heparins potentiate platelet activation, whereas bivalirudin inhibits platelet aggregation by blocking thrombin signalling to the protease activated receptor (PAR) family of platelet receptors.[45,46,47,48,49]

Therefore, bivalirudin is again the ideal anticoagulant compound to be used in the setting of a study comparing two different anti-platelet therapies, as its use would not negatively affect the degree of platelet reactivity during or soon after the accomplishment of PCI.

Synthesised chemically, bivalirudin is a short peptide of 20 amino acids that binds to both the active site and substrate recognition exosite of thrombin, thus directly and specifically inhibiting all known actions of thrombin[50]. The binding of bivalirudin to thrombin is reversible; thrombin is able to recognize the drug as a substrate and cleave it, restoring its haemostatic function. The plasma half-life of bivalirudin is 25 minutes.

4.1.5 Previous clinical trials with bivalirudin

Bivalirudin approval in Europe was based on three pivotal studies showing that bivalirudin has similar efficacy in reducing ischemic events with a better bleeding profile when compared to heparins plus GPIIb/IIIa inhibitors in patients undergoing elective PCI or with moderate or high risk ACS managed by PCI.[44,51,52,53 54,55,56,57]

In the REPLACE-2 trial[44] a total of 6010 patients undergoing urgent or elective PCI were randomly assigned to receive intravenous bivalirudin, or heparin plus GP IIb/IIIa inhibition. The key objective of this study was to evaluate the composite incidence of clinically significant events reflecting ischemic complications (death, MI, urgent revascularisation) and haemorrhage associated with PCI up to 30 days post-PCI as represented by the quadruple and triple composite endpoints. Bivalirudin was non inferior to the comparator group of heparin plus planned GP IIb/IIIa inhibition with regard to the composite incidence of clinically significant events reflecting ischemic complications and haemorrhage associated with PCI up to 30 days post-PCI, or the composite incidence of ischemic events (death, MI, urgent revascularisation). However, the bleeding incidence was significantly lower in the bivalirudin arm for all components (2.4% versus 4.1%; OR 0.59; $p<0.001$).

In the ACUITY trial[56] a total of 13,819 patients with moderate or high risk UA/NSTEMI were randomised to receive one of the following anti-thrombotic regimens: unfractionated heparin or enoxaparin plus a GP IIb/IIIa inhibitor; bivalirudin plus a GP IIb/IIIa inhibitor; or bivalirudin alone.

All pre-specified tests of the primary and secondary objectives were met for all 30-day endpoints and support the efficacy of bivalirudin for use in all ACS patients undergoing an early invasive strategy. Use of bivalirudin alone was superior to heparins + GP IIb/IIIa inhibitor, for the net clinical outcome endpoint (incidence of death, MI, unplanned revascularisation for ischemia, or major bleeding 10.1% versus 11.7%, p=0.0147), and for major bleeding using the ACUITY scale (3.0% versus 5.7%, p<0.0001), bivalirudin alone was non-inferior for the composite ischemic endpoint (7.8% versus 7.3%, p=0.0107).

The HORIZONS AMI[57] was a prospective, randomised, open label, double arm, single blinded trial in 3,602 STEMI patients undergoing primary PCI. Eligible patients were randomised to receive either bivalirudin monotherapy with a provisional GP IIb/IIIa inhibitor or UFH plus a routine GP IIb/IIIa inhibitor. At 30 days, bivalirudin monotherapy demonstrated statistical superiority versus UFH plus GP IIb/IIIa inhibitor for the two primary endpoints of net adverse clinical outcomes (9.2% versus 12.1% p=0.006) and major bleeding (4.9% versus 8.3% p=0.0001), and no significant differences for the secondary endpoint of major adverse cardiovascular events (5.4% versus 5.5% p=0.95). Treatment with bivalirudin rather than heparin plus a GP IIb/IIIa inhibitor also resulted in significantly lower 30-day rates of cardiac mortality (1.8% versus 2.9%, RR[95%CI] = 0.62 [0.40, 0.95], P=0.028) and all-cause mortality (2.1% versus 3.1%, RR[95%CI] = 0.66 [0.44, 1.00], P=0.047), with non significantly different rates of re-infarction, target vessel revascularisation, and stroke.

Interestingly, the incidence of acute stent thrombosis resulted to be significantly higher in the bivalirudin monotherapy arm as compared to UFH plus a routine GP IIb/IIIa inhibitor. This difference was not carried over at 30 days, when the cumulative risk for stent thrombosis was identical in the two study groups. It is highly possible that the difference in acute stent thrombosis rate observed in the HORIZONS-AMI trial reflects the slow onset of action of clopidogrel, even when given at a higher loading dose, in STEMI patients[58].

While patients receiving intravenous GP IIb/IIIa inhibitor are protected towards stent thrombosis for the first 24 hours, patients treated with bivalirudin and clopidogrel may suffer from a lack of anti-thrombotic effect in the first hours after PCI, in which bivalirudin effect on thrombin has quickly weans after stopping drug infusion and P2Y12 inhibition is not accomplished yet.

There is therefore great interest in evaluating the combination of bivalirudin and ticagrelor, especially in the setting of STEMI patients. Ticagrelor, being a direct ADP receptor blocker, unlike clopidogrel,

can achieve a much more potent and quicker inhibition of P2Y12 receptor and as such it may prove to be the ideal anti-platelet agent to be used in conjunction with bivalirudin during PCI.

A meta-analysis has been conducted by the GLOBAL LEADERS investigators incorporating the data coming from the three above-mentioned RCT, comparing short versus long DAPT duration after DES implantation has been performed, comprising 5622 participants. Compared with patients receiving short-term therapy, participants receiving longer DAPT duration had a pooled OR of 1.26 (95% CI, 0.88 to 1.80; P=0.21, random-effects) for the primary outcome of cardiac death, MI or stroke, OR of 1.29 (95% CI, 0.85 to 1.93; fixed-effects) for all-cause mortality, 1.23 (95% CI, 0.78 to 1.93; fixed-effects) for cardiac death, 0.91 (95% CI, 0.58 to 1.42; random-effects) for MI, 1.93 (95% CI, 1.01 to 3.69; fixed-effects) for stroke and 2.51 (95% CI, 1.10 to 5.71, fixed-effects) for TIMI major bleeding. The number needed to treat for an additional harmful outcome was 217.6 for stroke and 243 for TIMI major bleeding (data not published yet).

Recently, a meta-analysis of extended DAPT duration after stenting (including also patients who received BMS at the time of intervention) has included four trials that randomized 8,231 patients (50.2%, extended DAPT duration vs. 49.8%, control duration). A total of 8,158 patients (99.1%) were available for final analyses. The median DAPT duration was 16.8 vs. 6.2 months for the extended DAPT and control groups, respectively. At follow-up (median 16.8 months) extending DAPT duration did not reduce all-cause death [odds ratio (95% confidence interval) = 1.15 (0.85–1.54), P 1⁄4 0.36], MI [0.95 (0.66–1.36), P = 0.77], ST [0.88 (0.43–1.81), P = 0.73], or CVAs [1.51 (0.92–2.47), P = 0.10]. Conversely, extended DAPT duration clearly increased the risk of TIMI major bleeding [2.64 (1.31–5.30), P = 0.006].[59]

4.2 Description of Study Treatments

4.2.1 Stent platform

The stent devices used in this trial, are part of the BioMatrix family drug-eluting stents (Biosensors Europe SA Morges, Switzerland) is CE marked and commercially available in all participating countries. Biolimus is released from the stent through a biodegradable polymer matrix.[21,60,61]

4.2.2 Clinical studies with the biolimus A9/BA9™-eluting stent

STEALTH study: The STEALTH study[60] was a first-in-man safety trial comparing the biolimus A9/BA9™-eluting (the BioMatrix™) stent with a BMS, known as S-Stent™. A total of 120 patients were randomly assigned to treatment with the BioMatrix™ stent in 80 patients, and to the control BMS in 40 patients, at two German centres and one centre in Brazil. The BioMatrix™ stent not only achieved the primary endpoint of non-inferiority for 6-month in-segment late loss compared with the bare-metal S-Stent™, but demonstrated statistical superiority for both in-segment (0.09±0.31 vs. 0.48±0.43, p <0.001) and in-stent (0.19±39 vs. 0.76±0.45, p <0.001) late loss at 6 months. This benefit was achieved without an

increase in adverse safety outcomes assessed as MACE in the first 30 days (3.7% vs. 2.5%) and after 360 days (5.1% vs. 5.0%). Continued follow-up, available at 720 days in 62/80 (78%) BioMatrix™ and 37/40 (93%) S-Stent™ patients showed continued safety in both groups with one additional TLR in the BioMatrix™ group and one additional non-Q-wave MI in the S-Stent™ group between 360 and 720 days with a cardiac death 6 days later. There was one acute stent thrombosis in the BioMatrix™ group and no sub-acute or late stent thromboses in either group.

LEADERS study: The LEADERS study[21] is a randomised, single-blinded, non-inferiority trial comparing the safety and efficacy of the biolimus A9/BA9™-eluting stent to the Sirolimus-eluting stent (Cypher, Cordis, Miami Lakes, FL) in subjects with an indication for PCI (stable or those with ACS, including STE-ACS). A total of 1707 patients with 2472 lesions were randomly assigned to treatment with the BioMatrix Flex™ Biolimus A9/BA9™-eluting stent (857 patients) and to the control stent (Cypher) in 850 patients, at 10 European centres. Data management and analysis as well as angiographic analysis were performed by an independent clinical research organisation and in a core laboratory (Cardialysis BV). Patients with one or more coronary artery stenoses with a diameter stenosis >50% in native coronary arteries or saphenous bypass graft with a reference diameter of 2.25 to 3.5 mm and no limitations on the number of treated lesions and vessels or lesion lengths were eligible. No direct stenting was permitted. As it involved a real-world, all-comers population, only patients who were pregnant, intolerant to aspirin, clopidogrel, heparin, stainless steel, sirolimus, biolimus or contrast material, unable to provide informed consent, concurrently participating in another trial before reaching the primary endpoint, and those who had planned surgery within 6 months of PCI were excluded. Clinical follow-up visits were performed at 30 days and 9 months (including randomly assigned angiographic follow-up in a fourth of the patients). Telephone follow-up at 6 months and 1-5 years has been completed.

The results at 9-month follow-up (the primary endpoint for the study) were published in The Lancet in 2008. [21] The primary endpoint, a composite of cardiac death, MI, or clinically-indicated target vessel revascularisation (TVR) at 9 months, occurred in 9.2% of patients treated with biolimus-eluting stents and 10.5% of patients treated with sirolimus-eluting stents, thus establishing non-inferiority ($P_{non\text{-}inferiority}$=0.003; rate ratio 0.88, 95%-CI 0.64-1.19, $P_{superiority}$=0.39). Rates of cardiac death (1.6% versus 2.5%, P=0.22), MI (5.7% versus 4.6%, P=0.30), and clinically-indicated TVR (4.4% versus 5.5%, P=0.29) were similar for both stent types. Biolimus-eluting stents were also non-inferior to sirolimus-eluting stents in in-stent percent diameter stenosis (20.9% versus 23.3%, $P_{non\text{-}inferiority}$=0.001, $P_{superiority}$=0.26), the principal angiographic endpoint of the study.

The longer term results were recently reported at the TCT Congress (October 2012, Miami, FL, USA). At 5-years the rates of MACE (22.3% vs. 26.1%, $P_{superiority}$=0.07); cardiac death (8.0% vs. 8.4%, $P_{superiority}$=0.72), and clinically-indicated TVR (12.8% vs. 15.5%, p=0.12) were also similar between stents. Rates of very late definite stent thrombosis were significantly lower with the biolimus-eluting stent compared to the sirolimus-eluting stent (0.66% vs. 2.5%, $P_{superiority}$==0.003).

In summary, the biolimus A9/BA9™-eluting stents with biodegradable polymer represent a safe and effective alternative to the sirolimus-eluting stents with durable polymer in patients with on- and off-label indications. Longer-term follow-up and studies in larger populations will be necessary to determine whether the biodegradable polymer is associated with a reduced risk of late stent thrombosis or is able to support an alternative duration of dual antiplatelet therapy.

Both studies, along with data from partner studies, give evidence to support the safety and efficacy of the Biolimus A9/BA9™-eluting stent.

4.2.3 DAPT regimens

The optimal duration of dual anti-platelet treatment (DAPT) after coronary stenting is a matter of ongoing debate.

4.2.3.1 Bare metal stents and duration of dual anti-platelet treatment

The coronary implantation of BMS prevents the acute recoil and post-injury arterial shrinkage (constrictive remodelling) associated with balloon angioplasty. Yet, it also replaces atherosclerotic coronary disease with the iatrogenic condition of in-stent neointimal hyperplasia which may frequently result in in-stent restenosis (ISR). As vascular healing rapidly occurs after implantation, a regimen of dual anti-platelet therapy for 30 days is generally recommended after BMS to reduce acute and sub-acute stent thrombosis. Nevertheless, prolonging treatment for up to 12 months has shown to be a beneficial secondary prevention measure in either non-ST segment elevation acute coronary syndromes (NSTEACS) undergoing PCI with BMS, or in symptomatic stable or unstable coronary artery disease patients undergoing elective BMS implantation.

The Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) trial[62] showed that pre-treatment with clopidogrel (300 mg loading dose, followed by 75 mg daily) in addition to aspirin for a median of 10 days before PCI, compared to aspirin alone, reduced the composite of cardiovascular death, MI or urgent TVR by 30% (absolute risk reduction 1.9%, p= 0.03) after one month. After PCI, stented patients received an open-label thienopyridine (>80% in both groups, either clopidogrel or ticlopidine) in combination with aspirin for 2–4 weeks, indicating that the observed early post-procedural benefit at 30 days was mainly due to the effects of clopidogrel pre-treatment.

At one month, administration of the randomly assigned study medication (i.e. clopidogrel versus placebo on top of aspirin) resumed until the end of the scheduled follow-up (3–12 months after randomisation).

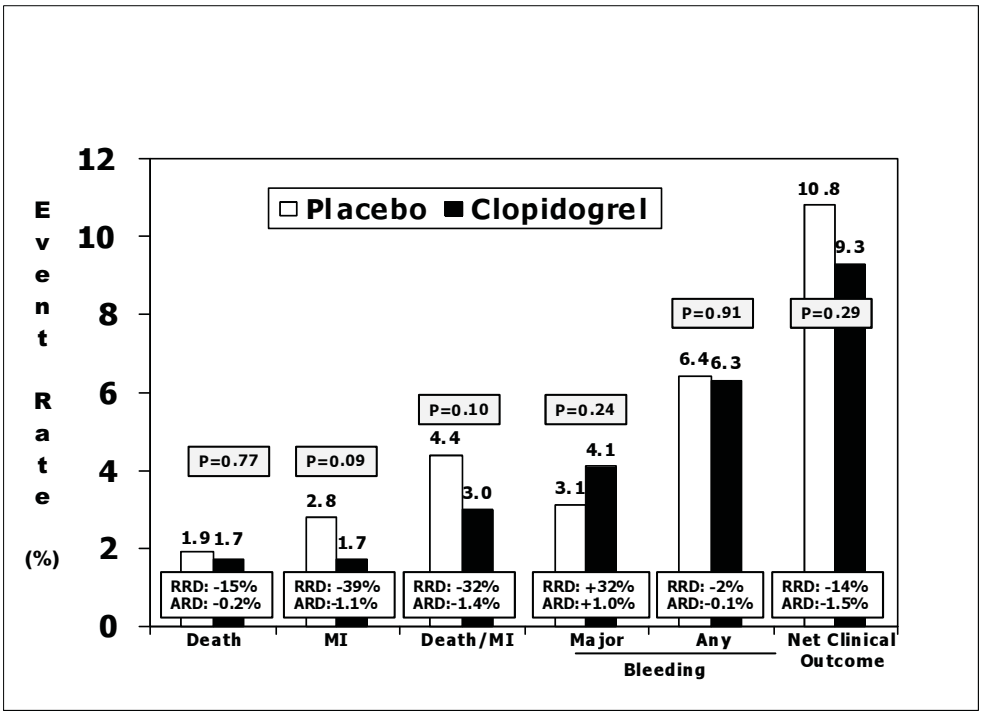
At the end of follow-up (mean 8 months), there was no effect of treatment beyond 30 days on cardiovascular mortality (1.4% in the clopidogrel vs. 1.3% in the placebo group). The rate of MI was similar (2.4% vs. 2.5%, respectively) yet the composite of cardiovascular death or MI (3.9% vs. 3.1%, RR[95%CI]:0.79 [0.53–1.20]) was numerically, even if not significantly, lower in the clopidogrel arm.

Prolonging treatment with clopidogrel beyond 30 days and up to a mean of 8 months did not increase the rate of major bleedings. However, the rate of minor bleeds, the composite of major or minor and the rate of major non life-threatening and minor bleeds were all significantly increased in the clopidogrel arm by at least 50% compared to the placebo arm. Hence, the net clinical outcome consisting of cardiovascular death, MI and the rate of major or minor bleedings did not significantly differ in the two groups and numerically it even favoured placebo treatment.

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial[63] was a blinded, placebo-controlled trial powered to identify the benefit of clopidogrel pre-treatment plus long-term therapy in stable (32.8% of the overall sample size; n=694 patients) or unstable (67.2% of the overall sample size; n=1408 patients) patients undergoing a planned PCI, or who were highly likely to undergo a PCI, on the 1-year combined incidence of death, MI and stroke. Although not designed to show any significant benefit between day 29 and one year, a statistically significant 37% relative risk reduction of death, MI or stroke and 1.9% absolute risk reduction were observed (HR 0.63 [95% CI 0.40-0.98]; p=0.04).

The effect of prolonging therapy with clopidogrel beyond day 29 after stenting in the CREDO study on death, MI, death or MI and on major or minor bleedings is shown in figure 1.

Figure 1: CREDO study results



Interestingly, the benefit was shown to be consistent in both stable and unstable patients.

While PCI-CURE and CREDO studies[62,63] have been interpreted as proof of beneficial value in prolonging therapy with clopidogrel after bare metal stenting, both studies suffer from a major methodological limitation: the value of long-term treatment with clopidogrel post-PCI isolated from pre-treatment is impossible to determine. Only patients who received pre-procedural clopidogrel continued to receive it long-term in both PCI-CURE and CREDO, while control patients were given a placebo after the first four weeks. The actual effect of long-term clopidogrel would have been possible to ascertain if the groups had been re-randomised after 1 month, or if both groups had been pre-treated with clopidogrel.

Importantly, however, despite these limitations and the fact that neither of these two studies was powered to assess the effect of prolonging clopidogrel beyond 30-days, both ACC/AHA[36] and ESC[64] guideline committees have endorsed the recommendation to prolong clopidogrel therapy for up to 12 months after acute coronary syndromes, irrespective of the implanted stent type.

4.2.2.2 Drug-eluting stents and duration of dual anti-platelet treatment

Considerable effort has gone into the development of stents with an active coating to inhibit in-stent restenosis — the DES. The eluted drugs are selected to be able to inhibit the complex cascade of events that lead to neointimal formation after stent implantation. The inflammatory and proliferative mechanisms of the general tissue-healing response are crucial targets for therapeutic approaches aimed at reducing neointimal proliferation. As a consequence, inhibition of neointimal proliferation through DES implantation invariably results in delayed vessel healing after mechanical injury. Prolonged dual platelet therapy with aspirin and clopidogrel is therefore believed to be of paramount importance to avoid late (>30-days) or sometimes even very late (>1 year) DES thrombosis. While this recommendation is supported by multiple mechanistic investigations suggesting a delayed healing process or a prolonged inflammatory response of the vessel wall after DES implantation, clinical evidence is controversial and largely limited to registry data. As the success of eluting devices is highly dependent on each component of the complex, including the platform (the stent), the carrier (usually a polymer), and the agent (a drug) to prevent restenosis, as well as on the interactions among these elements, it is unlikely that DES have a class effect, since there is a myriad of possible therapeutic combinations. Importantly, different DES vary in their ability to inhibit neointimal growth, which may impact the differential need for prolonged dual antiplatelet treatment after stent placement. As a direct relationship between anti-intimal hyperplasia stent potency and the risk of late and very late stent thrombosis has been hypothesized, the benefit of a prolonged duration of dual anti-platelet treatment may vary according to the specific stent potency towards inhibition of intimal hyperplasia after implantation. On the other hand, both pre-clinical and some clinical studies suggest that the degree of stent healing may not be simply related to the magnitude of expected late loss after intervention. The intrinsic biocompatibility of each stent component may play a more relevant role in long-term safety than the actual anti-intimal hyperplasia stent potency. Studies comparing different durations of dual anti-

platelet therapy after stent implantation should therefore be corrected for both stent types and anti-intimal hyperplasia stent potency to avoid potential confounders.

While intrinsically limited by the retrospective nature of the investigation, findings from the Basel Stent Kosten Effektivitäts (BASKET)-Late Thrombotic Events (LATE) trial [65] showed an increase in death and MI in patients undergoing DES implantation 6 to 18 months after clopidogrel discontinuation which occurred six months after stenting. Registry data from the Duke Heart Centre revealed clopidogrel use at 12 months in patients receiving DES to be associated with lower rates of death and MI at 24-month follow-up[66].

Recommendations for prolonged dual antiplatelet therapy need to be made with caution given the heightened bleeding risk and increased financial costs. Moreover, several further studies have failed to confirm that clopidogrel discontinuation after 6 months is a risk factor for late or very late stent thrombosis or is even associated to worse cardiovascular outcomes.

The first randomised comparison of short- term versus long-term continuation of DAPT after DES comes from South Korea. From July 2007 through September 2008, a total of 2701 patients were enrolled at 22 cardiac centres in South Korea: 1625 enrolled in the REAL-LATE trial and 1076 enrolled in the ZEST-LATE trial [67]. Of these patients, 1357 were assigned to receive clopidogrel plus aspirin and 1344 were assigned to receive aspirin monotherapy. The two groups were well balanced with regard to most baseline characteristics. The mean age was 62 years; 30% of the patients were women, and 26% had medically treated diabetes. Nearly half the patients had multi-vessel disease, and more than 60% had an acute coronary syndrome as the clinical indication for the initial PCI. Sirolimus-eluting stents were the type of drug-eluting stent most commonly used. Almost 90% of the patients were enrolled 12 to 18 months after the index procedure. The median duration of follow-up was 19.2 months (interquartile range, 13.2 to 24.1) after randomisation and 33.2 months (interquartile range, 28.1 to 37.6) after the index procedure. During the follow-up period, adherence to the assigned study treatment was approximately 90% at 12 months and approximately 80% at 24 months in the dual-therapy group, and more than 90% at both 12 months and 24 months in the aspirin-alone group. Follow-up with respect to the primary endpoint (the first occurrence of MI or death from cardiac causes) was complete for 99.4% of patients in the dual-therapy group and for 99.3% of those in the aspirin-alone group. During the follow-up period, 33 patients died, 21 of cardiac causes. A total of 17 patients had an acute MI, 13 had a stroke, and 9 had definite stent thrombosis. Repeat revascularisation was performed in 62 patients, and major bleeding occurred in 4 patients. No fatal bleeding was reported. The Kaplan–Meier estimate of the event rate for the primary endpoint (MI or death from cardiac causes) at 2 years was 1.8% in the dual-therapy group, as compared with 1.2% in the aspirin-alone group (hazard ratio, 1.65; 95% confidence interval [CI], 0.80 to 3.36; P = 0.17). There was no differential treatment effect between the REAL-LATE participants and the ZEST-LATE participants[67]. There was also no significant difference between the two treatment groups in the risk of individual secondary endpoints (MI, stroke, stent thrombosis, repeat revascularisation, or death from any cause). However, among patients assigned to receive dual antiplatelet therapy, as compared with those assigned to receive aspirin alone, there was a non-

significant increase in the risk of the composite endpoint of myocardial infarction, stroke, or death from any cause (hazard ratio, 1.73; 95% CI, 0.99 to 3.00; P = 0.051) and of the composite endpoint of MI, stroke, or death from cardiac causes (hazard ratio, 1.84; 95% CI, 0.99 to 3.45; P = 0.06). The risk of TIMI defined major bleeding was similar in the two groups.

The second study to evaluate the non-inferiority of a shorter course of DAPT as compared to 12-month DAPT duration was the EXCELLENT study. Six-month versus 12-month dual antiplatelet therapy after implantation of DES: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomised, multicenter study. [68]Authors randomly assigned 1443 patients undergoing implantation of DES to receive 6-month or 12-month DAPT (in a 1:1 ratio). The primary end point was a target vessel failure (TVF) defined as the composite of cardiac death, MI, or ischemia driven TVR at 12 months. Rates of TVF at 12 months were 4.8% in the 6-month DAPT group and 4.3% in the 12-month DAPT group (the upper limit of one-sided 95% confidence interval [CI], 2.4%; P=0.001 for noninferiority with a pre-defined noninferiority margin of 4.0%). Although stent thrombosis tended to occur more frequently in the 6-month DAPT group than in 12-month one (0.9% versus 0.1%; hazard ratio 6.02, 95% CI 0.72-49.96; P=0.10), the risk of death or MI did not differ in the 2 groups (2.4% versus 1.9%; hazard ratio 1.21, 95% CI 0.60-2.47; P=0.58).

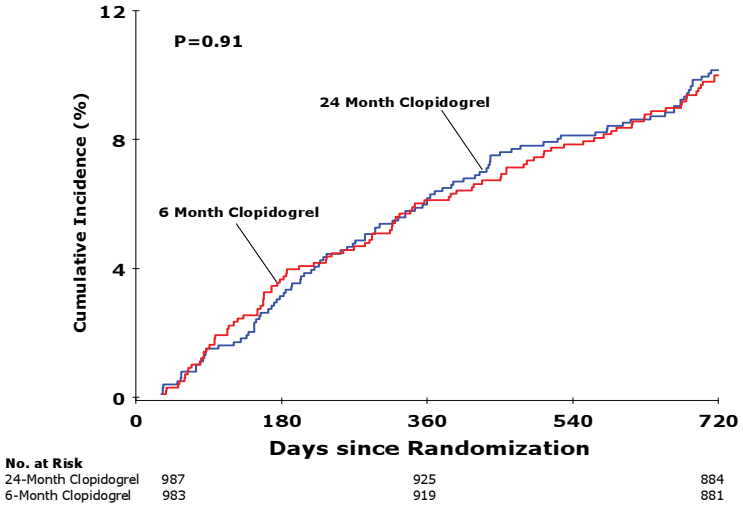
The PROlonging Dual antIplatelet treatment after Grading stent-induced intimal hYperplasia (PRODIGY) trial, a 4-by-2 randomised, multicenter, clinical trial was designed to evaluate the efficacy and safety of prolonging duration of clopidogrel therapy up to 24 months in all- comer patients receiving a balanced mixture of stents with various anti-intimal hyperplasia potency.[69] Patients undergoing elective, urgent or emergent PCI with intended stent implantation were randomly assigned in a 1:1:1:1 fashion to one of four stent types, including third-generation thin-strut BMS, ENDEAVOR SPRINT™ zotarolimus-eluting stent (ZES), TAXUS™ paclitaxel-eluting stent (PES) or XIENCE™ V everolimus-eluting Stent (EES). At 30 days, patients in each stent group were randomised in a balanced fashion to 6 months of dual anti-platelet treatment (SHORT arm) versus prolonging aspirin and clopidogrel for 24 months (LONG arm). Clopidogrel discontinuation at any time after 30 days was allowed in keeping with current ACC/AHA and ESC[64] recommendations in patients who were randomised to the BMS-SHORT arm in which coronary intervention was indicated by the presence of stable coronary artery disease (CAD).

Clinical follow-up at 2 years with respect to the primary and secondary end points was complete for 99.7% of patients in the long-term clopidogrel group and for 99.6% of those in the short-term clopidogrel group.

During the follow-up period, 130 patients died, 73 of cardiovascular causes. A total of 80 patients had an acute MI, 35 had a cerebrovascular accident of which 14 were confirmed as having intracranial haemorrhage and 12 had definite stent thrombosis. There were overall 181 bleeding events according to the Bleeding Academic Research Consortium classification[70], of which 107 were included in the key safety endpoint and 14 were reported to be fatal.

The Kaplan–Meier estimate of the event rate for the primary end point (death from any cause, MI or cerebrovascular accident) at 2 years was 10.1% in the 24-month clopidogrel group, as compared with 10.0% in the 6-month clopidogrel group (hazard ratio, 0.98; 95% confidence interval [CI], 0.74 to 1.29; P = 0.91) (Figure below).

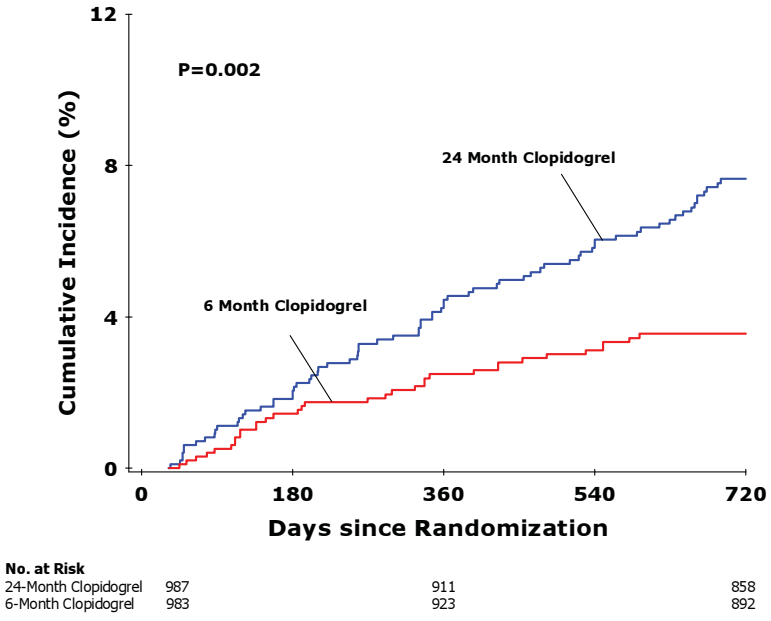
Figure 2: PRODIGY Kaplan-Meier estimate of primary endpoint



There was also no significant difference between the two treatment groups regarding the risk of individual secondary end points (death from any cause, death from cardiovascular causes, MI, stroke or stent thrombosis). Among the patients assigned to receive long-term dual antiplatelet therapy, as compared with those assigned to receive short-term clopidogrel plus aspirin, there was a roughly two-fold greater risk of type 5, 3 or 2 (hazard ratio, 2.17, 95% CI, from 1.44 to

3.22;p=0.00018) (Figure below) as well as type 5 or 3 bleeding events (hazard ratio, 1.78, 95% CI, from 1.02 to 3.13;p=0.037) according to the Bleeding Academic Research Consortium classification[70]. The risks of TIMI defined major bleeding and red blood cell transfusions were also increased in the 24-month clopidogrel group. Consistent findings were also obtained by applying the Bleedscore.

Figure 3: PRODIGY Kaplan-Meier estimate of seconday endpoint



4.2.2.3 Ticagrelor

Ticagrelor, a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor P2Y12, provides faster, greater, and more consistent P2Y12 inhibition than clopidogrel. Currently, ticagrelor is approved in use in patients with acute coronary syndrome. In a dose-guiding trial, there was no significant difference in the rate of bleeding with the use of ticagrelor at a dose of 90 mg or 180 mg twice daily and the rate with the use of clopidogrel at a dose of 75 mg daily. However, dose-related episodes of dyspnea and ventricular pauses on Holter monitoring, which occurred more frequently with ticagrelor, led to the selection of the dose of 90 mg twice daily for Phase III study (Platelet Inhibition

and Patient Outcomes (PLATO)[35]. PLATO was a multicenter, randomised, double blind trial. Patients were eligible for enrolment if they were hospitalized for an acute coronary syndrome, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours. For patients who had an acute coronary syndrome without ST-segment elevation, at least two of the following three criteria had to be met: ST-segment changes on electrocardiography, indicating ischemia; a positive test of a biomarker, indicating myocardial necrosis; or one of several risk factors (age ≥60 years; previous MI or coronary-artery bypass grafting (CABG); coronary artery disease with stenosis of ≥50% in at least two vessels; previous ischemic stroke, transient ischemic attack, carotid stenosis of at least 50%, or cerebral revascularisation; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction, defined as a creatinine clearance of <60 ml per minute per 1.73 m2 of body surface area). For patients who had an acute coronary syndrome with ST-segment elevation, the following two inclusion criteria had to be met: persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a new left bundle-branch block, and the intention to perform primary PCI. Major exclusion criteria were any contraindication to the use of clopidogrel, fibrinolytic therapy within 24 hours before randomisation, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer.

Patients were randomly assigned to receive ticagrelor or clopidogrel, administered in a double-blind, double-dummy fashion. Ticagrelor was given in a loading dose of 180 mg followed by a dose of 90 mg twice daily. Patients in the clopidogrel group who had not received an open-label loading dose and had not been taking clopidogrel for at least 5 days before randomisation received a 300-mg loading dose followed by a dose of 75 mg daily. Others in the clopidogrel group continued to receive a maintenance dose of 75 mg daily.

Patients undergoing PCI after randomisation received, in a blind fashion, an additional dose of their study drug at the time of PCI: 300 mg of clopidogrel, at the investigator's discretion, or 90 mg of ticagrelor for patients who were undergoing PCI more than 24 hours after randomisation. In patients undergoing CABG, it was recommended that the study drug be withheld - in the clopidogrel group, for 5 days, and in the ticagrelor group, for 24 to 72 hours. All patients received acetylsalicylic acid (aspirin) at a dose of 75 to 100 mg daily unless they could not tolerate the drug. For those who had not previously been receiving aspirin, 325 mg was the preferred loading dose; 325 mg was also permitted as the daily dose for 6 months after stent placement.

The primary endpoint occurred significantly less often in the ticagrelor group than in the clopidogrel group (in 9.8% of patients vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). The difference in treatment effect was apparent within the first 30 days of therapy and persisted throughout the study period. The hierarchical testing of secondary endpoints showed significant reductions in the ticagrelor group, as compared with the clopidogrel group, with respect to the rates of the composite endpoint of death from any cause, MI, or stroke (10.2% vs. 12.3%, P<0.001); the composite endpoint of death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, transient ischemic attack, or other arterial thrombotic events (14.6% vs. 16.7%,

P<0.001); MI alone (5.8% vs. 6.9%, P = 0.005); and death due to vascular causes (4.0% vs. 5.1%, P = 0.001). This pattern was also reflected in a reduction in the rate of death from any cause with ticagrelor (4.5%, vs. 5.9% with clopidogrel; P<0.001). The rate of stroke did not differ significantly between the two treatment groups, although there were more haemorrhagic strokes with ticagrelor than with clopidogrel (23 [0.2%] vs. 13 [0.1%], nominal P = 0.10). Concerning our first secondary objective of ascertaining the effect in patients for whom invasive treatment was planned, the rate of the primary endpoint was also lower with ticagrelor (8.9%, vs. 10.6% with clopidogrel; P = 0.003). Among patients who received a stent during the study, the rate of definite stent thrombosis was lower in the ticagrelor group than in the clopidogrel group (1.3% vs. 1.9%, P = 0.009). The results regarding the primary endpoint did not show significant heterogeneity in analyses of the 33 subgroups, with three exceptions. The benefit of ticagrelor appeared to be attenuated in patients weighing less than the median weight for their sex (P = 0.04 for the interaction), those not taking lipid-lowering drugs at randomisation (P = 0.04 for the interaction), and those enrolled in North America (P = 0.045 for the interaction). In the ticagrelor group, there was a higher rate of non–CABG-related major bleeding according to the study criteria (4.5% vs. 3.8%, P = 0.03) and the TIMI criteria (2.8% vs. 2.2%, P = 0.03). With ticagrelor as compared with clopidogrel, there were more episodes of intracranial bleeding (26 [0.3%] vs. 14 [0.2%], P = 0.06), including fatal intracranial bleeding (11 [0.1%] vs. 1 [0.01%], P = 0.02). However, there were fewer episodes of other types of fatal bleeding in the ticagrelor group (9 [0.1%], vs. 21 [0.3%] in the clopidogrel group; P = 0.03).

In PLATO, the observed regional effect was substantial (HR, 1.25 in North America, 1.27 in the United States, and 0.84 overall) and carried potential clinical and regulatory implications, should it be true [71,72]. Thus, after the exclusion of systematic errors or differences in study conduct between regions, it was important to explore whether these findings might be due to chance or could be explained by some baseline or post-randomisation factor.

Comprehensive statistical analyses of treatment interactions with baseline and post-randomisation factors, including two different analytic approaches, one based on Cox analysis and the other based on landmark analyses, independently identified aspirin dose as a potential factor explaining in part the treatment-by-region interaction observed [71,72]. These analyses also excluded as explanations many investigated pre-randomisation and post-randomisation factors. By both statistical analyses, high-dose aspirin was associated with a higher HR for the primary end point with ticagrelor compared with clopidogrel in both the United States and the rest of the world. Within the ticagrelor group, the lowest event rates were observed in patients receiving low-dose aspirin and the highest in those receiving high-dose aspirin. In contrast, event rates in clopidogrel-assigned patients were similar to rates with high or low-dose aspirin.

Currently, no definitive biological rationale explains why ticagrelor should be less effective than clopidogrel in the presence of a high aspirin maintenance dose. However, there are some potential hypotheses to explain why higher aspirin doses may attenuate the treatment effect of ticagrelor.

Aspirin exerts an antithrombotic effect through inhibition of platelet cyclooxygenase, thus reducing thromboxane A2 release, but it also inhibits endothelial release of prostacyclin in a dose-dependent fashion at daily doses >80 mg. Prostacyclin reduces platelet reactivity and may contribute synergistically *in vivo* to the antiplatelet effects of P2Y12 inhibitors.

Consequently, the therapeutic effects of a higher mean level of P2Y12 inhibition, as achieved by ticagrelor in the PLATO study compared with clopidogrel,[35] may be attenuated when endogenous prostacyclin production is inhibited. The effects of aspirin on platelet reactivity are relatively limited compared with P2Y12 inhibition[10] Furthermore, it has been suggested that P2Y12 inhibition alone may partially inhibit platelet thromboxane A2 synthesis,[11,12] and in the presence of strong P2Y12 inhibition, the additional effects of higher aspirin doses may result in a reduction of prostacyclin release, potentially shifting the influence of aspirin to a prothrombotic effect[13] Consistent with the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT/OASIS 7) trial[73], no association of aspirin maintenance dose with ischemic event rates in the clopidogrel group was observed. Further investigations in vitro and in animals and humans, and preferably prospective randomised, controlled trials, are needed to understand the role of these complex pathobiological interactions. Therefore, current data would suggest that ticagrelor may be more effective when a low dose of aspirin is concomitantly administered to patients taking the drug. It remains therefore possible that ticagrelor monotherapy may not result in lower efficacy whereas the omission of concomitant aspirin may improve the safety profile of the treatment. This hypothesis is supported by the findings of the Management of ATherothrombosis with Clopidogrel in High-risk patients (MATCH) trial [74]. Authors compared aspirin (75 mg/day) with placebo in 7599 high-risk patients with recent ischemic stroke or transient ischemic attack and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/day. Duration of treatment and follow-up was 18 months. The primary endpoint was a composite of ischemic stroke, MI, vascular death, or re-hospitalisation for acute ischemia (incl. re-hospitalisation for transient ischemic attack, angina pectoris, or worsening of peripheral arterial disease). Analysis was by intention to treat, using logrank test and a Cox's proportional-hazards model. 596 (15.7%) patients reached the primary endpoint in the group receiving aspirin and clopidogrel compared with 636 (16.7%) in the clopidogrel alone group (relative risk reduction 6.4%, [95% CI –4.6 to 16.3]; absolute risk reduction 1% [–0.6 to 2.7]). Life-threatening bleedings were higher in the group receiving aspirin and clopidogrel versus clopidogrel alone (96 [2.6%] vs 49 [1.3%]; absolute risk increase 1.3% [95% CI 0.6 to 1.9]). Major bleedings were also increased in the group receiving aspirin and clopidogrel but no difference was recorded in mortality. Authors concluded that adding aspirin to clopidogrel in high-risk patients with recent ischemic stroke or transient ischemic attack is associated with a non-significant difference in reducing major vascular events. However, the risk of life threatening or major bleeding is increased by the addition of aspirin. Importantly, adding aspirin on top of clopidogrel also led to a significant increase of symptomatic intracranial haemorrhage. Emerging mechanistic data would also suggest that once the P2Y12 pathway is fully blocked with ticagrelor, the additional value of aspirin to further inhibit platelet activity is marginal. This further supports the concept that the addition of aspirin to ticagrelor may increase the bleeding events disproportionally with respect to the contribution of this drug to the prevention of ischemic endpoints.

In the PLATO trial dyspnea was more common in the ticagrelor group than in the clopidogrel group (in 13.8% of patients vs. 7.8%). Few patients discontinued the study drug because of dyspnea (0.9% of patients in the ticagrelor group and 0.1% in the clopidogrel group).

5. STUDY OBJECTIVE

5.1 Primary Objective

To demonstrate in *all-comers* patients, undergoing percutaneous coronary intervention (PCI) under standardised treatment (including the use of the BioMatrix family of drug-eluting stents and bivalirudin), whether treatment with 1 month of ticagrelor plus aspirin followed by 23 months of ticagrelor monotherapy at two years is superior with respect to all-cause mortality or non-fatal new Q-wave MI compared to treatment with 12-month standard DAPT, being aspirin plus ticagrelor in ACS patients and aspirin plus clopidogrel in stable patients, followed by 12 months of aspirin monotherapy.

5.2 Secondary Objectives

The key secondary safety objective is to compare the occurrence of investigator-reported clinically relevant bleeding events between the experimental treatment strategy and the reference treatment strategy in an all-comers patient population undergoing PCI.

Other secondary objectives of the study will include the assessment of the independent components of the primary composite endpoint of all-cause mortality and non-fatal new Q-wave MI up to two years between the experimental treatment strategy and the reference treatment strategy.

The following data will be collected in the CRF as *investigator-reported* information but will not be adjudicated by a Clinical Event Committee:
- Safety endpoint: a composite of BARC3 or BARC5 bleeding according to BARC definitions[70] up to 2 years
- Ischemic stroke up to 2 years follow-up
- Haemorrhagic stroke up to 2 years follow-up
- Composite of all-cause mortality, stroke and non-fatal new Q-wave MI up to 2 years follow-up
- Coronary revascularisation up to 2 years follow-up
- Definite stent thrombosis up to 2 years follow-up

6. TRIAL DESIGN

6.1 Design Overview

This is an investigator-initiated, prospective, multi-centre, multi-national, randomised, open-label superiority trial, testing two different pharmaco strategies in patients following coronary artery stenting:

A. **Experimental treatment strategy:**
Anti-thrombotic treatment with ticagrelor and aspirin for 1 month followed by 23 months of ticagrelor monotherapy.

B. **Reference treatment strategy:**
Anti-thrombotic treatment with DAPT for 12 months, being aspirin plus ticagrelor in ACS patients and aspirin plus clopidogrel in stable patients, followed by an additional 12 months of aspirin monotherapy.

Subjects who do not violate any of the predefined exclusion criteria and have provided informed consent will be randomly assigned in a 1:1 fashion to one of the two pharmaco treatment strategies and will undergo PCI with the BioMatrix family of drug-eluting stents (see figure 4).

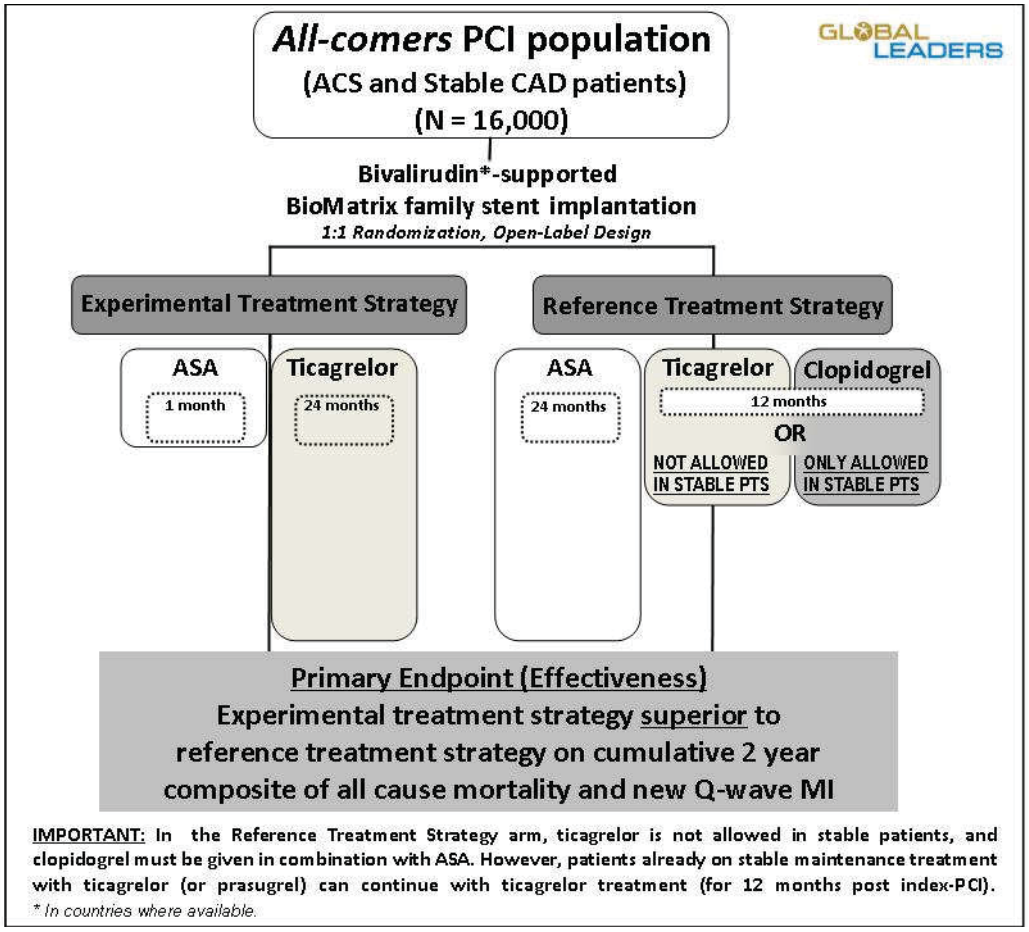
Randomisation will be performed via web-based software with random, permuted blocks at the time of the index procedure prior to PCI. Subjects will be stratified according to centre and according to the indication for PCI (Stable Coronary Artery Disease (CAD) vs. Acute Coronary Syndrome (ACS)).

The study will be conducted at approximately 60-80 interventional cardiology centres in Europe, North America, South America, and Asia-Pacific.

An independent Data Safety and Monitoring Board (DSMB) will monitor the individual and collective safety of the patients enrolled in the study on an ongoing basis. A DSMB Charter, signed by the DSMB members, is maintained by ECRI with roles and responsibilities of the DSMB members.

Angiography data (Syntax Score) and ECGs (post-PCI and at 3 months and 2 years follow-up) will be analysed off-line by an independent Core Lab. The Core Lab will be blinded to the treatment arms. All treatment information will be removed from review material, if applicable.

Figure 4: Schematic diagram of trial design



Multiple target vessel treatment is allowed either within the index procedure or as a staged procedure. However, **staging of the index PCI is only allowed within 3 months after the first part of the PCI.**

In the experimental treatment arm:

- **In the case of a staged procedure or a reintervention – PCI or CABG – (other than for definite stent thrombosis or STEMI), the 30-day treatment period with ASA should re-start at the time of the staged procedure or reintervention.** The patient remains on ticagrelor for 2 years following the start of the index procedure.
- **In case a surgery reguires discontinuation of ticagrelor, the anti-coagulation regimen is left at the discretion of the investigator. However the following is advised:**
    - **For surgery within 1 month of index procedure: keep the patient on aspirin (75-100 mg qd) and stop ticagrelor at least 72 hours before the surgery. Ticagrelor treatment should be resumed as soon as possible in the post-operative period.**

- **For surgery more than 1 month after index procedure: restart 30-day aspirin treatment (75-100 mg qd) and stop ticagrelor at least 72 hours before the surgery. Ticagrelor treatment should be resumed as soon as possible in the post-operative period.**

The study drug ticagrelor will be provided free of charge for the 2-year period of patients in the experimental treatment arm and in the 12-month period of patients in the ACS-stratified arm of the reference treatment arm.

In the reference treatment strategy arm: If a stable/elective patient is taking clopidogrel but subsequently develops STEMI (i.e. post-index PCI in the follow-up phase), the patient can switch to, for example, ticagrelor at the physician's discretion. **Important: Switching to ticagrelor in the reference treatment arm – after randomisation - is considered a medical need and will not be covered by trial drug supply.**

All patients will be followed for two years post-procedure. **For patients undergoing a staged procedure in either arm, the 2-year follow-up period will be calculated from the date of the *start* of the index procedure.** After two years, the medical therapy regimen is left to the discretion of the physician.

7. STUDY ENDPOINTS

7.1 Primary Endpoint

The composite of all-cause mortality or non-fatal new Q-wave MI up to 2 years post-randomisation.

7.2 Secondary Endpoints

Safety endpoint:

A composite of investigator-reported BARC3 or BARC5 bleeding according to BARC definitions up to 2 years post-randomisation.

Components of the primary composite endpoint up to 2 years:

- All-cause mortality
- Non-fatal new Q-wave MI

Investigator reported endpoints up to 2 years:

- Ischemic stroke, including stroke of undetermined cause
- Haemorrhagic stroke
- Composite of all-cause mortality, stroke and non-fatal new Q-wave MI
- Coronary revascularisation
- Definite stent thrombosis

7.3 Trial Endpoint Definitions

Detailed information about the trial endpoint definitions and other clinical/angiographic definitions can be found in Appendix I.

8. STUDY POPULATION

8.1 Sample Size

A total of 16,000 subjects will be enrolled in approximately 50-80 international interventional cardiology sites during an expected enrolment period of approximately 9 months.

8.2 Type of Patients

Subjects either male or female eligible for percutaneous coronary intervention (PCI) with lesions suitable for stent implantation who meet all eligibility criteria specified below and provide written informed consent will be included. Of note, inclusion criteria will be kept comprehensive to reflect routine clinical practice (i.e. "real world, all-comers" patients).

8.3 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for treatment in the study:

1. Age ≥18 years;
2. Presence of one or more coronary artery stenoses of 50% or more in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation. The vessel should have a reference vessel diameter of at least 2.25 mm (no limitation on the number of treated lesions, vessels, or lesion length);
3. Able to provide informed consent and willing to participate in 2 year follow-up period.

8.4 Exclusion Criteria

Subjects must be excluded from the study if any of the following criteria are met:

Drug- related	1.	Known intolerance to aspirin, P2Y12 inhibitors, bivalirudin, stainless steel or biolimus;
	2.	Known intake of a strong CYP3A4 inhibitor (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor;
	3.	Known moderate to severe hepatic impairment (alanine-aminotransferase ≥ 3 x ULN);
Treatment-related	4.	Planned surgery, including CABG as a staged procedure (hybrid) within 12 months of the index procedure, unless dual antiplatelet therapy is maintained throughout the peri-surgical period;
	5.	Need for chronic oral anti-coagulation therapy;
Medical	6.	Active major bleeding or major surgery within the last 30 days;
	7.	Known history of intracranial haemorrhagic stroke or intra-cranial aneurysm;
	8.	Known stroke (any type) within the last 30 days;
General	9.	Known pregnancy at time of randomisation;
	10.	Female who is breastfeeding at time of randomisation
	11.	Currently participating in another trial before reaching primary endpoint.

9. STUDY PROCEDURES

9.1 Patient Information

Eligible patients must sign informed consent prior to undergoing any study-specific procedures and prior to receiving any study-related medication. A summary of the trial time schedule is provided on page 12.

9.2 Patient History

At inclusion in the study, the following routine examinations will be captured:

1. Physical examination, relevant medical and cardiac history and concomitant medication;
2. Anginal status;
3. Full angiogram for Syntax Score assessment. **Please note that both the right coronary artery (RCA) and left coronary artery (LCA, incl. LAD and LCX) must be imaged.** The pre-procedure diagnostic angiogram should be sent to the Angiographic Core Lab (see Chapter 14).

Known pregnancy is an exclusion criterion in this trial, not an exclusion from treatment (e.g. STEMI). All drugs mandated in the Global Leaders trial have been used in the trial's treatment scenarios and should be used according to their labelling. The investigator should weigh risks and benefits of treatment given the subject's specific pathology, and take all necessary precautions. If required by local regulations a pregnancy test is needed before randomisation in elective patients who are not using effective contraceptives to verify that they are not pregnant; such a test is considered impractical in the context of STEMI. Effective contraceptives should be discussed with females of childbearing potential.

9.3 Procedures

9.3.1 Randomisation

Randomisation will be performed via web-based software with random blocks according to centre. Randomisation will occur at the time of the index procedure prior to PCI.

Patients will be randomised to one of two groups:

Experimental treatment strategy
All patients in the treatment group will receive Acetylsalicylic Acid (ASA) and ticagrelor for 1 month followed by 23 months of ticagrelor monotherapy.

Reference treatment strategy
ACS patients incl. unstable angina (UA) patients: ASA and ticagrelor for 12 months followed by 12 months of ASA monotherapy.
Stable CAD patients*: ASA and clopidogrel for 12 months followed by 12 months of ASA monotherapy.
* Biomarker negative, no clinical signs and/or symptoms of ongoing myocardial ischemia.

9.3.1.1 Stratification

To ensure appropriate distribution of variables that may affect primary endpoints, the randomisation will be stratified based on the indication for PCI (ACS and stable Coronary Artery Disease) and per centre.

9.3.1.2 Measures to minimise/avoid bias

- Randomisation will occur through a module in the eCRF.
- Patients will be randomised at a 1:1 ratio to the experimental or reference treatment strategy. This will result in two groups of an expected equal size.
- Other measures to avoid or minimise bias will include intent-to-treat principles of analysis and blinding of the Core Laboratory to treatment assignments.

9.3.2 Stent implantation

The investigator will choose the appropriate length and diameter of the stents to be implanted by visual estimate.

The choice of the length of the stent should ensure complete coverage of the lesion. If more than one stent is implanted, at least 2 mm overlap should be achieved. In case of insufficient stent expansion, the stent will be post-dilated with an appropriately sized balloon.

For each individual lesion treated, a separate lesion form in the eCRF needs to be completed.

Treatment of multiple target vessels (within the same procedure) and staged procedures which occur within 3 months of the initial implant procedure are allowed.

Staged procedures are defined as interventions planned at the time of the index study procedure. For the purpose of this protocol, the conduct of staged procedures is *strongly discouraged*. If staged procedures are inevitable for medical or logistic reasons, the reason should be documented in the eCRF and patient file. In the "index procedure" form of the eCRF the investigator will indicate this lesion was present at the time of the first procedure. The investigator will also have to complete a "staged procedure" form. The staged procedure should occur within 3 months of the start of the index procedure, and the subject should receive the same type of study stent (BioMatrix family of drug-eluting stents).

If a staged procedure occurs outside the time window of 3 months after the start of the index procedure, it is advised to stay as close as possible to the trial treatment, i.e. implant BioMatrix family of drug-eluting stents. This procedure is considered to be a reintervention and should be reported as a Serious Adverse Event.

Important: In the experimental treatment arm (ASA up to 30 days post index procedure), ASA should be re-started for another 30 days at the time of the staged procedure.

Example 1: For a patient undergoing the final staged procedure 10 days after the start of the index PCI, the 30-day ASA period will end 40 days after the index PCI.

Example 2: For a patient undergoing the final staged procedure 45 days after the start of the index PCI, the patient should receive ASA for 30 days after the index PCI, then discontinue for 14 days and then re-start ASA for 30 days at the time of the staged procedure.

For patients undergoing a staged procedure, the follow-up schedule will be calculated from the date of the start of the index procedure. *Example*: For a patient undergoing the final staged procedure 10 days after the index PCI, the 30-day follow-up visit will still be on day 30 post index PCI.

9.3.3 Drug treatment

For patients not previously exposed to ASA, a loading dose of ASA 325 mg (160-500 mg allowed) or 250-500 mg i.v. should be administered. For patients already on ASA, a maintenance dose of 75mg qd (- ≤ 100 mg qd) should be administered as the first dose and continued thereafter as per protocol.

Patients assigned to a ticagrelor treatment who are P2Y12 inhibitor naïve, will receive a loading dose of 180 mg (two 90 mg tablets). For patients already on ticagrelor, a maintenance dose of 90mg should be administered as the first dose and continued thereafter at 90 mg b.i.d. as per protocol. For patients who have been assigned to ticagrelor who are not P2Y12 inhibitor naïve, the following switching strategy is recommended:

Previous exposure to clopidogrel: Ticagrelor at a loading dose of 180 mg should be given and continued at 90 mg b.i.d. irrespective of previous clopidogrel maintenance or loading regimen.

Previous exposure to prasugrel: in patients who have received prasugrel at 60 mg loading dose within 5 days prior to randomisation, and continued thereafter with a daily 10 or 5 mg maintenance regimen without interruption, ticagrelor 90mg should be administered as the first dose and continued thereafter at 90 mg b.i.d. as per protocol. For patients who started prasugrel therapy with or without loading dose more than 5 days prior to randomisation, or for patients who discontinued prasugrel for 1 day or more within 5 days prior to randomisation or for those who started prasugrel therapy within 5 days without the on-label 60 mg prasugrel loading dose, ticagrelor should be started with a loading dose of 180mg followed by 90 mg b.i.d. as per protocol.

Patients assigned to a clopidogrel treatment who have not yet received a loading dose of clopidogrel or have not been taking prasugrel for ≥5 days before randomisation will receive a 600 mg loading dose. For patients already on clopidogrel, a maintenance dose of clopidogrel study drug 75 mg qd should be administered as the first dose.

In patients undergoing CABG or any other unplanned surgery, it is recommended that the study drug be withheld — in the clopidogrel group, for 5 days, and in the ticagrelor group, for 72 hours prior to the surgery.

Ticagrelor is manufactured and provided free of charge by AstraZeneca to participating sites. At each visit, patients will be dispensed enough ticagrelor tablets (with adequate overage) to last until their next visit.

Ticagrelor tablets are presented as 90mg, film-coated tablets and supplied in HDPE (heavy duty polyethylene) bottles, with child resistant caps and tamper evident induction seals. All tablet bottles contain 130 tablets, providing a 2 monthly pack. Fisher Clinical Services have been contracted to undertake ticagrelor packaging, labelling and distribution activities for this trial. Labelling (including translations) will be the responsibility of Fisher Clinical Services and will be compliant with Annex 13 of the Good Manufacturing Guidelines (GMP) and all applicable local regulatory requirements. No drug will be distributed to participating centres unless ECRI is satisfied that the required approvals and agreements and initiation procedures are complete. The sites ongoing supply requirements will be monitored between ECRI and Fisher Clinical Services.

Discontinuation of ticagrelor for intolerance

In line with the PLATO trial, discontinuation of ticagrelor therapy due to known side effects, such as dyspnea, may occur but in such cases patients should be placed on standard dose of prasugrel (i.e. 10 mg qd) IF INDICATED and otherwise clopidogrel (there will be patients with contra-indications to prasugrel and there will be patients with NO INDICATION for prasugrel (e.g. elective patients)).

Anti-coagulation

All patients will receive anticoagulation with bivalirudin during PCI (in the countries where bivalirudin is approved). Bivalirudin should always be given as an IV bolus of 0.75 mg/kg followed immediately by an IV infusion of 1.75 mg/kg/h for at least the duration of the PCI. The 1.75 mg/kg/hour IV infusion may be continued for up to 4 hours post-PCI as clinically warranted. After this, a reduced IV infusion dose of 0.25 mg/kg/hour may be continued for up to 12 hours as clinically necessary.

In Europe, the use of bivalirudin is contraindicated for patients with severe renal impairment (GFR <30ml/min) and in patients with moderate renal impairment (GFR 30-59 ml/min) the infusion dose should be reduced to 1.4 mg/kg/hour, while in Canada an infusion dose of 1.0 mg/kg/hour should be considered in patients with severe renal impairment (GFR<30 ml/min). In case of severe renal impairment (GFR <30ml/min) bivalirudin is contra-indicated, however the patient can be included in the trial under the use of heparin under standard clinical practice.

For more detailed instructions on the preparation, administration and approved dosing of bivalirudin please refer to the Package Insert or Summary of Product Characteristics (SPC), the Package Information Leaflet (PIL) and the dosing cards.

In PCI patients treated with bivalirudin, the routine use of GPIIB/IIIA inhibitors is prohibited. Provisional use may be considered for cases with giant thrombus or no reflow at end of PCI.

Important: In case of staging, the anticoagulation during the staged procedure should also be accomplished with bivalirudin as described above.

If the patient needs full anti-coagulant therapy (e.g. in case of CABG or valve replacement) local guidelines should be followed.

9.4 Informed Consent

All potential subjects must be consented prior to undergoing any study-specific procedures and prior to receiving any study-related medication. Once the subject's general eligibility for the study is met, the background of the proposed study and the benefits and risks of the procedures and study must be explained to the subject prior to obtaining informed consent. Only those subjects who sign the Ethics Committee (EC) approved informed consent form prior to any study-specific procedures are candidates for actual enrolment in the study. Failure to provide written informed consent renders the subject ineligible for the study.

In this all-comers study, there may be occasions where the subject cannot sign the EC-approved informed consent form prior to undergoing any study-specific procedures (for instance, in the treatment of STE-ACS subjects). In the event that the subject is unable to consent, a written consent from a legally acceptable representative will be accepted to facilitate the participation in this clinical study. The legal representative may provide written consent – if approved by local IRB regulations – on behalf of the subject only after he or she is fully informed about the study. In case the subject is unable to read, an impartial witness (this can be any person who is independent of this study) must be present during the entire informed consent discussion. Once the subject gives oral consent, the witness must sign and personally date the consent form. This will confirm that the information in this informed consent and any further information provided by the investigator was explained to and understood by the subject and that consent was freely given. In case of the subject's verbal consent or in case a legal representative consents on behalf of the subject, the subject will be asked to sign the consent form himself/herself when the investigator decides the subject is able to understand the contents of the subject information sheet and is able to sign and date the informed consent form.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of obtaining informed consent confirms the subject's willingness to participate in the study. It is the investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP, EC requirements and country specific regulations.

See Appendix II for "Patient Information and Informed Consent Form".

9.5 Hospital Discharge (post-PCI to hospital discharge)

At discharge, from the hospital where the index procedure took place, an assessment of the patient's clinical status will be performed. Assessment of the cardiovascular drug use and any Serious Adverse Events will be recorded. An ECG will be performed and an anonymised copy of the ECG (showing patient ID and recording date) should be sent to the ECG Core Lab (see Chapter 14).

9.6 Follow-up Period

Patients will be followed after hospital discharge for up to 2 years after the index procedure (in case of a staged index procedure: for up to 2 years after the start of the index procedure). This includes 6 clinic visits (at 1 month, 3 months, 6 months, 1 year, 1.5 years, and 2 years) to obtain information regarding cardiovascular drug use, hospitalisations and serious adverse events. A summary of required follow-up procedures is given in Section 2: Schedule of Investigations.

In case of definite stent thrombosis or STEMI, patients will be treated according to best clinical practice. Patients will stay in the study (intention-to-treat) and will be required to return for all follow-up visits.

In case of subsequent unplanned repeat intervention in absence of definite stent thrombosis or STEMI, the physician should try to adhere to the study stent and treatment strategy, i.e. implant BioMatrix family of drug-eluting stents and stick to the original assigned treatment in terms of duration of DAPT (meaning 30 days of aspirin with continuation of ticagrelor in the experimental arm, or 12 months of ticagrelor/clopidogrel and aspirin in the reference arm).

If, at any time during the trial, the patient requires anticoagulation and is taking ticagrelor, the patient will be switched to clopidogrel. This means that a patient in the experimental arm will be on ASA, clopidogrel and anticoagulant in the first month, and thereafter only on clopidogrel and anticoagulant; in the reference treatment arm, the patient will be on clopidogrel, ASA and anticoagulant in the first month, and also thereafter.

In case of bleeding, *management* is not different in the two arms of study, and the patient should be maintained as long as possible in his/her treatment arm.

9.6.1 Hospital visits at 1 month (+14 days), 3 months (+14 days), 6 months (+30 days), 1 year (+ 30 days), 1.5 years (+30 days) post-procedure

An assessment of the cardiovascular drug use and any Serious Adverse Events, including possible bleedings, will be recorded during clinical follow-up visits. Information will be requested from the patients regarding their adherence to medication intake, including the antiplatelet therapy treatment prescribed by the physician and the reason for discontinuation, duration and type of therapy prescribed.

At the 3-month follow-up visit, an ECG is required. An anonymised copy of the ECG (showing patient ID and recording date) should be sent to the ECG Core Lab (see Chapter 14).

For treatment compliance, patients will be asked if they are taking the study medication at each visit. The following compliance will be checked:

1. Never missed a dose
2. Interrupted for 1 day
3. Interrupted for 2-3 consecutive days
4. Interrupted for 4-5 consecutive days
5. Fully discontinued

Missed doses of ticagrelor should not be made up for, i.e. if a dose is missed, the next regularly scheduled dose should be taken and should not be doubled. An exception to this approach is if a patient has been off study medication and then has an acute coronary syndrome or needs to undergo urgent percutaneous coronary intervention. In this case, patients should take loading doses.

During the follow-up, the patient will be provided with sufficient medication to cover the period until the next follow-up hospital visit. Patients should be advised to finish taking all the pills in one bottle before starting on the next.

The subject's General Practitioner (GP) will be informed of the subject's participation in the trial by means of a letter from the investigator. Information will be included on the treatment strategies.

9.6.2 Final hospital visit at 2 years (+ 30 days) post-procedure

An assessment of the cardiovascular drug use and any Serious Adverse Event, including possible bleedings, will be recorded. Information will be requested from the patients regarding their adherence to medication intake, including the antiplatelet therapy treatment prescribed by the physician and reason for discontinuation, duration and type of therapy prescribed. After the final follow-up visit, study medication will no longer be provided and the patient should continue treatment according to standard hospital practice.

At the final 2-year follow-up visit, an ECG is required. An anonymised copy of the ECG (showing patient ID and recording date) should be sent to the ECG Core Lab (see Chapter 14).

9.7 Withdrawal from the Study

After entering into the study, the patients are asked to complete all scheduled follow-up visits. Patients will be exempt from follow-up only if they withdraw their consent.

Every patient should be encouraged to remain in the study until he/she has completed the protocol requirements during the 2-year follow-up period.

Possible reasons for premature discontinuation may include, but are not limited to, the following:

- Withdrawal of consent: Patient decides to withdraw from the study. The decision must be an independent decision that is documented in the patient study files.
- Physician discretion: The investigator may choose to withdraw a patient from the study if he/she considers follow-up too burdensome for the patient.
- Lost to follow-up: All patients should be encouraged to return for all scheduled follow-up visits, and to provide appropriate contact information to accommodate completion of required telephone follow-ups. The investigator will attempt to contact the patient at each follow-up visit, independent of any missed follow-ups. The investigator should make 3 documented attempts per required follow-up visit.

Patients who have discontinued the trial prematurely will not be replaced.

10. STUDY TERMINATION

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms, dose steps, centres]) at any time, which may be due but not limited to the following reasons:

- If the risk-benefit ratio becomes unacceptable owing to, for example:
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate, drop-out rate, data quality, protocol compliance) does not suggest a proper completion of the trial within a reasonable timeframe.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the last reason). The EC/competent authority needs to be notified about the end of the trial (last subject/subject out) or early termination of the trial.

The investigator has the right to close his/her centre at any time under the conditions stipulated in the Participating Site Agreement.

The DSMB will have the responsibility of recommending early termination of the study to the Steering Committee and the sponsor, which will have ultimate authority/responsibility for making the decision. The criteria that the DSMB will follow to determine whether/when to recommend termination of the study will be detailed in a separate DSMB Charter.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. EC(s)/IRB(s), competent authority(ies), study centre, head of study centre) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

11. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1 General Considerations

The Global Leaders trial has a 1:1 randomised design comparing two types of anti-platelet regimens. The schedule in paragraph 2.1.1 gives an overview of the two treatment arms.

Analyses will be undertaken by a statistician of an academic clinical trials unit in STATA (version 11.0 or higher). Comparison groups will be coded during all analyses, and the statistician and his/her supervisor will be blinded to the allocated treatments. Principal Investigators will have full access to the data and will vouch for the data and the analyses.

11.2 Populations

11.2.1 Intention-to-treat population

All patients who undergo randomisation will be included in the primary analysis of clinical outcome in the groups to which they were originally allocated to (intention-to-treat principle).
Analysis of the primary composite endpoint and secondary endpoints will be performed according to the intention-to treat principle in the intention-to-treat population.

11.2.2 Per protocol population

Definition and analysis of a per-protocol population will depend on assessing drug intake and compliance with the protocol.

11.3 Statistical Analysis

11.3.1 Methods used

The primary and all secondary endpoints will be analysed using the Mantel-Cox method accompanied by the log rank test to calculate corresponding p-values. Corresponding survival curves will be constructed using Kaplan-Meier estimates. Baseline characteristics will be described using counts and percentages if categorical, and means and SD, if continuous. We will use Stata (version 11.2 or higher) for all analyses.

11.3.2 Analysis of the primary endpoint

The primary endpoint of a composite of all-cause mortality and non-fatal new Q-wave MI at 2 years post-randomisation will be analysed according to the intention-to-treat principle in the intent-to-treat population.

11.3.3 Analysis of secondary endpoints on intention-to-treat-population

Secondary endpoints as specified in the protocol will be analysed according to the intention-to-treat principle in the intent-to-treat population.

11.3.4 Analysis on per-protocol population

Per-protocol analyses of the primary composite effectiveness endpoint and secondary safety endpoint will be performed as sensitivity analyses.

11.3.5 Stratified analysis

Stratified analysis of the primary endpoint will be performed according to the following patient characteristics (presence or absence):

- ACS (vs stable CAD)
- Age ≥75 yr (vs age <75 years)
- Female gender (vs male gender)
- Diabetic patients (vs non-diabetic patients)
- Geographic Region: West Europe vs Eastern Europe vs Asia vs Canada vs South America.
- Renal function: Creatinine Clearance > 60 ml/1.73m²/min (vs ≤ 60 ml/1.73m²/min based on the MDRD formula)
- History of peripheral vascular disease (symptoms, confirmed stenosis of ≥ 50%, or treatment)

Angiographic characteristics (pre-procedural):

- (Logistic) Syntax Score
- Left Main involvement

Stratified analyses will be accompanied by a χ^2 test to assess interaction between treatment effect and characteristics used for stratification.

11.3.6 Landmark analyses

Landmark analyses will be performed according to 2 pre-specified landmark points at 30 days and at 1 year (365 days), with RR calculated separately for events up to the landmark point and for events occurring after the landmark point up to 2 years. For each type of event, patients will be censored at the time of the first event—a patient who experienced an event contributing to the primary composite endpoint during the first year, for example, will be censored at the time of the event and excluded from the analysis of subsequent years after the landmark point. Landmark analyses will be accompanied by a test for interaction between treatment effect and time (before versus after the landmark point).

11.3.7 Sample size calculation

The primary outcome variable is a composite of all-cause mortality or non-fatal new Q-wave MI at 2 years after stent implantation and will determine whether the experimental treatment strategy is superior to the reference treatment strategy. The assumptions regarding event rate for the composite of all-cause mortality and Q-wave MI are based on actual data of the Biolimus arm in the Leaders trial at 2 years after the index procedure.

With an expected event rate of 5.0% within the experimental treatment strategy at 2 years and a two-sided Type I error of 5%, we estimate that the sample size of 8000 patients per arm will provide 84% power to detect a 20% relative risk reduction and 92% power to detect a 22.5% relative risk reduction of the experimental treatment strategy as compared with the control treatment strategy. The table below presents the power according to relative risk reductions of 25%, 22.5% and 20% and 17.5%, respectively:

Treatment effect (%)	Power (%)	Attrition rate (%)	Total sample size
17.5	73	4	16.000
20.0	84	4	16.000
22.5	92	4	16.000
25.0	96	4	16.000

12. SAFETY REPORTING

The investigator will monitor the occurrence of Serious Adverse Events (SAEs) for each subject during the course of the study. For the purpose of this protocol, the reporting of SAEs begins directly after randomisation. All Adverse Events (AEs) reported by subject, observed by the investigator, or documented in medical records will be listed on the AE Case Report Form pages. The investigator will also report all AEs to the IRB/EC according to the clinical site's reporting requirements.

An SAE form should be completed within 24 hours of the investigator's and study staff's awareness of the event.

12.1 Adverse Event (AE) Definition

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject who has been administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

12.2 Serious Adverse Events (SAEs) Definitions

An AE is classified as "serious" if the event:

- Led to death;
- Led to serious deterioration in the health of a patient that:
  - Resulted in a life threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in patients hospitalisation or prolongation of existing hospitalisation;
  - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

All SAEs will be followed until the event has been resolved (with or without sequelae).

12.3 Anticipated Adverse Reactions

Anticipated adverse reactions for ticagrelor, clopidogrel and ASA in the Summary of Product Characteristics.

12.4 Expected Rate of Adverse Reactions

The rate of adverse reactions for ticagrelor, clopidogrel and ASA are described in the Summary of Product Characteristics.

12.5 Reporting to Competent Authorities and Local EC

Safety reporting to the competent authorities and to local ECs will be in accordance with the "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use" by the European Commission (2011/C 172/01) and in compliance with local country law.

In the Global Leaders study, investigators are instructed to interview each patient carefully at each study visit to determine if an adverse event may have occurred. If an event fulfils the criteria for SAE, then this shall be reported in the eCRF within 24 hours of the clinic study staff having become aware of this, including their judgement regarding causal relationship of the event to the trial. At the time the event is reported in the eCRF, no event-supporting source documentation needs to be sent to the Safety Group, except at the request of the Safety Group (see below).

The Safety Group of the data management CRO scrutinises the study data to identify potential SAEs that have not been described in the Summary of Product Characteristics of ticagrelor, clopidogrel and ASA. For the suspected unexpected serious adverse reactions (SUSARs), the Safety Group may request supporting source documentation from the clinic. The monitoring organisation may be involved to facilitate this. The SUSAR shall then be reported by the Safety Group to the competent authorities within the legal timeframe and in the required data format. Expected Serious Adverse Reactions will not be subject to expedited reporting.

SAEs that are an endpoint in the study (BARC3 or BARC5 bleeding according to BARC definitions, all-cause mortality, non-fatal new Q-wave MI, overall ischemic stroke, coronary revascularisation, and definite stent thrombosis) will not be subject to expedited reporting, as these events are considered disease related. This reporting scheme is similar to that of the PLATO study[35]. All-cause mortality cases that are unexpected and suspected to be related to ticagrelor, clopidogrel and/or ASA will not be excluded from expedited reporting. In addition to SAEs that are endpoints, myocardial ischemia related events other than new Q-wave MI (e.g. non Q-wave MI, unstable angina pectoris, stable angina pectoris and silent ischemia) are also considered disease related and therefore will not be subject to expedited reporting

All (S)AEs will be MedDRA coded by the Safety Group. This allows categorising them by body system, which facilitates their reporting as frequency counts to competent authorities, local ethics committees yearly, as well as to the Data Safety Monitoring Board (DSMB) on a monthly basis or more frequently if requested by the DSMB.

In addition to the above, the investigator must collect post index PCI a "baseline"12-lead ECG of each patient. An independent ECG Core Lab will compare the 3-month and 2-year follow-up ECGs to the baseline ECG to identify the occurrence of new pathological Q-wave myocardial infarction during follow-up. This information will be supplied to DSMB in a timely fashion as well.

12.6 Data Safety Monitoring Board (DSMB)

Serious adverse events (events leading to serious disability or admission to hospital, life-threatening events or death) will be periodically reviewed and analysed by an independent DSMB. Members of this board are not affiliated with any (interventional) cardiology site enrolling patients into the trial, are not participating in the trial, and will declare any conflicts of interest should they arise.

The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB Charter. Based on safety data, the DSMB may recommend that the Steering Committee modify or stop the clinical trial. All final decisions regarding clinical trial/investigation modifications, however, rest with the Steering Committee.

All analyses are carried out aiming to protecting the safety of the trial participants, in particular with respect to the incidence of all-cause mortality, Q-wave MI and their composite. If the data at hand suggests a substantial safety concern about the experimental treatment strategy, the DSMB will carefully balance the observed risk profile against possible signs of improved efficacy. The DSMB will seriously consider recommending early termination of the trial if the experimental treatment strategy shows a statistically significant (two-sided $p < 0.01$) increased rate of all-cause mortality.

The DSMB should only under exceptional circumstances recommend early termination of the trial for overwhelming evidence of effectiveness of the experimental treatment arm, as this would compromise the scientific validity of the final analysis. The DSMB may consider early termination of the trial for effectiveness if the experimental treatment shows a reduced rate of the primary composite endpoint at an stringent significance level of two-sided $p < 0.001$ (Haybittle-Peto boundary), provided that all other effectiveness and safety endpoints strongly and consistently favour the experimental treatment. The DSMB will use all available evidence and its collective judgement as a basis for its recommendation to stop or modify the trial.

12.7 Risk Analysis

In the phase 3 pivotal trial PLATO (PLATelet Inhibition and Patient Outcomes, 18,624 patients), key exclusion criteria included an increased risk for bleeding, clinically important thrombocytopenia or anaemia, previous intracranial bleed, gastrointestinal bleed within the past 6 months and major surgery within the past 30 days. Patients with acute coronary syndromes treated with ticagrelor and ASA showed an increased risk of non-CABG major bleeding and also more generally bleeds requiring medical attention i.e. major and minor PLATO bleeds, but not fatal or life-threatening bleeds.

12.8 Manner in which Risks will be Minimised

The use of ticagrelor in patients at known increased risk of bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. If clinically indicated, ticagrelor should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding). The use of ticagrelor is contraindicated in patients with active pathological bleeding, in patients with a history of intracranial haemorrhage, and in patients with moderate to severe hepatic impairment (see section 4.2.2.3).
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of ticagrelor dosing.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Compliance to Standards and Regulations

The protocol, informed consent form and other study-related documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB) and competent authorities, if applicable. The study will be performed in accordance with the Declaration of Helsinki (Appendix III) and Good Clinical Practices (GCP).

The trial will only start at a clinical site after written approval of the study has been obtained from the appropriate national EC/IRB and the competent authorities.

13.2 Data Recording

It is the expectation of the Sponsor that all data entered into the eCRF has source documentation available at the clinical site. The site must implement processes to ensure this happens.

13.3 Quality Assurance and Monitoring

Monitoring the clinical investigation at the study site is the responsibility of the monitoring organisation through trained and qualified Clinical Research Associates (CRAs).

The CRA will set up **site initiation meetings** for the trial. The agenda and contents of these meetings will be the responsibility of the Sponsor with input from the monitoring organisations and the Steering Committee, and will cover scientific questions and the protocol outline, study requirements, the eCRF, site contracting and remuneration, the Investigator Site File, responsibilities of the study staff to satisfy regulatory and ethical requirements, etc

The Sponsor ultimately decides when all requirements are fulfilled to allow a site to start patient enrollment. The requirements include: country submission to competent authorities, IRB/EC approval, the local contract, study drug on site, protocol and eCRF review (through WebEx meetings, as mentioned above). The decision will mainly be based on feedback from the monitoring organisations.

The monitoring organisation will discuss the investigator's patient enrollment prediction at the time of contracting.

A **baseline monitoring visit** will be scheduled when the first patient has been enrolled. The visit must be performed within 2 to 3 weeks after inclusion of the first patient and data of all enrolled patients have been entered into the eCRF. This serves to confirm the quality of site study execution and to discuss practicalities with the site study staff. During on-site monitoring, the Informed Consent Forms will be checked and a sample of clinical data will be verified against eCRF data. Subject confidentiality will be maintained at all time. Emphasis will be on the complete reporting by the study staff of SAEs as well as the availability of baseline angiograms and per protocol required 12-lead ECGs for the Core Laboratories.

Each clinical site will be visited several times during the study to ensure a high degree of data quality. These **site monitoring visits** will be conducted to verify that the data are authentic, accurate and complete, that the safety and rights of subjects are protected, that the study is conducted according to the protocol, and that any other study agreements, GCP and all applicable regulatory requirements are met. The investigator and the head of the medical institution (where applicable) agree to allow the CRA direct access to all relevant documents. It is important that the investigator and the study staff are available during the monitoring visit and possible audits and that sufficient time is devoted to the process. Findings from the review and source documents will be discussed with the investigator. The number of monitoring visits will depend on Key Performance Indicators (KPI) derived from data management.

Remote site monitoring will also be performed to ensure complete quality study data and patient adherence to the protocol. Each six weeks as a minimum, the monitoring organisation will contact each site to discuss the progress of the study with respect to patient enrollment, timely attendance of patients to their follow-up visits and adherence to allocated antiplatelet treatment, and other relevant study aspects such as data query resolution.

Each participating clinic will receive a **close-out visit** to resolve any outstanding issues, to perform the final source data verification and a final drug accountability check,

There will be regular teleconferences between the Sponsor and the monitoring organisation to discuss site management issues.

13.4 Quality Assurance and Data management

The data collection will be performed through an electronic CRF (eCRF). The investigator or an authorised member of the investigational team must sign all completed eCRFs by using an electronic signature (a password will be provided by the data management centre at the start of the study).

Clinical data management will be performed in accordance with data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. angiographies, ECGs, etc.). Appropriate computer edit programs will be run to verify the accuracy of the database. The investigator will be queried on on incomplete, inconsistent or missing data.

13.5 On-site Audits

To ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit, may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator agrees to cooperate with the Sponsor and/or its designee in the conduct of these audits and provide access to medical records and other relevant documentation, as required. The investigator/institution will be informed of the audit outcome.

Regulatory authorities worldwide may inspect the investigator during and after the study. The investigator should contact the sponsor immediately if this occurs, and must cooperate with the regulatory authority inspections as required.

14. ORGANISATION

14.1 Sponsor

In this investigator-initiated trial, the European Cardiovascular Research Institute (ECRI) will act as Sponsor (ECRI-Trials B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands,). The Sponsor's responsibilities are described in chapter 18.

14.2 Steering Committee

The Steering Committee is responsible of the overall management of the study at the highest level.

The Steering Committee is comprised of eight voting members (PIs, Co-PIs, investigators, ECRI and statistician). Their names, roles and responsibilities are described in a separate Steering Committee Charter.

14.3 Country Leaders

Country Leaders will have an important role in site qualification and selection, and site initiation (through WebEx training). During regulatory submissions, they will help guide the other sites in their country, where required. In case of study management issues (e.g. protocol-related questions), Country Leaders will support the sites and help them to solve any other problems that are particular to their clinic.

The names of the Country Leaders and their roles and responsibilities are listed in the Appendix of the separate Steering Committee Charter.

14.4 Data Safety Monitoring Board (DSMB)

The DSMB is described in section 12.6. The composition, guiding policies and operating procedures governing the DSMB are described in a separate DSMB Charter.

14.5 Data Management

Data management will be conducted by the Clinical Research Organisation (CRO) Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands).

14.6 Site Management and Monitoring

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) will be responsible for site management and monitoring in the European countries. Theorem Clinical Research (headquarters at 1016 West Ninth Ave, King of Prussia PA, 19406, U.S.A.) will be the monitoring organisation for countries outside of Europe.

14.7 Safety Reporting

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for entering Suspected Unexpected Serious Adverse Reactions (SUSARs) from the eCRF in a safety database, for coding all Serious Adverse Events (SAEs) using MedDRA coding and for reporting SUSARs to competent authorities according to European Directive 2001/20/EC and national requirements.

Vigilex (Vigilex B.V., Oudedijk 9B, 3062 AB Rotterdam, The Netherlands) will monitor the data entered by the Safety Team of Cardialysis and the Cardialysis safety reports.

14.8 Packaging, labeling and drug distribution of Study Medication

Fisher Clinical Services (Fisher Clinical Services UK Ltd., Langhurstwood Road, Horsham, West Sussex RH12 4QD, UK) is responsible for the supply of study drug (ticagrelor) to the clinical sites.

14.9 Core Laboratories

14.9.1 Angiography Syntax Score assessment

The independent Angiographic Core Lab at Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) will screen all pre index procedure diagnostic angiograms. Members of the Angiographic Core Lab are not involved as investigators or co-investigators in this study.

The SYNTAX Score will be centrally assessed from the angiograms collected.

14.9.2 ECG

The clinical sites will record ECGs as indicated in the schedule of investigations (section 6.2) and send these for central analysis to the independent ECG Core Lab at Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands)[75].

A missing ECG or a non-interpretable ECG will be queried and the investigator will be requested to forward a new recording.

14.10 Statistical Analysis

Statistical analysis of the study data will be performed by the independent Clinical Trials Unit (CTU) in Bern, Switzerland (Universität Bern, CTU Bern, Finkenhubelweg 11, 3012 Bern, Switzerland).

15. DATA HANDLING AND RECORD KEEPING

15.1 Source Documentation (SD)

Regulations require that investigators maintain information in the patient's medical records that corroborate data collected in the electronic Case Report Form (eCRF). In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained and made available as required by monitors and/or regulatory inspectors:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify investigational plan entry criteria;
- Dated and signed notes on the day of entry into the study, protocol number, clinical site, patient number assigned and a statement that informed consent was obtained;
- Notations on abnormal lab results;
- Adverse events reported and their resolution, including supporting documents such as discharge summaries, cath lab reports, ECGs, lab results;
- Notes regarding investigational plan-required and prescription medications taken during the study (including start and stop dates);
- Study patient's condition upon completion of or withdrawal from the study.

15.2 Case Report Form Complication

All required data will be accurately recorded by authorised personnel documented on the authorised signature log in the eCRF.

15.3 Record Retention

All eCRF information, study records, reports and source documents that support the eCRF must be retained in the files of the responsible investigator for a minimum 2 years following notification by the Sponsor or designee that all investigations have been completed, and will further be retained in accordance with local and international guidelines as identified in the Investigator Site Agreement. This documentation must be accessible upon request by international regulatory authorities or the Sponsor (or designee). The Sponsor or designee must approve archiving or transfer of the documentation for relocation purpose of premises, in writing, prior to the actual file transfer. The investigator must notify the Sponsor, in writing, of transfer location, duration, and the procedure for accessing study documentation. The investigator must contact the Sponsor, or designee, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

If the investigator retires, relocates, or for other reasons withdraws from assuming primary responsibility for keeping the study records, custody per written notice must be submitted to the Sponsor, or designee, indicating the name and address of the person accepting primary responsibility. The EC/IRB must be notified in writing of the name and address of the new custodian.

16. PUBLICATION POLICY

The Steering Committee and investigators are committed to the publication and widespread dissemination of the results of the study. Data from this study will not be withheld regardless of the findings.

The Global Leaders trial is an investigator-initiated and scientifically driven study nested within the European Cardiovascular Research Institute (ECRI) and set up in collaboration with Biosensors, Astra Zeneca and The Medicines Company. All public presentations and manuscript generation and submissions will be led under the auspices of the four Principal Investigators who will organise and lead a Publications Committee. However, this study represents a joint effort between investigators, ECRI and collaborators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

The final locked database will be housed at the data management centre, Cardialysis. Cardialysis will not publicly release data or study-related material, presentations, or manuscripts without the express permission of the four Principal Investigators. All four Principal Investigators will be listed as authors on all abstracts and publications, and as such must agree to their submission. The publication and/or presentation of results from a single trial site are not allowed until publication and/or presentation of the multi-centre results. All single site data for public dissemination must be generated from the central database – local database projects are not permitted. All proposed publications and presentations resulting from or relating to the study (whether from multicenter data or single site analysis) must be submitted to the **Publications Committee** for review and approval prior to submission for publication or presentation.

The Steering Committee will receive any proposed publication and/or presentation materials prior to submission of the presentation or the initial submission of the proposed publication in order for the materials to be timely reviewed by all parties.

17. INVESTIGATOR RESPONSIBILITIES

17.1 Investigator Responsibility/Performance

Prior to starting enrolment of patients, the investigator must read and understand this study protocol, and must sign and date the Protocol Signature page. The Investigator Site Agreement documents agreement to all conditions of the study protocol and agreement to conduct the study accordingly. This study will be conducted in accordance the Declaration of Helsinki and other applicable regulatory requirements or any conditions of approval imposed by the IRB/EC or regulatory authorities.

17.2 Required Documents

The following documents must be submitted to Sponsor, or designee prior to patient enrolment:

- Signed Protocol Signature Page
- Recent signed and dated English Curriculum Vitae (CVs) of the Principal Investigator and co-investigators of the clinical site. These CVs should clearly show the investigator's and co-investigators' qualifications and experience.
- Copy of the written confirmation of the EC/IRB regarding approval of the protocol including version number and date, patient information sheet and informed consent form, including version and date and other adjunctive patient material.
- List of EC/IRB members, including name, title, occupation and any institutional affiliation of each member. If the EC/IRB member list is not available, the General Assurance or EC/IRB Recognition Number should be provided.
- Signed Investigator Site Agreement.

17.3 Ethics Committee (EC) / Institutional Review Board (IRB) Approval

According to the local regulations, the investigator must have all necessary approvals, including written approval from the EC/IRB of the clinical site or other accepted EC/IRB prior to enrolling patients in the study. A copy of the written approval must be provided to Sponsor and should include the following:

- Statement of EC/IRB approval for the proposed study at the clinical site
- Date the study was approved and the duration of the approval
- Listing of any conditions attached to the approval
- Identification of the approved Primary Investigator
- Signature of the EC/IRB chairperson
- Acknowledgement of the Co-Investigators
- EC/IRB approval of the informed consent form (if applicable)
- EC/IRB approval of the final protocol (if applicable).

Any substantial amendments to the protocol, as well as associated consent form changes, will be submitted to the EC/IRB and written approval obtained prior to implementation. Minor changes which do not affect the subject's safety will be subject to notification.

Serious Adverse Event (SAE) reports will be submitted to the EC/IRB as requested by the Sponsor, EC/IRB and/or local regulations. Annual and final reports will be provided to the EC/IRB as required.

17.4 Informed Consent

Study subjects must provide written informed consent using an EC/IRB-approved informed consent form. The study must be explained to the study subjects in lay language. The investigator, or representative, must be available to answer all of the study subject's study-related questions. Study subjects will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated.

17.5 Protocol Deviation

The investigator will report all protocol deviations to the Sponsor and will inform the EC/IRB according to the EC/IRB requirement.

17.6 Drug Storage

All study medication should be kept in a secure place under appropriate storage conditions. The study medication label on the study supplies and the Investigator Brochure specify the appropriate storage conditions (excursions permitted between 15C° and 30C°).

17.7 Reporting Requirements

The investigator should notify the EC/IRB in writing within three months after completion, termination, or discontinuation of the study at the site. The same procedure will be applied to Competent Authority where required.

Site responsibilities for submitting data and reports:

Type of CRF/Report	Completed by Site Within	Process
Adverse Events	Ongoing Basis	Collected in the eCRF
Serious Adverse Event Notification eCRF (including death, MACE)	24 hours	Enter eCRF pages within 24 hours of knowledge of event
Suspected Unexpected Serious Adverse Reactions	24 hours	Enter eCRF pages to within 24 hours
eCRF (Baseline, In-hospital summary, Follow-up, Non-compliance, Reconciliation Form, Patient Withdrawal)	Ongoing basis	Collected in the eCRF
ECGs and Angiographic Films	Ongoing basis	Collected by site and shipped to Core lab within 7 days
Annual Reports	Annually, as requested by EC/IRB	Copy to be provided to Sponsor and EC/IRB
Final Report	Within 3 months of study completion or termination	Copy to be provided to Sponsor and EC/IRB

17.8 Audits / Inspection

In the event that audits are initiated by the Sponsor (or its designee) or national/international regulatory authorities, the investigator allows access to the original medical records and provides all requested information. In the event that audits are initiated by a regulatory authority, the investigator will immediately notify the Sponsor.

18. SPONSOR RESPONSIBILITIES

18.1 Role of ECRI

As Sponsor, ECRI has the overall responsibility for the conduct of the study, including assurance that the study satisfies international standards and the regulatory requirements of the relevant competent authorities.

General duties

Prior to allowing the sites to start enrolling patients into the study, the Sponsor is responsible for selecting investigators, ensuring EC/IRB approvals are obtained where applicable, and signing the Investigator Site Agreement with the investigators and/or hospitals. It is the Sponsor's responsibility to ensure that the study is conducted according to ISO 14155, the Declaration of Helsinki, and other applicable regulatory requirements, the study protocol, and any conditions of approval imposed by the EC/IRB or regulatory authorities. Additionally, the Sponsor will ensure proper clinical site monitoring.

Selection of clinical investigators and sites

The Sponsor will select qualified investigators and facilities which have adequate study patient population to meet the requirements of the investigation.

Training of investigator and site personnel and site monitoring

The training of the investigator and appropriate clinical site personnel will be the responsibility of the Sponsor, or designee, and may be conducted during an investigator meeting, a site initiation visit, or other appropriate training sessions.

Periodic monitoring visits will be conducted frequently enough to ensure that all clinical patient data are properly documented and that the study is properly conducted.

Investigator's Brochure for ticagrelor

The Sponsor will be responsible for providing the Investigator's Brochure for ticagrelor and any updates of this document to the investigators.

Summary of Product Characteristics (SmPC) for clopidogrel

The Sponsor will be responsible for providing the Summary of Product Characteristics (SmPC) for clopidogrel to the investigators.

Documentation

The Sponsor will collect, store, guard and ensure completion by the relevant parties of the following documents;

- All study relevant documents (protocol, Investigator's Brochure, EC/IRB approval and comments, competent authority notification and comments, patient information and informed consent template, relevant correspondence, etc.)
- Signed and dated Case Report Form

- Records of any unanticipated adverse events and any Serious Adverse Events (SAEs) reported to the Sponsor during the clinical investigation
- Any statistical analyses and underlying supporting data
- Final report of the clinical investigation

18.2 Supplemental Applications

As appropriate, the Sponsor will submit changes to the study protocol to the investigators to obtain EC/IRB re-approval.

18.3 Submitting Reports

The Sponsor will submit the appropriate reports identified by the regulations. This includes unanticipated adverse device effects, withdrawal of any EC/IRB approval, yearly summary of adverse events, interim (if any) and final reports.

18.4 Maintaining Records

The Sponsor will maintain copies of correspondence, data, unanticipated adverse device effects, SAEs and other records related to the clinical study. The Sponsor will maintain records related to the signed Investigator Site Agreements according to requirements set forth by ICH-GCP.

All Core Laboratories and clinical sites will maintain study records according to local requirements for this type of study.

18.5 Audit

The Sponsor is responsible for auditing the study to ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit and may arrange to conduct an on-site audit to assess the performance of the study at the study site and of the study documents originating there.

18.6 Confidentiality

All data and information collected during this study related to the participating subject will comply with the standards for protection of privacy based on applicable local/ national requirements for subject's confidentiality. All data used in the analysis and summary of this study will be anonymous, and without reference to specific study subjects' names. Access to study subject files will be limited to authorised personnel of the Sponsor, the investigator, and research staff. Authorised regulatory personnel have the right to inspect and copy all records pertinent to this study, but all efforts must be made to remove the subject's personal data.

19. REFERENCES

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APPENDIX I DEFINITIONS

ACUTE CORONARY SYNDROME (ACS)

Acute coronary syndrome covers the spectrum of clinical conditions ranging from unstable angina to non-Q-wave myocardial infarction and Q-wave myocardial infarction. Unstable angina and non-ST-segment elevation myocardial infarction are very common manifestations of this disease.

BLEEDING

From BARC Bleeding definition table below, BARC 3 or BARC 5 sub-types will be used as composite safety endpoint.

Bleeding Academic Research Consortium (BARC) Definition[1]

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 haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal).
    - Subcategories; Confirmed by autopsy or imaging or LP
- Intra-ocular bleed compromising vision

[1] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011 Jun 14;123(23):2736-47.

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

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. * Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL hemoglobin). † Cell saver products will not be counted.

DEATH

All-cause mortality.

ELECTIVE PROCEDURE

An elective procedure is one that is performed on a patient with cardiac function that has been stable in the days or weeks prior to the procedure. Elective cases are usually scheduled at least one day prior to the procedure.

EMERGENT PROCEDURE

Patients requiring emergency intervention will have ongoing refractory, unrelenting cardiac compromise, with or without haemodynamic instability, and not responsive to any form of therapy except the procedure proposed. An emergency procedure is one in which there should be no delay providing intervention.

END OF PCI PROCEDURE

End of procedure is the removal of the guidewire and the transfer of the subject from the cath lab facility.

INDEX PROCEDURE

PCI procedure from crossing the target lesion with the guidewire until removal of the guiding catheter and the transfer of the subject from the cath lab facility.

MYOCARDIAL INFARCTION

New Q-wave MI

Development of new pathological Q-waves, not present on subject's baseline ECG, in 2 or more contiguous leads (as assessed by the ECG Core Laboratory). The Minnesota Code for pathological Q-waves will be used [2].

Patients without an ECG or with a non-interpretable ECG will fall under the non-Q wave group.

STAGED PROCEDURE

Staged procedures are defined as interventions planned at the time of the study procedure. For the purpose of this protocol, the conduct of staged procedures is *strongly discouraged*. If staged procedures are inevitable, the reason should be documented in the eCRF and source documents. The staged procedure should occur within 3 months post index procedure and the subject should receive the same type of study stent.

If a staged procedure occurs outside the time window of 3 months after the baseline procedure, the subject should receive whichever stent is considered standard of care at your institution. These procedures will be analysed as reinterventions (secondary endpoint).

Important: In case of staging in the experimental treatment arm, the 30-day ASA time clock should be re-started with the final staged procedure.

STENT THROMBOSIS

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathological confirmation:

a. 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: Troponin or CK-MB > 99th percentile of URL)
- 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

[2] Prineas R, Crow R, Blackburn H. The Minnesota code manual of electrocardiographic findings. Littleton, MA: John Wright-PSG, 1982.

stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation 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)

b. Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

†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

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 myocardial infarction (MI) which 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.

Possible stent thrombosis:

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow up.

STROKE

4 criteria (ranking scale for stroke severity):

1. Rapid onset of focal/global neurological deficit
2. Duration ≥24 hours or <24 hours if
   - Therapeutic intervention
   - Neuro-imaging
   - Death
3. No non-stroke cause (e.g. tumor, drug side effect, trauma, etc.).
4. Confirmation by at least one of:
   - A neurologist or neurosurgeon
   - Neuro-imaging (CT, MRI or Angio)
   - Lumbar puncture (intracranial haemorrhage)
   - Other compelling evidence of stroke

APPENDIX II. PATIENT INFORMATION AND INFORMED CONSENT

The GLOBAL LEADERS Study

Dear patient,

You are being asked by your physician to participate in a clinical study that aims to compare two medication strategies after your stent has been placed.

Before you decide whether or not you wish to participate in this study, it is important that you understand why the study is being carried out and what participation in this study means for you. With this patient information leaflet, we want to inform you about the background to and reasons for the study.

Please read the following information carefully and, if necessary, discuss your possible participation in the study with friends, family and/or your family doctor. You will be given sufficient time to do this. If anything is not clear or if you have any further questions, please do not hesitate to ask your doctor and/or study staff about this.

1) Introduction

The symptoms that you are suffering from are due to a narrowing of your coronary artery, resulting in a poor blood flow to your heart. In order to improve the blood flow and to relieve your symptoms, the artery should be opened. Balloon inflation, if applicable and the placement of a stent are standard procedures to achieve this. A stent is a metallic scaffold that is expanded and “plastered” against the vessel wall to keep it open.

You have been identified by your physician as having the appropriate condition for this treatment. The stent that will be used is the Biolimus (BioMatrix family) stent. This stent is approved by the authorities and is used in daily practice.

After a stent procedure, it is common practice to prescribe anti-platelet medication to prevent the blood from clotting. The main objective of this study is to determine if there is a better medication strategy to prevent your blood from clotting and at the same time minimising the number of complications.

Approximately 16,000 patients will be treated in up to 60 to 80 centres in Europe, North America, South America and Asia-Pacific.

2) Purpose of the trial

Currently, it is common to treat patients with two forms of anti-platelet medicine at the same time for a few months after a stent is placed. Although this has benefits (e.g. less risk of blood clots), there are also complications associated with this (e.g. higher risk of bleedings). The medications in this trial are used in daily practice, but in this trial the aim is to determine if there are fewer complications using a different medication strategy. This will be done by comparing two different medication strategies.

3) Trial treatment and procedures

If you agree to participate in this study, you will by chance (50%) be assigned to one of the medication strategies:

- Study group: Dual anti-platelet therapy (ticagrelor combined with aspirin) for 1 month, and then ticagrelor alone for another 23 months

OR

- Control group: Standard treatment, being dual anti-platelet therapy (ticagrelor or clopidogrel combined with aspirin) for 12 months, and then aspirin alone indefinitely

You will be asked to start the medication before the stenting procedure, except if you need an emergency stenting procedure. Your physician will treat the narrowing in your coronary artery with the BioMatrix family of drug-eluting stents. The procedure itself is the same as the routine procedures conducted in other patients. After the stenting procedure, you will continue with the assigned medication strategy as per the instructions you will be given. It is of extreme importance that you take your medication as prescribed.

Throughout your hospital stay, you will be monitored. We will collect data about your medical status and blood values. Also at discharge, an electrocardiogram (ECG/EKG) will be recorded. After being discharged from the hospital, you will be asked to return to the hospital for a follow-up at 1 month, 3 months, 6 months, 1 year, 1.5 years and 2 years. During the 3-month and 2-year visits, ECG's/EKG's will be recorded as well.

4) Potential risks and discomforts

Stenting and the prescription of two anti-platelet medications (one being aspirin) is a standard procedure. The potential risks are <u>not</u> specific for this study and are identical to the risks of standard care for your condition.

The risk associated with stent implantation in general is, among others, dependent on the severity of the narrowing(s) in your coronary arteries, your symptoms but also other factors. Your physician will inform you about the risks in your particular situation.

As in this study we are comparing medication strategies, we will focus on potential risks associated to the study group. The potential risks of stopping aspirin one month after stenting and continuing with only one form of anti-platelet treatment (i.e. ticagrelor) are not fully known yet and are subject of this study. Ticagrelor, although a more potent agent than clopidogrel, might not provide sufficient protection without aspirin and result in more repeat blockages called “thrombotic events”. If no anti-platelet treatment is taken, there is in any case an increased risk of getting blood clots. It is therefore of extreme importance that patients take their medication as instructed, particularly in the study group where there is only one form of anti-platelet medication.

The common side effects associated with taking ticagrelor are: shortness of breath and various types of bleeding (e.g. bruising and gastrointestinal bleeding). Occasionally, people have allergic reactions to medications. For ticagrelor, allergic skin reactions such as rash and itching have been observed in less than 1% of patients.

Please notify the study doctor or study staff if you experience any side effects during the study. You will be monitored throughout the study in order to minimise risks.

Pregnant women and women who breast-feed are excluded from this study. The risks to a foetus or embryo are unknown today, and we therefore ask women with childbearing capacity to use reliable contraception during the study.

There may be unforeseeable risks that are not known at this time.

You should be aware that the results of the stent placement cannot be guaranteed 100%. If the procedure is not successful, repeat intervention(s) and/or coronary by-pass surgery may be necessary.

5) Benefits

The benefits of the stenting procedure for both groups will be the alleviation of your symptoms.

Clopidogrel needs to be converted by your body into an active drug and some people seem to be less capable of performing this conversion. This results in patients with low response to clopidogrel therapy. If you participate in this study, you have a high chance of receiving ticagrelor, which is an active and more potent drug, with improved protection against the formation of blood clots.

The occurrence/severity of gastrointestinal bleeds seems to be linked with the prescription of anti-platelet agents in combination with aspirin. Ticagrelor has even been shown to work better in combination with low doses of aspirin. It is expected that the study group may have lower chance of bleedings.

When participating in this study, you will have more medical check-ups than when you would not be participating in the study.

There may be no direct benefit to you from being in this study. It is important for you to understand that the information obtained during this study will help to improve the treatment strategy in Coronary Artery Disease and could be used to help others.

6) Alternative treatment

The alternative methods that could be used for the treatment of your narrowed vessel are according to local hospital practice. Your doctor will give you more detailed information about those possibilities. For the study group, the alternative treatment would be the routinely given medication (as given in the control group).

7) Confidentiality

Your participation in this study is confidential. Your medical files and research data will be managed in accordance with the prevailing legal requirements. The research data will be entered on separate forms and stored under a code number. No names or other personal data will be stored. Only your physician will hold the information to link the code to you. The encoded research data related to you and that are important for the study will be processed, analysed and reported by the research employees of this study, who have an obligation of secrecy. The data will be kept according to regulatory requirements. The European Cardiovascular Research Institute (ECRI), the organisation responsible for the study, is responsible for the data and is also the owner of the data from the study.

Representatives of ECRI, members of the Ethics Committee (EC) or Institutional Review Board (IRB) and representatives of the regulatory authorities within and outside of Europe can go to the hospital and have access to your medical files in order to check the correctness of the research data. Study documentation may be provided to representatives and affiliates of the industries supporting the trial: AstraZeneca, Biosensors and The Medicines Company, anywhere in the world, and may be provided to local and/or foreign regulatory authorities. This check will take place in accordance with the legally prescribed rules for carrying out clinical research and the Personal Data Protection Act, under the responsibility of the treating cardiologist.

If you consent to take part in the study, then this also includes your consent for this inspection being carried out.

You have the right to ask to be shown what personal data has been collected, and if you think anything is incorrect, you may ask to have it corrected.

Your family doctor will also be informed about your participation in the study and will possibly be contacted to collect information relevant to the study.

It is possible that the results of this trial are presented or published. If this is done, your identity will remain confidential at all times. The data will only be used for purposes mentioned in this leaflet and possibility in publications in medical journals.

8) Participation and termination

You participation in this trial is voluntary. Participation in this trial will not affect the costs of your medical treatment in any way. In addition, you have the right to withdraw from the trial at any time, without having to provide a reason, even if the initial consent was given by a legal representative. This will not affect your relationship with your cardiologist or with any of the nursing staff at any time. This will also not affect your normal treatment and care. If you decide to withdraw your initially given consent for this trial, no further information regarding you will be made available for study purposes. If you decide to withdraw, you will have to contact your physician who will give you instructions on how to proceed with your medication.

Your cardiologist may also withdraw you from the study (without your permission) if she/he deems it in your best interest. It is also possible that ECRI decides to end the study. In both cases, you will be informed and you will receive the best standard of care.

9) Disqualifying factors

You cannot take part in the study if, for instance, you are allergic to specific drug(s) or contrast agent (required for angiography), are taking certain drugs, have a bleeding disorder, are pregnant or lactating, are currently participating in another clinical study or are unable to conform to the follow-up requirements. Please keep in mind that it is very important to inform your cardiologist of any of these problems. If you are a female of childbearing potential your physician will ask you to do a pregnancy test before the study starts in case required by local regulations. Also, your physician will discuss with you the use of effective contraceptives for the duration of the study. Your doctor will inform you about all the disqualifying criteria.

10) Insurance and costs

The organisation responsible for the study, ECRI, does have specific insurance coverage for this study. In the event of an injury during your participation in this study as a result of the procedure, your cardiologist will treat you according to the local hospital practice. It is important, however, that you inform your cardiologist or the study coordinator of any change in your health or any other medical treatments that you may require during the course of this study. Your cardiologist will notify ECRI.

No extra costs are associated with this study for the patient, and no payments will be made to patients in this study. ECRI will reimburse your doctor to cover all the research costs and the research fee. This investigator-initiated study is supported by AstraZeneca, Biosensors and The Medicines Company.

11) Approval

The competent authority [insert later] and the EC/IRB of [insert later] have given their approval to run the study.

12) Questions or problems

The organisation responsible for the study is ECRI, located at: Westblaak 92, 3012 KM Rotterdam, The Netherlands.

If you have any questions with regard to this study, your rights as a participant in clinical research, or any research-related injury, you can contact your doctor:

Name: _____
Telephone: _____

Alternatively, you may contact the following doctor who is not involved in this study:

Name: _____
Telephone: _____

Thank you very much for taking time to read this information sheet and considering to take part in this study. Your doctor will give you a copy to take home.

13) Consent document

If you agree to participate in this study, you will have to sign an informed consent form. Please retain a copy of this document for your reference and personal records.

INFORMED CONSENT FORM

I agree freely to participate in this study as described in the Patient Information version 1.4 dd 10 September 2013.

I was fully informed about the Global Leaders trial.

I confirm that I have read and understood the information concerning the Global Leaders study. I have had the opportunity to ask questions and I have had sufficient time to reflect.
I understand that the study follow-up involves clinical visits at 1, 3 and 6 months, and at 1, 1.5 and 2 years.
I know that the Ethics Committee/Institutional Review Board has examined this study and has given a favourable opinion.
I understand that all documents belonging to my medical file will remain strictly confidential. I also understand that my medical notes may be looked at by:
The responsible individual from ECRI or a representative
Ethics Committee/Institutional Review Board and/or regulatory authorities.
I give permission to these individuals to have access to my records.
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
At any time, I can ask for additional information.
I give permission for my general practitioner and/or treating physician to be informed about my participation in this trial.
I give consent to archive coded information for a maximum of 15 years after the end of this trial, and for its transmission outside the European economic area.
I give permission to the data processing of (anonymous) data as indicated on the Patient Information Form (PIF).

I will receive a copy of the Patient Information Form and Informed Consent Form, signed by the physician.

Patient or legal representative:

Name:_____ Signature: _____

Date:_____

Physician:

I herewith declare to have informed the patient about the purpose, potential risks and consequences of the above-mentioned investigation.

Name:_____Signature:_____

Date:_____

APPENDIX III. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The

responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimise the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

APPENDIX III: SYNTAX SCORE and ECG ACQUISITION GUIDELINES

Syntax Score :

- For an accurate Syntax Score assessment, it is of utmost importance to film the entire LCA as well as the entire RCA prior to the start of the index procedure, independent of the presence of any lesion(s).

- **In the situation where either the LCA or the RCA prior to the index procedure have not been filmed, please send a recent diagnostic angiography recording (< 6 months prior to the index procedure) showing the entire LCA and/or the entire RCA.**

- Film as many different projections for the right and left coronary artery to allow an accurate Syntax Score of all segments:
  There should be no overlap of the lesion to be dilated with other vessels, catheters or electrodes;
  Foreshortening of the segment should be avoided and stenoses should be viewed in their maximal severity;
  The segment of interest should preferably be located near the centre of the screen.

- In case of bypass patients, please film all grafts. A selective injection of the grafts is preferred to assure complete filling of the grafts and the distal vessel bed.

ECG :

To improve accuracy in ECG analysis, the following guidelines should be respected:

- Baseline and follow-up standard 12-lead ECGs must be obtained as required per protocol;
- A resting ECG is required;
- Attach a study label to the ECG, including the
  - Study name;
  - Date and time of the recording;
  - Site and patient number;
  - The study time point of the recording: discharge ,3-month, 2-year.

In addition, the following points are of key importance:

- Good quality ECG;
- Visible lead annotation;
- Original ECGs are preferred, otherwise only a good copy with clearly visible gridlines is acceptable;
- 12-lead ECGs should preferably be recorded on a single A4-size page using standard calibration of 1mV/cm and paper speed of 25mm/sec (50mm/sec is discouraged);
- More than 1 normal beat per lead. No average ECGs;
- The patient name should not be on the ECG;
- ECG without pace-maker beats is preferred.

Please send labelled angiographies and ECGs to the Angiographic or ECG Core Lab at Cardialysis:
Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands, tel: +31-10-206-2828.

APPENDIX IV: ABBREVIATIONS AND ACRONYMS

ACS	Acute Coronary Syndrome
ADP	Adenosine DiphosPhate
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
BARC	Bleeding Academic Research Consortium
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Surgery
CAD	Coronary Artery Disease
CRA	Clinical Research Associates
(e)CRF	(electronic)Case Report Form
DAPT	Dual AntiPlatelet Therapy
DES	Drug-Eluting Stent
DSMB	Data Safety Monitoring Board
DTI	Direct Thrombin Inhibitor
EC	Ethics Committee
ECG	Electrocardiography
ISR	In-Stent Restenosis
IB	Investigator Brochure
IRB	Institutional Review Board
IV	IntraVenous
GCP	Good Clinical Practice
GP	GlycoProtein
HIT	Heparin-Induced Thrombocytopenia
IFU	Instruction For Use
LAD	Left Anterior Descending artery
LCA	Left Coronary Artery
LCX	Left Circumflex artery
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTEACS	Non-ST segment Elevation Acute Coronary Syndrome
(N)STEMI	(Non-)ST segment Elevation Myocardial Infarction
PAR	Protease Activated Receptor
PCI	Percutaneous Coronary Intervention
RCA	Right Coronary Artery
(S)AE	(Serious) Adverse Event

SD	Source Documentation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIMI	The Thrombolysis in Myocardial Infarction
TLR	Target Lesion Revascularisation
TVF	Target Vessel Failure
UA	Unstable Angina
UFH	UnFractionated Heparin
ULN	Upper Limit of Normal