Short duration of dual antiplatElet therapy with SyNergy® II everolimus eluting stent in patients Older than 75 years undergoing percutaneous coronary Revascularization.The SENIOR trial.

Protocol number: 10-389

Version: 13.0

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Planned Number of Sites and Region

Around 40 sites in approximately 8 European countries including (but not limited to) Belgium, Finland, France, Latvia, Spain, Sweden, Switzerland and United Kingdom.

Sponsor

CERIC

21 La Vy Neuve

1287 Laconnex–

Switzerland

Trial Type:

Randomized Clinical Trial.Prospective, single blinded, randomized multicenter trial of 1,200 patients ≥75 years with significant coronary artery disease requiring percutaneous coronary intervention for stable angina, silent ischemia or acute coronary syndrome.Patients will be randomized to receive either a latest generation drug eluting stent with a bioresorbable polymer or a bare metal stent. Dual antiplatelet duration will be short and similar between the two groups of patients.

Data Monitoring:

CERC

7 rue du théâtre – 91300 Massy

France

Data Analysis:

CERC

7 rue du théâtre – 91300 Massy

France

Angiographic Core Laboratory only for end point related events

CERC

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France

Electronic Data Capture:

CLINIGRID

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Clinical Investigation Plan(CIP) Signature Page

Study name	SENIOR Trial
Study number	10-389
Site name (Hospital, City, Country)	

By my signature below, I confirm that I have read, fully understood and agree to comply with all conditions, instructions contained in the clinical investigational plan number , Version 13.0 dated 14/01/2014 and that I shall conduct the SENIOR trial in accordance with the laws and regulations described in the clinical investigational plan and all applicable local regulations. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and will ensure that the study is conducted in compliance with all the regulations listed above.

Principal Investigator's Name	Principal Investigator's signature	date (dd/mm/yyyy)

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Protocol Summary

Trial Name	SENIOR trial Short duration of dual antiplatelet therapy with Synergy® II everolimus eluting stent in patients older than 75 years undergoing percutaneous coronary revascularization.
Objectives	- To establish the **efficacyand safety** of the Synergy® II everolimus eluting stent with abluminal biodegradable polymer (EESabp) associated with a short dual antiplatelet therapy in patients ≥75 years old, suffering from stable angina, silent ischemia or acute coronary syndromes related to significant coronary artery disease and requiring percutaneous coronary intervention. - To demonstrate that EESabp in patients ≥75 years old is associated with a **lower rate of the composite** of all-cause mortality, myocardial infarction, stroke or ischemia driven target lesion revascularization (efficacy) and a **similar risk of major bleeding** (safety) than bare metal stent at an anticipated median follow-duration of one year.
Study devices	-everolimus eluting stents (Synergy® II stents): 2.25 mm x 8, 12, 20, 28, 32, 38 mm 2.50 mm x 8, 12, 20, 28, 38 mm 3.00 mm x 8, 12, 20, 28, 38 mm 3.50 mm x 8, 12, 20, 28, 38 mm 4.00 mm x 8, 12, 20, 28, 38 mm -bare metal stents (Omega®, Rebel®) 2.25 mm x 8, 12, 20, 28, 32, 38 mm 2.50 mm x 8, 12, 20, 28, 38 mm 3.00 mm x 8, 12, 20, 28, 38 mm 3.50 mm x 8, 12, 20, 28, 38 mm 4.00 mm x 8, 12, 20, 28, 38 mm
Antiplatelet regimen	-Dual antiplatelet therapy will be **similar** and administered for a **similar duration** after Synergy® II and BMS implantation. DAPT duration will be **one month** after percutaneous coronary intervention for stable angina and silent ischemia,or **six months** after percutaneous coronary intervention for acute coronary

	syndrome, **irrespective of the type of stent** (Synergy® II or BMS®). -Aspirin will be prescribed to all patients at an initial intra venous or oral loading dose of 150-300mg and at a maintenance dose of 75-100 mg orally daily, indefinitely. ADP $P2Y_{12}$ receptors inhibitors will be added to aspirin after percutaneous coronary intervention and maintained over **1 month** (stable angina or silent ischemia) or **6months** (acute coronary syndrome). - Patients could be treated by different $P2Y_{12}$ inhibitors: - clopidogrel 300/600mg loading dose and 75mg/d **OR** - prasugrel 60mg loading dose and 5mg/d orally **OR** - ticagrelor 180mg loading dose and 90mg/bd orally The choice of ADP $P2Y_{12}$ receptors inhibitors is left to the physician's discretion but need to be determined **before** the randomization process.
Study design	**Randomized Clinical Trial (RCT)** Prospective, single blinded, randomized multicenter trial of 1,200 patients enrolled in approximately *40* international centers. After diagnostic angiography demonstrating significant coronary artery disease requiring PCI and if the patients meet **all** the study inclusion criteria and **none** of the exclusion criteria, after signing the informed consent, they will be randomized 1:1 to: a) PCI using one or more Synergy® II (N=600), with DAPT including aspirin AND one $P2Y_{12}$ inhibitor (clopidogrel OR prasugrel OR ticagrelor), b) PCI using BMS (N=600), with DAPT including aspirin AND $P2Y_{12}$ inhibitor (clopidogrel OR prasugrel OR ticagrelor). Follow-up for all randomized subjects will continue for **one year** with an additional follow-up to 2 years.
Primary End Point	-Composite measure of MACCEs: **all-cause mortality**, **myocardial infarction**, **stroke** and **ischemia-driven target lesion revascularization (by PCI or CABG)** at **one year** (with all randomized subjects having reached the one year follow-up).

Secondary end points	- **Primary endpoint** at 30 days,180 days and 2 years - **All individual component of the primary endpoint** at 30 days, 180 days, 1 year and 2 years: -cardiac death -Myocardial Infarction (according to Third Universal Definition) -Stroke -Ischemia-driven target lesion revascularization (by PCI or CABG) - **All revascularization** (ischemia-driven and non-ischemia driven) at 30 days, 180 days, 1 year and 2 years: -all target lesion revascularization (TLR) -all target vessel revascularization (TVR) -all non target vessel revascularization (non TVR) - **complete revascularization at baseline procedure**, anatomic and functional - **Net benefit** at **30 days, 180 days, 1 year and 2 years**: association of composite events (all cause mortality, myocardial infarction, stroke, ischemia driven target lesion revascularization, and **major bleedings**). - **Major bleeding** complications (**type 2, 3 and 5 BARC definition**) at **30 days, 180 days,1 year and 2 years. (6)** - **Stent thrombosis** according to the definition of ARC symptomatic or asymptomatic (definite + probable) at **30 days, 180 days, 1 year and 2 years. (5)** **- QoL**, 12 months and 24 months **- Depression scale** at 12 months and 24 months **- Cost effectiveness** at 12 months
Pre-defined subgroup analyses	- Acute Coronary Syndrome vs non Acute Coronary Syndrome (stable angina and silent ischemia) - Patients ≥ 85 years old - Women - Patients with type 2 diabetes mellitus

	- Patients with atrial fibrillation
Quality of life (QoL)	Quality of life (QoL) will be assessed alongside the core clinical trial to evaluate the impact of the Synergy® II on a range of relevant quality of life (QoL) domains. QoL and functional status will be assessed using a combination of generic and disease-specific measures selected to cover a broad range of health domains that may be affected by coronary artery disease, its treatment, and its complications. Mental health and depression will be assessed using the Geriatric Depression Scale. Health utilities will be assessed using the Euro QoL (EQ-5D 5L). These measures will be assessed using standardized, written questionnaires at baseline (prior to randomization), at 12 months and 24 months
Subject enrollment	A total of 1,200 subjects will be enrolled in approximately *40* international sites.
Subject follow up	Clinical follow-up at in-hospital, 30, 180 days, and one year, with an additional follow-up to 2years.
Treatment Strategies	All subjects participating in this clinical trial will have informed consent obtained prior to randomization. **Inclusion Criteria** (**ALL** must be present): - Patient is ≥ 75 years old - One or more significant coronary artery stenosis is/are present (defined as ≥70% by visual assessment or ≥50% with Fractional Flow Reserve <0.80) or a left main coronary stenosis ≥50% by visual assessment) suitable for PC Iwith one of the following present: - **Silent ischemia,** - stress-induced myocardial ischemia ≥ 10% of myocardium in a asymptomatic patient or - stress-induced myocardial ischemia < 10% of myocardium AND FFR ≤0.80

	or - **Stable angina,** in a patient with objective ischemia despite optimal medical therapy or - **acute coronary syndrome** including: unstable angina, non ST- and ST elevation myocardial infarction. - All patients must also sign informed consent as per local law and comply with all study process during follow up for at least one year.
Exclusion criteria	- The subject is not eligible for randomization if **ANY** of the following is present: - Indication for myocardial revascularization by coronary artery bypass grafting, - Subjects unable to tolerate, obtain or comply with dual antiplatelet therapy for at least one month (stable angina or silent ischemia) or at least six month (acute coronary syndrome), - Subjects requiring additional surgery (cardiac or non-cardiac) within one month, - Non cardiac co-morbidities with life expectancy less than 1 year, - Prior hemorrhagic stroke, - Known allergy to aspirin or $P2Y_{12}$ inhibitors, - At least one contra indication to **ALL** the authorized $P2Y_{12}$ inhibitors at the requested dose (in case of contra indication to only one of two of the $P2Y_{12}$ inhibitors, the investigators are allowed to use the $P2Y_{12}$ inhibitors for which no allergy is known). - Silent ischemia <10% of the myocardium with FFR ≥0.80. - Participation in another clinical trial
Primary analytical population	The primary analysis of the composite endpoint of all-cause mortality, myocardial infarction, stroke and ischemia-driven target lesion revascularization will be performed on the intent-to-treat (ITT) population.
Statistical Method	The primary endpoint is a composite of all-cause mortality, myocardial infarction, stroke or ischemia-driven TLR with an

	anticipated median follow-up of one year (**efficacy**). The SENIOR study is powered to test the **superiority** of the Synergy® II with a relative 25% reduction of the primary endpoint Assuming the following: • primary endpoint event rate is 31% in control treatment arm at 1 year (interpolated from the most contemporary and accurate references) • minimum time to follow-up is 1 year • a constant dropout rate yielding 15% lost to follow-up at 1 year • two-sided alpha = 0.05 • then a sample size population of **560 subjects per arm** will provide 80% power to demonstrate superiority using a chi-square test comparing the event rates at 1 year from the Kaplan-Meier curves. The definitive total number will be 1.200 patients (600 in each arm).

1-Introduction

Coronary artery disease is a prevalent disease in patients ≥ 75 years with or without other risk factors. Aging of the population leads to frequent hospitalizations and significant medical and economic burden. However, there is currently no clear recommendation for how to treat specifically patients above 75 years suffering coronary artery disease (CAD). Patients above 75 years of age have been systematically underrepresented and highly selected in major clinical randomized trials underlying current recommendations for general population suffering stable or unstable CAD (1).

2-Background

Patients ≥ 75 years are a growing population among patients with acute coronary syndromes (ACS) or more stable situations. CAD is often diffuse and severe in this population. Age ≥75 years, is associated with a poor prognosis after CABG, so that PCI is often the best option for patients with ACS or for patients with stable angina/silent ischemia despite optimal medical treatment. In patients ≥75 years, PCI is often more difficult, because of lesion complexity, diffuseness and calcifications. Lesion length, small diameter of coronary arteries, bifurcated lesions are also common and are associated with an increased risk of in stent restenosis. Drug eluting stents (DES) have been shown to reduce angiographic and clinically restenosis in a wide variety of patients and lesions. The real rate of clinically relevant in stent restenosis in patients ≥ 75 years is difficult to determine, because this population is underrepresented in clinical trials evaluating DES. Furthermore, restenosis economical impact is far from being futile in this population. In their retrospective analysis based on the Medicare Standard Analytic File including all percutaneous coronary interventions performed in a year among unselected patients older than 65 years of age, Clark et al reported an independent cost of repeat revascularization of $19,074 (95% CI 18,440 to 19,907) (2). In this analysis, among the

3,927 patients aged 75 years or above, a repeat revascularization was observed in 38% and a restenosis in 32% assuming that 85% of repeat revascularization procedures over the first year of follow-up are attributable to restenosis (2). In addition, patients with repeat revascularization were more likely to have experienced a MI during the follow-up. The estimated economic burden of restenosis was evaluated to be $1,521 per patient for those ≥ 85 years of age. It is important to note that in multivariate analysis, congestive heart failure, cerebrovascular disease and chronic renal failure among others, were significantly associated to an increase in total medical care and cardiovascular costs, those figures being highly prevalent in the patients ≥75 years(2).

Therefore, all therapeutic devices that could reduce the rate of restenosis and recurrent revascularizations will have a major impact on rehospitalizations, and healthcare costs in that population. Unfortunately, because long-term dual antiplatelet therapy is associated with a significant high bleeding risk in patients ≥ 75 years, bare metal stent are often the preferred choice for PCI despite a similar efficacy of DES in this population.

New generations DES appear to be both effective and safe. In their recent meta-analysis including 50,844 patients, Palmerini et al. reported a 1-year definite stent thrombosis significantly lower with cobalt-chromium everolimus eluting stents (CoCr-EES) than with baremetal stents (odds ratio [OR] 0.23, 95% CI 0.13–0.41) (3). The significant difference in stent thrombosis between CoCr-EES and bare-metal stents is evident as early as 30 days (OR 0.21, 95% CI 0.11–0.42) and is also significant between 31 days and 1 year (OR 0.27, 95% CI 0.08–0.74) after PCI. In randomized studies, CoCr-EES has the lowest rate of stent thrombosis within 2 years after implantation. The finding that CoCr-EES could reduce stent thrombosis compared with bare-metal stents, if confirmed in future randomized trials, would represent an important finding, especially for the patients ≥ 75 years, but has never been evaluated specifically in this population.

First generations DES have been strongly criticized because of the small increased risk of late and very late stent thrombosis. Polymer hypersensitivity reactions, positive remodeling with late acquired malposition, delayed arterial healing, late stent fracture, and endothelial dysfunction are a few among the possible causes of the increased risk of very late stent thrombosis with first generations DES. The reduced rates of stent thrombosis with new generations of CoCr-EES stents may be attributed to the thromboresistant nature of the fluoropolymer or more rapid re-endothelialization, or both(3).Furthermore, an abluminal, fully biodegradable polymer-coated, thin struts DES, eluting everolimus such as the Synergy® II stent could therefore improve DES safety without reducing efficacy compared to BMS(4). In the recently published final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, non inferiority trial, including 1,707 all comers patients, the biodegradable polymer-based DES (biolimus-eluting stents, BES) were compared to durable polymer DES (sirolimus eluting stents, SES). At 5 years, the BES was non-inferior to SES for the primary endpoint (186 [22.3%] vs. 216 [26.1%], rate ratio [RR]: 0.83 [95% confidence interval (CI): 0.68 to 1.02], p for non-inferiority <0.0001, p for superiority = 0.069); a composite of cardiac death, MI, or clinically indicated target vessel revascularization. Furthermore, BES was associated with a significant reduction in very late definite ST from 1 to 5 years (n = 5 [0.7%] vs. n = 19 [2.5%], RR: 0.26 [95% CI: 0.10 to 0.68], p = 0.003), corresponding to a significant reduction in ST-associated clinical events (primary endpoint) over the same time period (n = 3 of 749 vs. n = 14 of 738, RR: 0.20 [95% CI: 0.06 to 0.71], p = 0.005).

The ideal solution to reduce the unnecessary restenosis risk and the correlated rehospitalizations and the iatrogenic bleeding risk would be to treat patients ≥ 75 years with a DES and a short dual antiplatelet therapy similar to the one recommended with bare metal stents to conjugate the efficacy of newest DES and the safety of short duration of dual

antiplatelet therapy.

3-Study objective

The primary objective of this study is to establish the efficacy and safety of the everolimus eluting stent (Synergy® II,Boston Scientific), in association with a reduced duration of dual antiplatelet therapy,(comparable to the one recommended when using a BMS) in patients ≥ 75 years by demonstrating that compared to BMS (Omega®, Rebel®, Boston Scientific), treatment of coronary stenosis with Synergy® II will result in lower rates of the composite events of all-cause mortality, myocardial infarction, stroke or ischemia driven target lesion revascularization at an anticipated median follow-up duration of one year.

4-Study design

4-1 Study design

A total of 1,200 subjects will be enrolled in this study. This study will be a prospective, single blinded, randomized multicenter trial at approximately 40 international centers. Following diagnostic angiography demonstrating significant CAD requiring PCI and if the subject meets all the study entry criteria, he/she will be eligible for the study and randomized to: a) PCI using the Synergy® II stent or b) PCI with BMS stent with dual antiplatelet therapy of similar duration for both groups. Follow-up for all randomized subjects will continue for 1 year.

4-2Subject Follow Up

All randomized subjects will be followed for at least 1-year period after baseline procedure. All randomized subjects will have a follow-up by telephone contact or office visit as described below:

- 30 days(+/- 5 days) visit: office visit

- 180 (+/-2weeks): telephone contact or office visit
- 1 year visit(+ 4 weeks): office visit
- 2 years (+/-4 weeks) visit: telephone contact or office visit.

4-3 Treatment strategy

All subjects participating in this randomized trial will have informed consent obtained after diagnostic angiography and prior to randomization. "Ad hoc" PCI is permitted as far as written informed consent has been obtained prior to the procedure. If more than one target lesion will be treated, all lesions must receive the treatment stent that has been assigned as per randomization (Synergy® II or Omega®/Rebel®).

5-Endpoints

5-1 Primary end point

The primary endpoint of this trial is the composite measure of MACCEs: all-cause mortality, myocardial infarction, stroke and ischemia driven target lesion revascularization (by PCI or CABG) at an anticipated median follow-up duration of 1 year (with all randomized subjects having reached the one year follow-up).

5-2 Secondary end points

- **Primary endpoints** at 30 days, 180 days and 2 years

- **All individual component of the primary endpoint** at 30 days, 180 days,1 year, and 2 years:

-Cardiac death

-Myocardial Infarction (according to Third Universal Definition)

-Stroke

-Ischemia-driven target lesion revascularization (by PCI or CABG)

-**All revascularization** (ischemia-driven and non-ischemia driven) at 30 days, 180 days, 1 year and 2 years:

-all target lesion revascularization (TLR)

-all target vessel revascularization (TVR)

-all non target vessel revascularization (non TVR)

-**complete revascularization at baseline procedure**, anatomic and functional

-**Net benefit** at **30 days, 180 days, 1 year and 2 years**: association of composite events (all-cause mortality, myocardial infarction, stroke, ischemia driven target lesion revascularization, and **major bleedings)**.

-**Major bleeding** complications (**type 2, 3 and 5 BARC definition**) at **30 days, 180 days, 1 year and 2 years (6)**

-**Stent thrombosis** according to the definition of definite and probable stent thrombosis according to ARC (symptomatic or asymptomatic) at 30 days, 180 days, 1 year and 2 years (5),

-**QoL** at 12 months and 24 months

-**Depression scale** at 12 months and 24 months

-**Cost effectiveness** at 12 months

6-Selection and withdrawal of the subjects

6-1 Subject population

Male and female subjects could be enrolled in the present study if they are 75 years old or older at the time of randomization. The randomized trial will enroll approximately 1,200 patients who need to meet ALL eligibility criteria and provide written informed consent prior to randomization. Each site should enroll a minimum of one randomized subject, and may not enroll more than a maximum of 120 randomized subjects.

6.2. Subject Screening

After local ethics committee approval is obtained, consecutive subjects ≥75 years of age in whom revascularization by PCI of at least one coronary artery stenosis with visually assessed diameter stenosis ≥ 50% is considered by interventional cardiologists participating in this trial will be identified and screened for study eligibility. Subjects eligible for enrollment per the general inclusion and exclusion criteria will be asked to sign an informed consent form for the SENIOR randomized trial. Subjects ≥ 75 years in the participating centers who do not satisfy inclusion and exclusion criteria but are treated by PCI during the same period will be documented on the patient log as well as the reason of non-inclusion.

6.3. Informed Consent

Prior to participation in the study, all eligible subjects must review, date and sign the Study Patient Informed Consent (PIC) form.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), EC approved informed consent, or, if incapable, and if required by local law or regulation, after such consent has been provided by a legally acceptable representative of the patient. In the case of witnessed verbal consent, written informed consent should be obtained within 24 hours of procedure and must be obtained before discharge. Failure to obtain signed informed consent renders the patient ineligible for the study.

According to the European Directive 2001/20/EC of 4 April 2001, in emergency cases, a consent must be given by a patient's legal representative (if present); if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided in national legislation. In this study, any verbal consent given by a patient in an emergency situation will be witnessed and documented. Written consent will be obtained as soon as the patient is able to provide written consent.

Any changes to the proposed consent form must be agreed to by the sponsor before

submission to the EC and a copy of the approved version must be provided to the CERC after EC approval.

The Investigator or designated member of the study site personnel must explain the study in detail, talking through all details described in the PIC. The patient must be given the opportunity to ask questions and ample time to consider his/her participation. If the patient is willing to participate in the study he/she or legal representative must sign and date two copies of the Informed Consent, which must be signed and dated at the same time, by the investigator or designee who explained the study. One copy of the PIC will be given to the patient and the other one will be retained in the study specific binder at the site. The process of obtaining informed consent should be documented in the patient source documents.

6.4. Eligibility Criteria

Subjects must meet **ALL** of the inclusion criteria to be considered for the randomized clinical trial. If **ANY** of the exclusion criteria are met, the subject cannot be included in the randomized clinical trial.

6.4.1. Inclusion Criteria

All subjects participating in the clinical trial will have informed consent obtained prior to randomization.

Inclusion Criteria (**ALL** must be present):

- Patient ≥ 75 years old

- One or more significant coronary artery stenosis (defined as ≥70% by visual assessment or ≥50% with Fractional Flow Reserve <0.80) or a left main coronary stenosis ≥50% by visual assessment) suitable for PCI with one of the following present:

-**Silent ischemia,**

-stress-induced myocardial ischemia ≥10% of myocardium in a asymptomatic

patient

or

-stress-induced myocardial ischemia < 10% of myocardium in an asymptomatic patient AND FFR ≤0.80

or

-**Stable angina,** in a patient with objective ischemia despite optimal medical therapy

or

-acute coronary syndrome including: unstable angina, non ST- and ST elevation myocardial infarction.

-All patients must also sign informed consent as per local law and comply with all study process during follow up for at least one year.

6.4.2. Exclusion Criteria

The subject is not eligible for the study if **ANY** of the following is present:

-Indication for myocardial revascularization by coronary artery bypass grafting,

-Subjects unable to tolerate, obtain or comply with dual antiplatelet therapy for at least six month (acute coronary syndrome) or at least one month (stable angina or silent ischemia),

-Subjects requiring additional surgery (cardiac or non-cardiac) within one month,

-Non cardiac co-morbidities with life expectancy less than 1 year,

-Prior hemorrhagic stroke,

-Known allergy to aspirin or $P2Y_{12}$ inhibitors,

-At least one contra indication to all the authorized $P2Y_{12}$ inhibitors at the requested dose (in case of contra indication to only one of two of the $P2Y_{12}$ inhibitors, the investigators are

allowed to use the $P2Y_{12}$ inhibitors for which no allergy is known).

-Silent ischemia < 10% of the myocardium with FFR ≥ 0.80.

-Participation in another clinical trial

6.4.3. Patients with atrial fibrillation requiring chronic anticoagulation

Patients with atrial fibrillation could participate to the study precluding that they meet all inclusion criteria and none of the exclusion criteria. In addition to their chronic anticoagulation, they will receive clopidogrel as the only accepted ADP $P2Y_{12}$ receptors inhibitors. Clopidogrel loading dose will be 300/600mg according to physician discretion. DAPT will be maintained for one month for all patients. After one month, aspirin will be stopped, and only clopidogrel will be maintained.

6.4.4. Patients enrollment

The patient is enrolled in the study when he/she has signed the informed consent (verbal consent is only acceptable as above), has a lesion that is treatable with a study stent, is randomized either through the eCRF and receives a study treatment assignment.

7-Baseline assessment

At inclusion into this study, routine examinations, if performed, will be captured: physical examination, including height and weight, heart rate and blood pressure and relevant medical history including detailed evaluation of bleeding risk and lesion characteristics as well as:

-Angina Status

-Routine Laboratory Tests including CK and/or CK-MB or troponin prior to the procedure (when available)

-12 Lead electrocardiogram

-The following questionnaires

- Geriatric Depression Scale
- EuroQoL-5D 5L questionnaire

8-Randomization procedure

Randomization will occur prior to PCI but after all eligibility criteria for the study have been met, including that a treatable lesion has been identified and informed consent has been signed according to section 6.3. Patients will be randomized using a eCRF. The type of ADP $P2Y_{12}$ inhibitor and the planned duration of DAPT will be determined before the randomization process.

Randomization will be stratified by the choice of ADP $P2Y_{12}$ and by center.

9-Treatment of the subjects

9.1Percutaneous coronary interventions.

After randomization, the patients will undergo PCI with the randomized stent Synergy® II or Omega®/Rebel® stent . Transradial 6F approaches are strongly recommended. The choice of guiding catheters, guidewires, predilatation, atherectomy devices, post dilatation and intra coronary imaging system (IVUS, OCT) is let to the investigators discretion. The available DES and BMS exist in different sizes and length.

-everolimus eluting stents (Synergy® II stents):

2.25 mm x 8, 12, 20, 28, 32, 38 mm

2.50 mm x 8, 12, 20, 28, 38 mm

3.00 mm x 8, 12, 20, 28, 38 mm

3.50 mm x 8, 12, 20, 28, 38 mm

4.00 mm x 8, 12, 20, 28, 38 mm

-bare metal stents (Omega® or Rebel® stent)

2.25 mm x 8, 12, 20, 28, 32, 38 mm

2.50 mm x 8, 12, 20, 28, 38 mm

3.00 mm x 8, 12, 20, 28, 38 mm

3.50 mm x 8, 12, 20, 28, 38 mm

4.00 mm x 8, 12, 20, 28, 38 mm

9.2. Adjunctive Treatment.

Antithrombotic regimen within the cathlab, including unfractionated heparin, low molecular weight heparin, bivalirudin, fondaparinux, is let to the physician discretion. GpIIb / IIIa inhibitors can be used in selected cases in patients with STEMI but are not recommended for stable patients or for patients with silent ischemia.

-Dual antiplatelet therapy will be administered for **similar duration** after Synergy® II and Omega®/Rebel® stent or any other BMS available implantation. DAPT duration will be one month after PCI for stable angina and silent ischemia, and six months after PCI for acute coronary syndroms, **irrespective of the type of stent** (Synergy® II or Omega®/Rebel® stent).

-Aspirin will be prescribed to all patients at an initial intra venous or oral loading dose of 150-300mg and at a maintenance dose of 75-100 mg orally daily, indefinitely (except in patients with chronic anticoagulation). For patients not already on $P2Y_{12}$ inhibitors they will be added to aspirin before or immediately after percutaneous coronary intervention and maintained over one month (stable angina or silent ischemia) or 6 months (ACS).

-All patients in the trial will be treated by either:

-clopidogrel 600mg loading dose and 150mg/d or 75mg/d

OR

-prasugrel 60mg loading dose and 5 mg/d orally

OR

-ticagrelor 180mg loading dose and 90mg/bd orally

over one month after PCI. The $P2Y_{12}$ inhibitor will be prolonged over 6 months only in patients with acute coronary syndrome, irrespective of the type of the stent.

Optimal medical treatment.

Anti ischemic treatment should be added to medical treatment and include beta blocker agents in patients without contra indication.

Calcium channel blocking agents can replace beta blocker agents in patients with contra indications to these agents.

A proton pump inhibitor (PPI) is strongly recommended according to physician discretion (pantaprazole 20mg, ezoprazol 20mg, lanzoprazole 20mg, rabeprazole 20mgoromeprazole 20mg).

10-Follow-up visits

Every effort should be made for collecting the subject data thanks to an on-site visit or telephone contact, as described below:

- 30 days(+/- 5 days) visit: office visit

- 180 (+/-2 weeks): telephone contact or office visit
- 1 year visit (+ 4 weeks): office visit
- 2 years (+/-4 weeks) visit: telephone contact or office visit.

These visits will include information regarding angina status, any adverse events including MACCEs and bleeding events, concomitant cardiovascular and other important medication use and any hospitalizations including any interventional treatment that occurred since the previous contact. If available the ECG results will be collected at each follow-up visit.

The following questionnaires

- Geriatric Depression Scale
- EuroQoL-5D questionnaire

will be collected at 12 months and 24 months.

If the patient cannot be contacted, information from the patient's identified point of alternative contact will be utilized.

10.1 Missed Follow-Up

If the patient cannot be reached for a follow up visit at least three telephone contacts (or attempts) should be made then a courier with the questionnaire should be sent to the patient prior to recording a missed follow-up visit. The patient however remains in the study until the 1 year follow-up. The patient will only be considered as 'Lost to follow-up' if he/she cannot be reached for the final 2 years follow-up.

10.2 Patient withdrawal

Every effort will be made by the investigator to keep the patient in the study; however should the patient decide to withdraw, the investigator is responsible for reporting the observations thoroughly, and completing the final evaluations and eCRFs.

10.3 Data Collection from withdrawn/ discontinued patients

In patients who withdraw their consent before the randomization has occurred no data collection will be carried out. These patients are considered screen failures and will be documented as such on the Subject Screening and Eligibility Log.

For patients who were declared eligible for the study and randomized but who are discontinued for any reason prior to the commencement of any PCI procedure, data until that time period will be collected and the patient will be immediately withdrawn from study. The reason for the early withdrawal must be documented in the case report form.

For patients who withdraw their consent after the commencement of any PCI procedure, a final study visit will be conducted. Data will be collected on the eCRF.

10.4 Data Collection for patients who receive non-study stents

Patients who receive non-study stents or who undergo any non-study procedure for the treatment of coronary artery disease (i.e. any procedure that is not PCI with a study stent) for any reason, are considered major protocol violations and will be followed for the intent to treat (ITT) analysis only. Patient care (i.e. medical treatment, additional procedures) is left to the discretion of the investigator, however, patients must continue to be followed per protocol scheduled follow-up.

11- Study discontinuation rules

If the Sponsor, Data Safety and Monitoring Board, Regulatory Agency, and/or the Principal Investigator discover conditions during the study that indicate the investigation should be terminated for patient safety reasons, an appropriate schedule for termination will be setup.

12-Statistical design and analysis

The trial is designed to be a superiority trial. This is a randomized, controlled, single blind, multicentric, prospective trial. The primary endpoint is a composite of all-cause mortality, myocardial infarction, stroke or ischemia-driven TLR with an anticipated median follow-up of one year (**efficacy**).

The SENIOR study is powered to test the superiority of the EESbp with a relative 25% reduction in the active group.

Assuming the following:

• primary endpoint event rate is 31% in control treatment arm at 1 year (interpolated from the most contemporary and accurate reference)

• minimum time to follow-up is 1 year

• a constant dropout rate yielding 15% lost to follow-up at 1 year

• one-sided alpha = 0.025

then a sample size population of 560 subjects per arm will provide 80% power to demonstrate superiority using a chi-square test comparing the event rates at 1 year from the Kaplan-Meier curves. To take into account potential patients loss during follow up, the definitive total number will be **1,200 patients** (600 in each arm).The sample size calculation was performed in SAS version 9.2 using 10.000 simulations.

All statistical analyses will be described in a statistical analysis plan, which will be finalized before the end of the study.

13-Safety reporting

Safety of the subjects participating in this clinical trial will be monitored throughout the trial using the Adverse Event reporting process to identify real and potential safety issues.

Adverse events will be reported according to the ISO 14155:2011(E) Clinical Investigation of medical devices for human subjects – Good Clinical Practice Guidelines, while recognizing and following other specific laws, regulations, directives, standards and/or guidelines as appropriate as required by the country(ies) in which the study is conducted.

13.1 Definitions

13.1.1-Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

Note 1: This includes events related to the investigational medical device or the comparator.
Note 2: This includes events related to the procedures involved.
Note 3: For users or other persons this is restricted to events related to the investigational medical device.
Note 4: Pre-Existing Medical Conditions: Any medical conditions (including planned surgeries and planned hospitalizations) present at baseline, which do not worsen in duration, severity or frequency during the study are not adverse events (AE). These pre-existing medical conditions should be adequately documented in the patient's medical history. **Medical conditions present at baseline which worsen after exposure to study treatment will be recorded as an AE on the Adverse Event Form of the CRF.**

13.1.2-Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. This also

includes any event resulting from the use error or intentional misuse of the investigational medical device.

13.1.3-Serious Adverse Event (SAE)

An adverse event that:

1. led to a death,

2. led to a serious deterioration in the health of the subject that either resulted in: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

3. led to foetal distress, foetal death or a congenital abnormality or birth defect

Note: In accordance with Note 4 above: **A planned hospitalization for pre-existing condition, a planned surgery or a procedure required by the CIP without a serious deterioration in health is not considered to be an adverse event (serious or otherwise).**

13.1.4-Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event identified in the current version of the risk analysis report. Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

13.1.5- Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Anticipated serious adverse

device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

13.1.6- Device Deficiencies (DD)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:

1. if either suitable action had not been taken,
2. if intervention had not been made, or
3. if circumstances had been less fortunate

13.1.7- Device Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

13.2 Safety reporting

All endpoints related events, serious or not, that occur to any subject implemented with Synergy® II or Omega®/Rebel® stent, regardless of attribution, that are identified for any subject from PCI till the 12 month follow-up visit will be collected in the eCRF.

All serious endpoints related events irrespective of potential causal relationship to the study must be reported to the CERC within 24 hours of the Investigator's first knowledge of the event. All serious endpoints related events must be followed up for outcome of the event. Follow-up information of the serious endpoints related events should be provided by the investigator within the same reporting period (i.e. within 24 hours of identification)

14- Scientific Committee (SC)

The SC will be responsible for maintaining the scientific integrity of the trial and will monitor the progress of the trial. The SC will approve the trial protocol and any subsequent amendments and the case record forms. The SC will meet prior to the start of the trial and as required during the trial progress.

15- Data Safety Monitoring Board (DSMB)

An independent DSMB will be established. The DSMB will consist of cardiologist, neurologist, statistician and clinician with experience of clinical trials. Their main role is to consider the data from any event analysis and specifically to assess any safety issues such as unexpected adverse events that occur and report back to the SC and CEC. The DSMB will develop a charter outlining their responsibilities and operational details.

16- Clinical Events Committee (CEC)

A clinical events committee (CEC) will be established to review the details of key trial adverse endpoint related events. Their reports will be used in the assessment of endpoints and for presentation of data to the DSMB.

17- General study conduct

17.1 Ethical and Regulatory Considerations

The study will be performed in accordance with the standard EN ISO 14155:2011 on clinical investigations with medical devices on human subjects and the latest version of the Declaration of Helsinki.

The clinical investigational plan, informed consent, any other specific study documents and all amendments to these study documents will be reviewed and approved by the appropriate

Ethics Committees (EC) and Competent Authority before enrolment of any patient. In addition, the sponsor will keep the Competent Authorities informed of any SA(D)Es throughout the study course.

17.2 Study protocol changes

Neither the Sponsor nor the Investigators can modify this clinical investigational plan without obtaining written concurrence from each other and, when appropriate, the site EC. The Sponsor will submit the clinical investigational plan modifications, if any, to the appropriate Competent Authorities, as required.

17.3 Supplemental applications - Amendments

As appropriate, the Sponsor will submit changes in the clinical investigational plan to Investigators to obtain EC re-approval.

17.4 Study protocol deviations

Any deviations from the study protocol undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to CERC within 48 hours of occurrence and if applicable the respective EC as soon as possible, but in no event later than five working days after the emergency occurs.

The DSMB is responsible for analyzing the deviations and assessing their significance.

17.5 Data collection and handling

Data will be collected through an electronic data capturing (EDC) system provided to the centers prior to study start. Automatic queries will be built into the system prior to study start and throughout the project. The site will enter study data directly into the electronic database during or as soon after the visit as possible. The follow-up data should be entered into the database within 10 business days of visit.

Data from each subject will be recorded in the EDC will be completed prospectively from patient medical chart by the study staff of each site. CERC will provide clinical monitoring, including review of EDCs with verification to the source documentation per the monitoring plan outlined for the study.

Once all patients complete the study and all queries are answered, the database will be frozen and the analysis will start.

Once the study is completed, the records will be kept as requested by local regulations, but in no case less than 15 years from study termination by the sponsor.

17.6 Confidentiality and data protection

Subjects will be aware of the fact that Sponsor's representatives, Competent Authority or Ethics Committees representatives will be granted access to their medical files, in order to check subject's personal data collected. These personal data will be managed in a confidential manner taking into account the fact that Sponsor's representatives, Competent Authority or Ethics Committees representatives are bound by professional secrecy with regard to all confidential information they have access to.

17.7 Archiving of documents and data collected

All clinical sites will maintain study records until the sponsor notifies them and the reviewing regulatory authorities are notified that research is completed / terminated under the clinical investigation in compliance with national law.

17.8 Financing and Insurance

The sponsor has a civil liability insurance policy which covers studies in all countries.

As the study sponsor of this clinical study, the sponsor has the overall responsibility for the conduct of the study, including funding of the study.

17.9 Publication policy

CERIC SARL, acting as the study sponsor, assumes full responsibility relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit. In order to allow this information to be used effectively, it is essential that the study results be communicated to the sponsor as soon as possible.

Any project of publication and/or communication shall be submitted to the sponsor at least 60 days for a publication and 30 days for an abstract before the forecasted date of communication and/or submission for a publication. The sponsor shall make comments on the project within 30 days for a publication and 15 days for an abstract, of receipt of the project. The investigator, who submitted the project, shall take the sponsor's comments into due consideration. In any case, should the investigator who submitted the project decide not to modify the project according to the sponsor's comments, it shall provide the sponsor with the grounds of its decision in writing.

18- Study responsibilities

18.1 Sponsor responsibilities

Sponsor has the overall responsibility for its conduct, including assurance that the study meets the regulatory requirements of the Standard ISO 14155 on Clinical Investigations with medical devices on human subjects. Sponsor or its representative will ensure adherence to the ISO 14155 standard and Sponsor’s general duties, selection of Investigators, monitoring, supplemental applications, maintaining records, and submitting periodic and final reports.

18.2 Investigator responsibilities

Study Investigators will ensure that all work and services they provide will be conducted in compliance with the standards of good clinical and research practice, i.e. ISO 14155.

The investigator will ensure that the study is conducted in compliance with the Clinical Investigation Plan and the Investigator's Agreement.

The Investigator will be responsible for the day to day conduct of the clinical investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

The Investigator will have the resources to conduct the clinical investigation properly and obtain from the sponsor information which he judges essential about the device and be familiar with this information.

The Investigator must obtain written EC approval prior to including any subject in the study.

The Investigator will be provided by the Sponsor with a sample informed consent that may be modified to meet individual EC (or Institutional Review Board (IRB)) requirements. Any modifications of the informed consent document must be submitted to the Sponsor for approval prior to submission to the EC/IRB. The Investigator shall ensure that adequate information is given to the subject both in oral and written form, on the nature of the study. This information shall be easily understandable by the subject. This information shall include the aims, expected benefits for him/her and/or others, risks and inconveniences and an explanation of any alternative methods, and of possible consequences of any withdrawal from the study. Subjects shall be allowed sufficient time to decide whether or not they wish to participate. The subjects shall be informed that his/her participation in the clinical investigation is confidential. Subjects shall be made aware that the data relating to the study may be made available to third parties while maintaining anonymity. Subjects shall sign the informed consent form prior to their inclusion in the study. A copy of the approved informed consent form along with a copy of each subject's signed consent form will be maintained by each Investigator in a

designated clinical study administrative file. A copy of the signed consent form must be given to each subject.

CERC will provide centres with a sample informed consent document.

Standardized eCRFs to be completed for all enrolled subjects into the study will be provided to the Investigator. Completion of standard CRFs should be accurate and must record of subject's data collected during the study according to ISO 14155 standard and Good Clinical Practices recommendations. It is the responsibility of the Investigator to ensure the quality of the data collected and recorded.

The Investigator will maintain study records for an appropriate time and the subject's identity shall not be released to third parties without the subject's prior consent. Record retention periods will be provided to all concerned by Sponsor. All information and data concerning subjects or their participation in this study will be considered confidential. Only authorized personnel will have access to this confidential information. All data used in the analysis and reporting of this evaluation will be without identifiable reference to individual subjects.

For the purpose of ensuring compliance with the Clinical Investigation Plan, Good Clinical Practices and applicable regulatory requirements, the Investigator should permit auditing by the Sponsor or Sponsor's representative and inspection by applicable Regulatory Authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the Authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

18.3 Monitor responsibilities

The Sponsor has appointed the CERC as Clinical Monitor for this study. CERC personnel are qualified by training and experience to oversee the conduct of the study. CERC will fulfill the responsibilities identified in its standard operating procedures (SOPs), available for review at CERC. These responsibilities include collecting and tracking data forms and trial compliance.

Under the supervision of the Sponsor and according to the Clinical Monitoring Plan agreed between CERC and the sponsor, monitors will conduct investigational site monitoring to ensure that all Investigators are in compliance with the regulatory requirements of the Standard ISO 14155 and the latest version of the Declaration of Helsinki, with the Clinical Investigation Plan and with the Investigator's Agreement.

The Investigator and his study team should be available during monitoring visit and possible audits.

19-Appendix: definitions, abbreviations and acronyms

19-1 Primary endpoint definition

19-1-1 Definition of Death

Death will be defined as cardiovascular, non-cardiovascular and from unknown reason.

• **Cardiovascular Death** includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure or cardiogenic shock, death due to ischemic or haemorrhagic stroke, death due to other cardiovascular causes, and death due to bleeding as follows:

o **Sudden Cardiac Death** refers to death that occurs unexpectedly:

§ Witnessed and instantaneous without new or worsening symptoms

§ Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms

§ Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic)

§ Subjects unsuccessfully resuscitated from cardiac arrest

§ Subjects successfully resuscitated from cardiac arrest but who die without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)

§ Unwitnessed death or other causes of death (information regarding the subject's clinical status preceding death should be provided, if available)

O **Death due to Acute ST Elevation Myocardial Infarction** refers to an acute myocardial infarction(STEMI) leading to death, within 30 days. Death due to known sequelae of MI including mechanical complications, arrhythmia, and/or pump failure, as well as death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should be considered death due to acute MI. The acute myocardial infarction should be verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus, and there should be no conclusive evidence of another cause of death. If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence. Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation, procedure, or operation should be classified as death due to other cardiovascular cause.

O **Death due to Heart Failure or Cardiogenic Shock** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death.

Death due to heart failure or cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or

cardiogenic shock following implantation of a mechanical assist device. New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

§ New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a subject already receiving maximal therapy for heart failure

§ Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema

§ Confinement to bed predominantly due to heart failure symptoms

§ Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

§ Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure. Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

· Cool, clammy skin *or*

· Oliguria (urine output < 30 mL/hour) *or*

· Altered sensorium *or*

· Cardiac index < 2.2 L/min/m2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mmHg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support. Note: Heart failure may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g. hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely possible to

distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. In other cases, the aggregation implied by the definition above may be more appropriate.

O **Death due to Stroke (Cerebrovascular Event: intracranial hemorrhage or non-hemorrhagic stroke)** refers to a cerebrovascular event or a complication of a cerebrovascular event that leads inexorably to death, generally within 30 days after the suspected event. These deaths may be based on clinical signs and symptoms as well as neuroimaging and/or autopsy. There should be no conclusive evidence of another cause of death.

O **Death due to Other Cardiovascular Causes** refers to death due to a cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease).

Mortal complications of cardiac surgery or PCI, even if “non-cardiovascular” in nature, should be classified as cardiovascular deaths.

O **Death Due to Bleeding** refers to fatal bleeding or bleeding which contributes to death, with categories being mutually exclusive.

§ **Fatal Bleeding:**

Fatal bleeding will be defined according to the type 5a and 5b in the BARC definition (see below).

• **Non-Cardiovascular Death** is defined as any death not covered by cardiac death or vascular death. Categories include but are not limited to:

o Pulmonary causes

o Renal causes

o Gastrointestinal causes

o Infection (includes sepsis)

o Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))

o Malignancy (i.e., new malignancy, worsening of prior malignancy)

o Accidental/Trauma

o Suicide

o Non-cardiovascular system organ failure (e.g., hepatic failure)

o Non-cardiovascular surgery

o Other non-cardiovascular

• **Undetermined cause of death** refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. *For this trial all deaths with undetermined causes will be included in the cardiovascular category.*

19-1-2 Definition of Acute Myocardial infarction(7)

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

• Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

Symptoms of ischaemia.

New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).

Development of pathological Q waves in the ECG.

Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Identification of an intracoronary thrombus by angiography or autopsy.

• Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

• Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

• Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

• Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (> 10 x 99th percentile URL) in patients with normal baseline cTn values (≤ 99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Table: Classification of myocardial infarction

Type 1: Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Secondary myocardial infarction

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction related to sudden cardiac death

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or

embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass graft surgery (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values > 10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

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

• Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.

• Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.

• Pathological findings of a prior MI.

19-1-3 Definition of coronary revascularization procedures

A coronary revascularization procedure may be either a coronary artery bypass graft (CABG) surgery or a percutaneous coronary intervention (PCI).

Coronary revascularization procedures may be further classified as follows:

 Emergert: an emergent procedure is performed as soon as possible after qualifying symptoms.

 Urgent: an urgent procedure is performed within 48 hours ofqualifying symptoms.

 Elective: an elective procedure is planned in advance and is not urgent or emergent.

Procedural Success may be defined as follows:

 PCI: successful balloon inflation with or without stenting and the achievement of a residual stenosis <50% of the coronary artery.

Target Lesion: A lesion revascularized in the index procedure.

Target Vessel: The main epicardial coronary artery or arteries (LM, LAD, LCX or RCA) which contains the target lesion(s), including its branches, or grafts (arterial or venous) supplying the target lesion territory.

Target Vessel-Non-Target Lesion: The target vessel but non-target lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography (QCA).

Non-Target Vessel: The main epicardial coronary artery or arteries (LM, LAD, LCX or RCA) which do not contain the target lesion(s), including its branches, or grafts (arterial or venous) supplying the target lesion territory.

Target Vessel Revascularization (TVR): Target vessel revascularization is any repeat PCI of the target vessel or bypass surgery of the target vessel.

Target Lesion Revascularization (TLR): Target lesion revascularization is defined as any repeat PCI of the target lesion or CABG of the target vessel.

All revascularization events will be adjudicated as either ischemia-driven or non ischemia-driven

Ischemia-Driven Target Lesion (or Vessel) Revascularization: A target lesion (vessel)

revascularization will be considered ischemia-driven if the target lesion diameter stenosis is ≥50% by visual assessment, involving the lesion itself and 5 mm of proximal and/or distal margin and any of the following criteria for ischemia are met:

- A positive functional study corresponding to the area served by the target lesion; or
- Ischemic ECG changes at rest in a distribution consistent with the target vessel; or
- Typical ischemic symptoms referable to the target lesion; or
- FFR of the target lesion ≤0.80.

Ischemia-Driven Non-Target Vessel Revascularization: A non target vessel revascularization will be considered ischemia-driven if any lesion the non target vessel has a diameter stenosis ≥ 50% by QCA with any of the above criteria for ischemia met.

Unplanned revascularization for ischemia: Any repeat revascularization of either a target vessel or non target vessel with any of the above criteria for ischemia met.

19-1-4 Other definitions

Bleeding Complication (6)

Bleeding complications are associated with DAPT especially with prolonged DAPT. Reducing the duration of DAPT will positively impact bleeding complication rates that will further improve patients safety. Many definitions have been used for bleeding complications, making difficult the comparisons between the trials. In the SENIOR trial, the bleeding academic research consortium (BARC) proposed a classification to characterize bleeding in six grades(6) : type 0 meaning no bleeding and type 5 fatal bleeding. Between them, there are different grades depending of the site, the abondance (hemoglobin, requiring transfusion of vasopressive agents) or the cause of bleeding. BARC definition will be used in the SENIOR trial.

BARC Criteria:

Type 0 : no bleeding

Type 1 : bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional ; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2 : any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria : (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a : Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed)

Any transfusion with overt bleeding

Type 3b : Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c : Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does not include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed compromising vision

Type 4 : CABG-related bleeding

Perioperative intracranial bleeding within 48h

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥ 5U whole blood or packed red blood cells within a 48-h period

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

Type 5 : fatal bleeding

Type 5a : Probable fatal bleeding ; no autopsy or imaging confirmation but clinically suspicious

Type 5b : Definite fatal bleeding ; overt bleeding or autopsy or imaging confirmation

Major Arrhythmia

Ventricular tachycardia or fibrillation requiring cardioversion or countershock; atrial fibrillation lasting >24 hours; bradycardia or conduction system disease requiring a permanent pacemaker.

Renal Failure

Serum creatinine increase by ≥1 mg/dL or need for dialysis.

Stent Thrombosis

For this trial, stent thrombosis will be defined as the occurrence of definite stent thrombosis according to the ARC criteria.

1. Stent Thrombosis: Timing

Type Timing(5)

Acute stent thrombosis: 0 to 24 hours after stent implantation

Subacute stent thrombosis > 24 hours to 30 days after stent implantation

Early stent thrombosis (0 to 30 days)

Late stent thrombosis† > 30 days to 1 year after stent implantation

Very late stent thrombosis† > 1 year after stent implantation

Stent thrombosis will be reported as a cumulative value over time and at the various individual time points specified above (except very late thrombosis for an endpoint related reason). Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the catheterization laboratory.

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

2. ARC Definitions of Definite, Probable, and Possible Stent Thrombosis (5)

 Definite 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:

1. Acute onset of ischemic symptoms at rest

2. New ischemic ECG changes that suggest acute ischemia

3. Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)

4. Non occlusive thrombus

a. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non calcified filling defect or lucency surrounded by contrast material(on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible

embolization of intraluminal material downstream

5. Occlusive thrombus

a. 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 theside 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

Probable Stent Thrombosis

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

a. Any unexplained death within the first 30 days

b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible Stent Thrombosis

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

†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

Acronyms definition

ACS	Acute coronary syndrome
AE	Adverse event
ARC	Academic Research Consortium
BMS	Bare metal stent
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CK-MB	Creatine kinase – muscle brain
CRF/eCRF	Case report form / electronic case report form
CRO	Clinical research organization
DAPT	Dual Antiplatelet Therapy
DES	Drug eluting stent
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EESabp	Everolimus Eluting Stent with Abluminal Biodegradable Polymer
FFR	Fractional flow reserve
GPIIb/IIIa	Glycoprotein IIb/IIIa
IRB	Institutional Review Board
ITT	Intent-to-treat
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LCX	Left circumflex artery

LM	Left main (coronary artery)
LVEF	Left ventricular ejection fraction
MACE	Major Adverse Cardiac Event
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MI	Myocardial infarction
MRI	Magnetic resonance imaging
PCI	Percutaneous coronary intervention
QoL	Quality of life
RCA	Right coronary artery
RCT	Randomized clinical trial
SAE	Serious adverse event
SAQ	Seattle Angina Questionnaire
ST	Stent thrombosis
TIMI	Thrombolysis In Myocardial Infarction
TLR	Target lesion revascularization
TVR	Target vessel revascularization
ULN	Upper limit of normal

20.References

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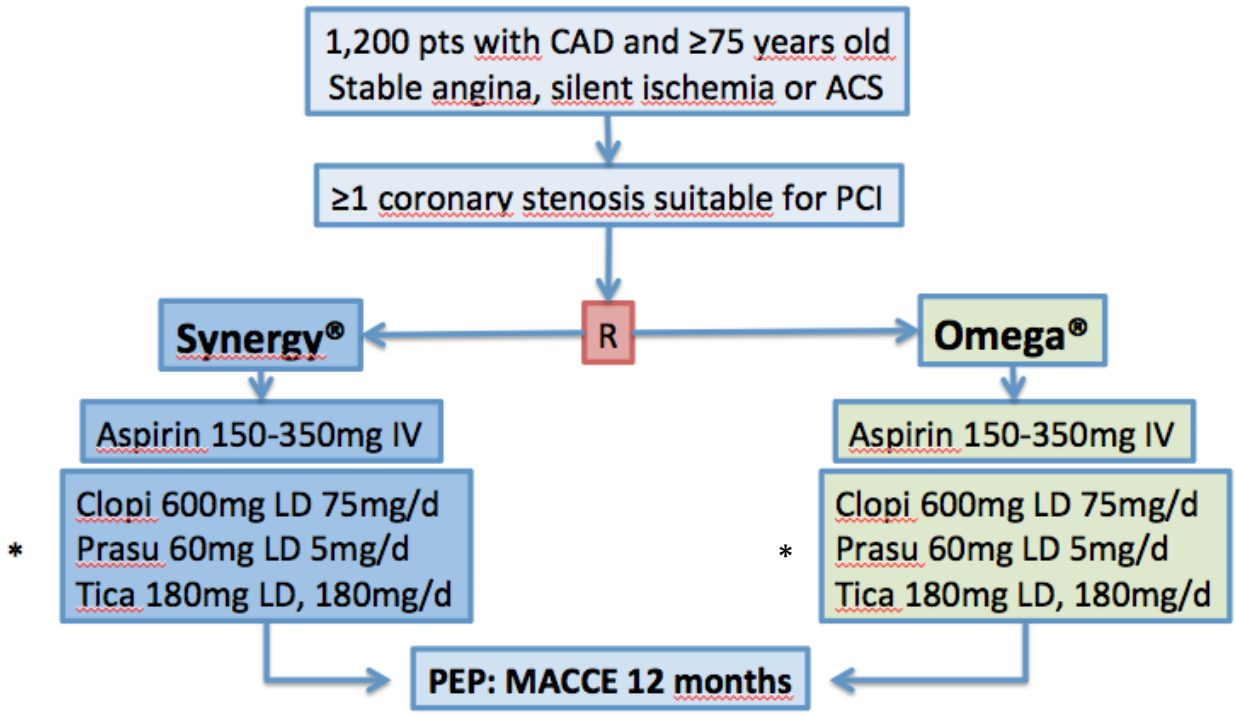
21.APPENDIX: Role of the Funding source

The funding source of the present study had no role in the design of the study, the data collection, analysis, and interpretation, or writing of the report.

The authors shared full access to the total data in the study and had final responsibility for the submission for publication.



*One of the following regimen

22.Medico-economic study

Medico economic evaluation of the SENIOR study:

The Elderly population is at higher risk of bleeding than the younger one and for this reason often receive bare metal stents (BMS) to avoid to be exposed of the risk of bleeding of the 6 months to one year treatment with dual antiplatelet required by the drug eluting stents (DES). A new generation of DES (Synergy, BSCI) seems to allow more rapid healing of the artery thanks to a rapid bioabsorbable coating) and permits an antiplatelet treatment as short as the one of a BMS; if so it provides the advantage of reducing restenosis rate like a DES being as safe as a BMS.

The SENIOR trial compares the BMS Omega®/Rebel® to the DES Synergy® II in a population older than 75.

The initial hospital costs of treating the patients should be the same, except the price of the DES which is superior to the BMS one. During the one year follow up, the potential costs associated to bleeding should be the same in the two groups as they receive the same antiplatelet treatment, but it is expected that the group receiving the DES should have less rehospitalisation for re-intervention and this should at least counterbalance the initial difference in the costs of the stents.

Economic evaluation

An economic evaluation along the SENIOR trial in the context of the healthcare systems in participating counties is performed. The incremental cost-effectiveness ratio (i.e. the net incremental cost of PCI treatment with the Synergy® II stent over the one of the Omega®/Rebel® stent divided by the net incremental health outcomes of each strategy) will be estimated. The time horizon is 1 year (i.e. the duration of follow-up). The perspectives chosen

for the economic analyses are: 1) the payer (National Health Service or Social Health Insurance) and 2) the hospital.

Analyses will be performed using direct medical costs. Given the time horizon, no discounting is required. The primary analysis will be a cost-effectiveness analysis. Effectiveness will be majored by the incidence of MACCE.

We do not account for indirect costs or for nonmedical costs. A secondary analysis will compare QALYs and an estimated cost-utility ratio.

Costs

Costs for each strategy include:

- the initial procedural costs for patients in the PCI+ DES arm
- the initial procedural cost for patients in the PCI+ BMS arm
- costs during the 1-year follow-up for all patients.

Per diem costs of CCU and ward admission will be added to procedure costs.

In order to limit data collection costs we propose to perform microcosting on a voluntary basis in centers where computerized information on resource utilization and costs is available.

Index procedure

Cost of the index procedure for patients randomized in the PCI + DES and PCI + BMS arm will be estimated from the latest DRG schedule at the date of the study completion in countries where DRGs are used and from the hospitals' billing in other countries. Physicians' fees will be added whenever relevant.

Follow up

Hospital costs

Costs of repeat PCI without MI, repeat PCI, MI, coronary artery bypass grafting, other adverse events are based on payer's reimbursement rate per diagnosis-related group.

Costs of admission in rehabilitation hospitals are also considered. The total number of days in rehabilitation centers is recorded on the CRF.

The national average reimbursement rate for each of DRG is publicly available. DRG information for each event is obtained either directly from the participating hospital's information system or by allocating DRGs from the diagnosis and procedure codes collected in the CRF. For rehabilitation centers the cost of admission is estimated either by a specific DRG or by a per diem, depending on the country.

Health Outcomes

QALYs are derived from health-related quality of life (EQ-5D -5 L) and MACCE and survival during the 1-year time horizon of the trial. Quality-of-life indexes (utilities) were evaluated at baseline, after 1 year and after 2 years using the EuroQuol 5 dimension health survey with weights from the participating countries where these weights are available (UK, Germany, France...). (8)

The overall QALYs are estimated as the area under the curve determined by these 3 values. Missing data are replaced with estimates using bootstrap resampling within the respective study arm.

Results of the economic evaluation are be presented in incremental cost effectiveness (MACE averted) and cost utility ratios (additional cost per additional QALY) (9-10)

Statistical Analysis

Categorical data are reported as frequencies, and continuous data are given as mean ± SD. Categorical data are compared by use of the χ^2 test. Continuous data (costs and QALYs) are compared by use of the Student *t* test. We report 95% confidence intervals when appropriate. Confidence intervals for both differences in QALYs and costs are estimated by the bootstrap

technique using the percentile method and 5000 replications. A 2-sided value of $P < 0.05$ is considered to indicate statistical significance.

An analysis of resource utilization can be performed by pooling data from participating centers. The analysis of costs requires a different approach because of differences in unit prices for labor and DRGs. We propose 2 different analyses, 1) an analysis per country, using the country-specific unit costs and resource utilization for the sub population of patients recruited in the country. This analysis can be performed only in countries with a large recruitment; 2) a pooled analysis with standardization of unit costs on country specific costs, for each country in turn. (9)

Sensitivity analyses are performed for a range of ±10% on all prices and for ±10% on utilities. All analyses are performed with the use of STATA (StataCorp, 2009).