ECRI-002

SYNTAX-II Clinical Investigational Plan

A single-arm trial to evaluate the effectiveness of PCI of de novo 3-vessel disease applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance, using an everolimus-eluting stent with biodegradable abluminal coating

Version 2.0, November 27th, 2013

Sponsor:

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Protocol approval page

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Protocol version: 2.0, dated 27 November 2013

We, the undersigned, have read and approved the protocol specified above, and agree upon the contents:

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1 PROTOCOL SYNOPSIS

Protocol Number	ECRI-002
Title	A single-arm trial to evaluate the effectiveness of PCI of de novo 3-vessel disease applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance, using an everolimus-eluting stent with a biodegradable abluminal coating.
Objective	• To evaluate the effectiveness of contemporary PCI treatment of de novo 3-vessel disease following the heart team selection applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance (SYNTAX II strategy) • To establish superiority of the SYNTAX II strategy compared to the PCI arm of the SYNTAX I study (Primary endpoint) • To prospectively assess the effectiveness of the SYNTAX Score II for heart team decision making • To prospectively validate the SYNTAX Score II for all-cause death at 1 and 2 year and 5 year follow-up; • To retrospectively validate the residual SYNTAX Score (academic research)
Treatment	SYNTAX II strategy consists of contemporary PCI of de novo 3-vessel disease following the heart team consensus applying the SYNTAX Score II for the heart team selection of patients, pressure wire functional assessment of lesions and IVUS optimization of DES implantation.
Study design	The SYNTAX II Trial is a multicenter, 3-vessel disease, all-comers, open-label, single-arm trial of approximately 450 patients in approximately 25 interventional cardiology centres in Europe. All patients will be treated with an everolimus-eluting stent with a biodegradable abluminal coating. Comparisons will be undertaken using the completed SYNTAX I Trial as a control: Primary endpoint: comparison with PCI (TAXUS Express[2]);.
Number of Subjects	450 subjects in total
Investigational Sites	Up to approximately 25 sites in Europe
Follow-up	In-hospital and additional follow-up visits at 1 month, 6 months and 12 months after enrolment.

	In addition, patients will be contacted annually by telephone up to 5 years to check survival status and other MACCE components (patient reported).
Primary Endpoint	The primary endpoint is a composite of MACCE rate (all-cause death, cerebrovascular event (stroke), documented myocardial infarction, or all-cause revascularization) at 1 year follow-up (SYNTAX I definition) compared to PCI arm of the SYNTAX I Trial (Patient Oriented Clinical Endpoint).
Secondary Endpoints	• Composite of all-cause death, cerebrovascular event (stroke), documented myocardial infarction at 1 year follow-up compared to the PCI arm of SYNTAX I; (Safety Endpoint) • Composite of cardiovascular death, documented target-vessel myocardial infarction and repeat target lesion revascularization at 1 year follow-up compared to the PCI arm of SYNTAX I; (Device Oriented Clinical Endpoint) • Rates of individual components of MACCE (all-cause death, cerebrovascular event (stroke), documented myocardial infarction and repeat revascularization) at 1 year; • The composite of MACCE and its individual components at 2-5 years follow-up (patient reported); • Myocardial Infarction – according to Universal MI definition 2012 at all timepoints; • Stent Thrombosis – according to ARC definitions at all timepoints;
Exploratory Endpoint	• Composite of MACCE (all-cause death, cerebrovascular event [stroke], documented myocardial infarction or all-cause revascularization) at 5 years follow-up compared to CABG arm of the SYNTAX I Trial.
General Inclusion and Exclusion Criteria	**Inclusion Criteria:** 1. At least 1 stenosis (angiographic, visually determined de novo lesions with ≥50% DS) in all 3 major epicardial territories (LAD and/or side branch, CX and/or side branch, RCA and/or side branch) supplying viable myocardium without left main involvement; (Patients with ostial LAD *or* ostial CX - Medina 0,0,1 *or* Medina 0,1,0 – may be enrolled)

2. Patients with hypoplastic RCA with absence of descending posterior and presence of a lesion in the LAD and CX territories may be included in the trial as a 3VD equivalent;
3. Vessel size should be at least 1.5 mm in diameter as visually assessed in diagnostic angiogram;
4. Patients with

a) stable (Canadian Cardiovascular Society Class 1, 2, 3 or 4) angina pectoris;

b) or unstable (Braunwald class IB, IC, IIB, IIC, IIIB, IIIC) angina pectoris and ischemia;

c) or patients with atypical chest pain or those who are asymptomatic provided they have myocardial ischemia (e.g. treadmill exercise test, radionuclide scintigraphy, stress echocardiography);

5. All anatomical SYNTAX Scores are eligible for initial screening with the SYNTAX Score II;
6. Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethical Committee of the respective clinical site;
7. Signed Heart Team Decision Form between local cardiologist and surgeon that the selected case meets all of the inclusion and exclusion criteria;

Exclusion Criteria:

Candidates will be ineligible for enrolment in the study if any of the following conditions apply:

1. Under the age of 21 years;
2. Known pregnancy at time of enrolment. Female of childbearing potential (and last menstruation within the last 12 months), who are not taking adequate contraceptives. Female who is breastfeeding at time of enrolment;
3. Prior PCI or CABG;
4. Ongoing acute myocardial infarction and enzymes CKMB >2x upper limit of normal;
5. Concomitant cardiac valve disease requiring surgical therapy (reconstruction or replacement);
6. Single or two-vessel disease (at time of Heart Team consensus);

	7. Participation or planned participation in another cardiovascular clinical study before one year follow up is completed; 8. Mental condition (psychiatric or organ cerebral disease) rendering the subject unable to understand the nature, scope, and possible consequences of the study or mental retardation or language barrier such that the patient is unable to give informed consent and potential for non-compliance towards the requirement in the study protocol.
Antiplatelet Medication	Dual Antiplatelet treatment is mandatory for at least 6 months; aspirin indefinitely. *Loading dose:* • All patients must receive aspirin ≥300 mg/day starting 12-24 hours prior to the procedure (even if the subject is on chronic aspirin therapy). • Clopidogrel loading dose must be 600 mg, starting 12-24 hours prior to the procedure (even if the subject is on chronic clopidogrel therapy). Alternatively: • Prasugrel 60 mg >1 hr before PCI; or • Ticagrelor 180 mg >1 hr before PCI if approved by the local regulatory authorities during the enrolment period of this protocol. *Maintenance dose:* Starting from the day after the procedure, aspirin 75-100 mg/day will be prescribed to all patients indefinitely. Additionally, all patients must receive platelet aggregation inhibition therapy for at least 6 months as currently recommended by the ESC/AHA/ACC guidelines which includes: • Clopidogrel 75 mg once daily. Alternatively: • Prasugrel 10 mg once daily; or (The dose of prasugrel may be decreased to 5mg od in patients with a weight <60 kg or age >75 years). • Ticagrelor (90mg bid)

2 INTRODUCTION

The anatomical-based SYNTAX Score (http://www.syntaxscore.com) has established itself as a tool to aid the Heart Team consensus in determining the optimal revascularization modality in patients with unprotected left main coronary artery (ULMCA) disease or de novo three vessel disease (3VD).[1-10] The anatomical based SYNTAX Score was designed and implemented in the landmark SYNTAX Trial,[4, 7, 10] as an instrument to force the interventional cardiologist and cardiac surgeon to examine the coronary angiogram, and agree that equivalent anatomical revascularisation could be achieved. Only after the publication of the SYNTAX Trial did the importance of the anatomical SYNTAX Score become clear. Namely, in appropriately guiding decision making between coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) for the treatment of complex coronary artery disease. Since publication of the SYNTAX Trial, the anatomical-based SYNTAX Score, has been validated in multiple studies, and has recently been advocated in both the US and European revascularization guidelines, as a tool to guide the clinician in determining the optimal revascularization modality (CABG or PCI) in patients with complex coronary artery disease.[8, 9, 11-13]

Dedicated studies in the post SYNTAX Trial era investigating 3VD remain scarce. As of present, current revascularization guidelines recommend that a low SYNTAX Score (0-22) may offer similar clinical outcomes between percutaneous coronary intervention (PCI) with drug eluting stents (DES) and coronary artery bypass graft (CABG) surgery.[11-13]

Diabetes

Outcomes in diabetic patients have historically lacked suitably powered randomized trials. Meta-analyses of trials comparing CABG against PCI in the pre-DES era (balloon angioplasty and bare metal stents) have shown a potential prognostic advantage of CABG compared to PCI.[14, 15] A major limitation of these studies were however that the studies were not all-comers in design, with patients 'cherry-picked' for randomisation based on restrictive inclusion and exclusion criteria, making application to clinical practice questionable.[16, 17]

In the DES era, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Trial,[18, 19] consisting of 1900 patients with two or 3VD, randomised to CABG or PCI with first generation DES, showed a prognostic advantage for CABG at a median follow up of 3.8 years. At 5 years follow up, only 678/1900 patients reached this time point, with 197 deaths recorded. In this subset of patients, there was no interaction between the SYNTAX Score and treatment (p=0.58). There was however a stepwise increase in death, MI, or stroke in patients that underwent PCI (low SYNTAX Score: 19.4%, intermediate SYNTAX Score: 22.2%, high SYNTAX Score: 31.0%), but not in those treated with CABG (low SYNTAX Score: 20.1%, intermediate SYNTAX Score: 21.5%, high SYNTAX Score: 16.0%). The FREEDOM Trial was however underpowered to assess the SYNTAX Score at 5 years.[9, 20]

Conversely, diabetics in the SYNTAX Trial (a pre-stratified powered subgroup), has shown that low SYNTAX Scores to be associated with comparable long term mortality and composite clinical outcomes (major adverse cardiac and cerebrovascular events [MACCE]).[20-22]

Left Main Coronary Artery Disease

Based on the results of the SYNTAX Trial, in which short and long term outcomes were similar between CABG and PCI in subjects with unprotected left main coronary artery (ULMCA) disease with an anatomical SYNTAX Score <33,[4, 7, 10] the EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was conceived (ClinicalTrials.gov Identifier: NCT01205776). EXCEL is an ongoing, international, multicentre trial, aiming to recruit 2600 patients with ULMCA disease and a SYNTAX Score <33 – randomized to surgical (n=1300) or percutaneous (with the XIENCE PRIME or XIENCE V DES [n=1300]) revascularization.[23] Notably the US Food and Drug Administration (FDA) mandated the anatomical-based SYNTAX Score as entry criteria within the EXCEL Trial.

SYNTAX Score II

The category based risk approach of the anatomical-based SYNTAX Score – i.e. "low", "intermediate," or "high" SYNTAX Scores – to guide decision making between CABG or PCI, has been shown to be potentially misleading in a post hoc analysis of the SYNTAX Trial.[24] Within this study, it was shown that low and high risk subjects existed in higher and lower SYNTAX Score tertiles, which appeared to have implications for the most appropriate revascularisation modality (CABG and PCI); e.g. there was a doubling of 3-year mortality in subjects with 3VD – with a low SYNTAX Score (<23) and a high additive EuroSCORE (≥6) – who underwent PCI compared to CABG.[24] In addition, a recent study pooling over 6000 PCI subjects treated with DES, demonstrated that the addition of clinical variables to the anatomical SYNTAX Score, substantially increased the accuracy of identifying low (and high) risk patients compared to the anatomical SYNTAX Score alone.[25]

The SYNTAX Score II[26, 27] was designed to improve decision making between CABG and PCI, by allowing for a long term, individualized risk assessment of patients with complex coronary artery disease. The SYNTAX Score II combined the anatomical based SYNTAX Score with clinical variables, that were shown to alter the threshold value of the SYNTAX Score so that equipoise was achieved between CABG and PCI for long term mortality. These included the presence of unprotected left main coronary artery disease, female gender,[28] chronic obstructive pulmonary disease, age and left ventricular ejection fraction. The SYNTAX Score II was developed in the randomized SYNTAX Trial (n=1800), and validated in the multicentre Drug Eluting stent for LefT main coronary Artery disease (DELTA) Registry (n=2891).[29] Importantly the DELTA Registry was a multinational, non-randomised, all-comers registry, conducted in 14 centres in Europe, US and South Korea. The study population was heterogeneous, and included complex coronary artery disease – anatomical SYNTAX Score ≥33 existed in 30%, and 3VD in 26%, of the DELTA Registry.

During development and validation of the SYNTAX Score II, it was shown that diabetes did not improve decision making between CABG and PCI. Findings that were consistent with a previous study of over 6000 patients treated with DES, where it was shown that the presence of diabetes minimally affected long term mortality predictions after PCI with DES, when age, kidney

function and left ventricular ejection fraction were accounted for.[25] Subsequent epidemiology/population based studies have further supported these findings.[30, 31]

By utilizing the individualized approach of the SYNTAX Score II, in contrast to the anatomical-based SYNTAX Score tertiles, a subset of patients with low, intermediate or high SYNTAX Scores were identified, that would have lower, similar, or higher 4-year mortality predictions for CABG or PCI. Specifically for 3VD, approximately 80%, 60% and 30% of patients in the respective low, intermediate and high SYNTAX Score tertiles of the randomised SYNTAX population would have similar long-term mortality between CABG and PCI (**Appendix II**).

Contemporary PCI Practice and the SYNTAX Trial

Overall, the amount of information gathered in the SYNTAX Trial has helped shape both clinical practice and international guidelines in the management of complex coronary artery disease. The conclusions drawn in the SYNTAX Trial since its publication do however not take into account areas in which the progress has been made in more contemporary interventional practice. Some of these are discussed in the following paragraphs:

1) ***Chronic total occlusion recanalization:*** In SYNTAX, the presence of a (chronic) total occlusion (C)TO was identified to be the strongest independent predictor of incomplete revascularisation in the PCI arm of the SYNTAX Trial.[32, 33] Over the last 10 years the practice of (C)TO recanalization has been largely modified by the systematisation in the approach to (C)TO recanalization and the development of new devices. Although acquaintance with these techniques is still limited among interventional cardiologists, international registries have consistently reported that skilled, dedicated (C)TO operators have success rates of 85-95%, a much higher success rate that that observed in SYNTAX operators (approximately 50%).[34] Major technical improvements include the development of new coronary wires, dedicated intracoronary cathethers (Corsair,® Tornus,® CrossBoss™) and re-entry devices (The Stingray™ CTO Re-Entry System).[35] Contemporary (C)TO procedures are performed both in anterograde or retrograde fashion (through collateral channels), frequently with the concourse of IVUS imaging. Virtually all these developments were not applied to (C)TO recanalization in SYNTAX. It will therefore be encouraged that each participating centre should select an expert

in (C)TO revascularisation who should be involved in the procedure whenever a (C)TO is involved.

2) ***Ischemia-driven revascularisation****:* A large body of evidence, largely based on the use of fractional flow reserve (FFR), has demonstrated that, compared with angiography, decision making of coronary revascularisation based on physiological assessment of stenosis severity results in improved patient outcomes.[36-39] Recalculation of the SYNTAX score by incorporating FFR-derived information of stenosis severity (functional SYNTAX score[40]) may decrease the number of higher-risk patients with multivessel disease undergoing PCI and contribute to a better discrimination of risk for adverse events in this subset of patients. A new pressure-derived index, instantaneous wave-free ratio (iFR), that allows faster adenosine-free assessment may be more ideally suited for multiple measurements performed in the context of multivessel disease.[41]

3) ***Imaging guidance of PCI procedures****:* While the proposal of using intravascular ultrasound (IVUS) to tackle restenosis made in the bare metal stent (BMS) era was virtually abandoned with the arrival of drug eluting stents (DES), a growing body of evidence suggests that DES implantation with IVUS guidance in complex anatomical subsets may contribute to better patient outcomes. Specifically, a recent meta-analysis of IVUS guided DES implantation in almost 20 000 subjects has reported significantly reductions in stent thrombosis and mortality.[42, 43]

4) ***Newer generation DES****:* Compared to first generation DES, newer generation DES have proven reductions in stent thrombosis and other clinical outcomes. This has largely been through the design of more biocompatible polymers, biodegradable polymers, limus based drugs, thinner stent struts through the incorporation of metallic alloys with greater radial strength, and increased deliverability of the devices.[44-49] Outcomes of the SYNTAX Trial related to newer generation DES are therefore unknown and will be investigated in the current study.

Purpose of Study

The purpose of the planned SYNTAX II Trial is to investigate the management of de-novo 3VD in order to prospectively assess which patients would have at least comparable short and long term clinical outcomes between CABG and PCI, using contemporary PCI practice. In SYNTAX II the effectiveness of a contemporary stent (the new generation SYNERGYTM DES, designed with thinner struts, biocompatible and biodegradable polymer, and a limus based drug[50, 51]), the use of pressure wire assessment of lesions to allow for ischemia-driven revascularisation, IVUS guidance to optimise DES deployment, and the treatment of (C)TO lesions with contemporary techniques, will be compared against PCI practice in the original SYNTAX trial. The proposed study would involve the SYNTAX Score II to prospectively recruit subjects on the grounds of patient safety.[26, 27]

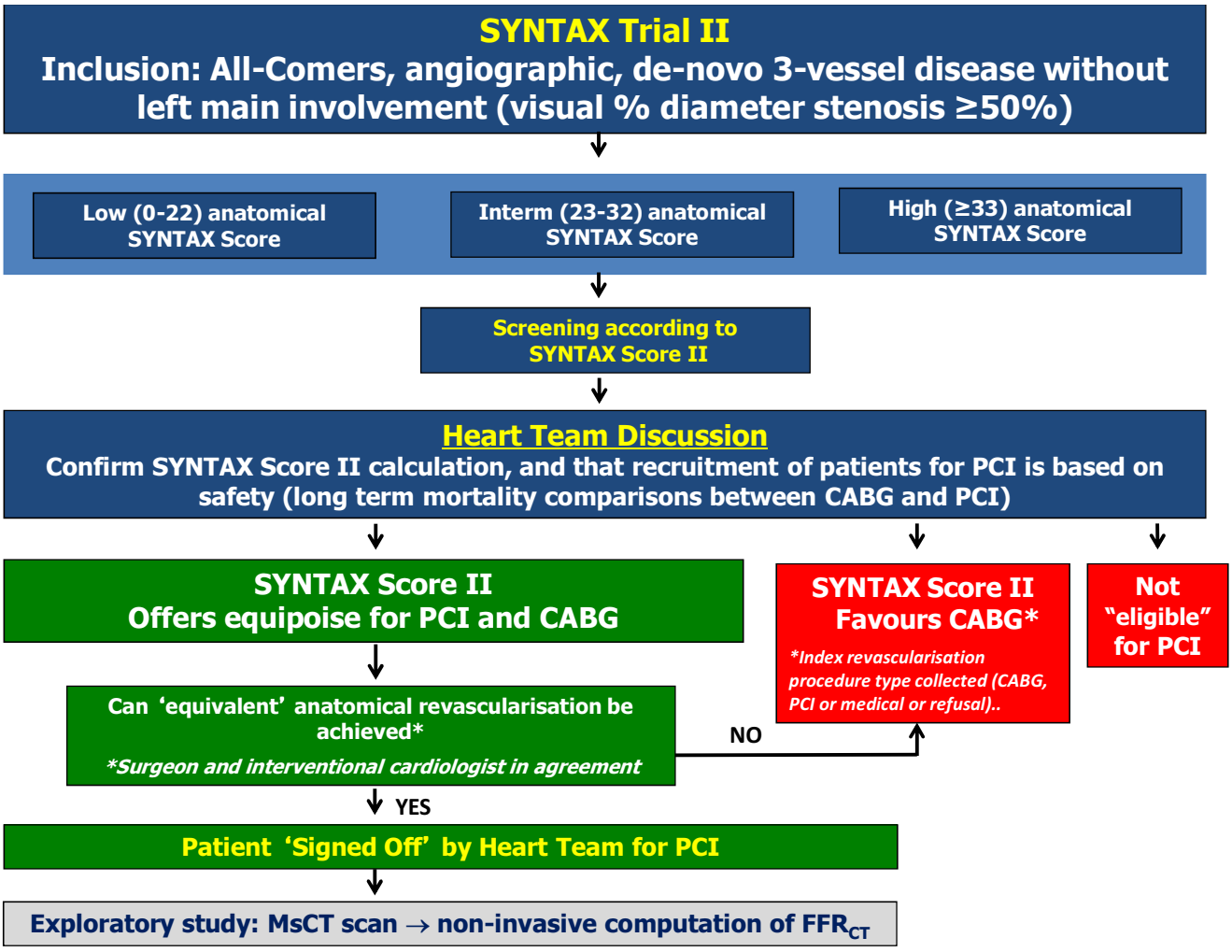
3 OBJECTIVE

- To evaluate the effectiveness of contemporary PCI treatment of de novo 3-vessel disease following the heart team selection applying the SYNTAX Score II with pressure wire functional assessment and IVUS guidance (SYNTAX II strategy).
- To establish superiority of the SYNTAX II strategy compared to the PCI arm of the SYNTAX I study (Primary Endpoint).
- To prospectively assess the effectiveness of SYNTAX Score II for heart team decision making.
- To prospectively validate the SYNTAX Score II for all-cause death at 1 and 2 year and 5 year follow-up.
- To retrospectively validate the residual SYNTAX Score (academic research)[52, 53].

Comparisons will be undertaken using the completed SYNTAX I Trial as a historical control:4
Primary Endpoint – PCI cohort (TAXUS Express2);

4 STUDY DESIGN

The SYNTAX-II Trial is a multicenter, 3-vessel disease, all-comers, open-label, single arm trial of approximately 450 patients in approximately 25 interventional cardiology centres in Europe. All patients will be treated with the Boston Scientific SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System.



Study Flowchart: Part-1: Heart Team algorithm

1. All patients with *de-novo* 3-vessel disease (DS ≥50%), with no left main involvement, will be screened by the local Heart Team (interventional cardiologist and cardiac surgeon). Initial enrolment criteria will be unrestrictive and similar to the SYNTAX Trial.[3, 4] As per the original SYNTAX Trial, prior CABG or PCI will be one of the very few exclusion criteria.
2. All patients will have anatomical SYNTAX Scores and EuroSCOREs (I and II)[54-58] undertaken, and will undergo further assessment by the Heart Team for enrolment in the study.
3. All patients will have the SYNTAX Score II prospectively determined by the Heart Team using an online calculator (**Appendix III**). The SYNTAX Score II will be used to objectively determine if the patient is suitable for PCI, CABG, or both revascularization modalities. Based on SYNTAX Score II in the SYNTAX Trial, approximately 80%, 60% and 30% of patients in the low, intermediate and high SYNTAX Score tertiles respectively, would have at least similar long-term mortality between CABG and PCI (**Appendix II**). Patients not suitable for PCI based on the SYNTAX Score II assessment will undergo CABG, unless contraindicated. In patients not eligible for SYNTAX II trial, the index revascularisation procedure type will be collected (i.e. CABG, PCI, medical treatment or refusal).

<u>Equivalent Anatomical Revascularization</u>

As per the SYNTAX Trial, patients must be able to undergo "*equivalent anatomical revascularization,*" based on the SYNTAX Trial definition of 1.5 mm vessels being revascularised, as agreed by the cardiac surgeon and interventional cardiologist during the Heart Team meeting.[3] Patients not suitable for equivalent anatomical revascularization will undergo CABG, unless contraindicated. For patients not eligible for SYNTAX II trial, the index revascularisation procedure type will be collected (i.e. CABG, PCI, or medical treatment or refusal).

Exploratory sub-study

After the Heart Team consensus, but prior to PCI procedure, a multislice computed tomography (MSCT) scan should be obtained (documentary only). MSCT will not be used in process of Heart Team discussion. The MSCT scan will be processed by HeartFlow Inc. (Redwood city, California, USA). HeartFlow's technology enables the computation of FFR_{CT} in a non-invasive manner.[8, 59-62] Results will only become available after completion of the SYNTAX II study.

Reporting of Study Endpoints

The primary endpoint will be reported at 1 year. At 2-5 years follow-up, all patients will be contacted by telephone to check survival status and other MACCE components (patient reported). From all screened patients the index treatment type (i.e. CABG, PCI, medical, other) will be collected.

Clinical data will be adjudicated by an independent Clinical Event Committee (CEC). Ongoing safety monitoring will be performed by a Data Safety Monitoring Board (DSMB).

4.1 Risk Factor Modification

Tight control of risk factors will be mandated in line with the European and US revascularisation guidelines.[11, 12] Cholesterol reduction, with a LDL ≤1.8, will be an additional protocol defined target the operator will be recommended to record and control.

In summary, patients (de-novo 3VD) will be treated according to ACC/AHA/ESC guidelines, i.e. Heart Team discussion (Ia); functional evaluation for diagnosis in absence of objective evidence of ischemia (Ia); and LDL levels ≤1.8mmol (Ia).

5 ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is a composite of MACCE at 1 year follow-up compared to PCI arm of the SYNTAX I Trial (acting as a historical control) (Patient Oriented Clinical Endpoint)

MACCE is defined as: all-cause death; cerebrovascular event (stroke); documented myocardial infarction or all-cause revascularization).

5.2 Secondary endpoints

Secondary endpoints of this study are to assess:

- Composite of all-cause death, cerebrovascular event (stroke), documented myocardial infarction at 1 year follow-up compared to the PCI arm of SYNTAX I; (Safety Endpoint)
- Composite of cardiovascular death, documented target-vessel myocardial infarction and repeat target lesion revascularization at 1 year follow-up compared to the PCI arm of SYNTAX I; (Device Oriented Clinical Endpoint)
- Rates of individual components of MACCE (all-cause death, cerebrovascular event (stroke), documented myocardial infarction and repeat revascularization) at 1 year;
- The composite of MACCE rate and its individual components at 2-5 years follow-up (patient reported);
- Myocardial Infarction – according to Universal MI definition 2012 at all timepoints;
- Stent Thrombosis – according to ARC definitions at all timepoints;

5.3 Exploratory endpoint

- Composite of MACCE (all-cause death, cerebrovascular event (stroke), documented myocardial infarction or all-cause revascularization) at 5 years follow-up compared to CABG arm of the SYNTAX I Trial

6 SUBJECT SELECTION

Patient selection will be from all-comers de novo 3VD patients. Anatomical SYNTAX and SYNTAX II Scores, will be undertaken to objectively determine if CABG or PCI offer a least similar long term mortality.

Approximately 450 3-vessel disease all-comers patients will be enrolled. The recruitment will be competitive.

6.1 Inclusion Criteria

1. At least 1 stenosis (angiographic, visually determined de novo lesions with ≥50% DS) in all 3 major epicardial territories (LAD and/or side branch, CX and/or side branch, RCA and/or side branch) supplying viable myocardium without left main involvement;
   (Patients with ostial LAD *or* ostial CX - Medina 0,0,1 *or* Medina 0,1,0 – may be enrolled)
2. Patients with hypoplastic RCA with absence of descending posterior and presence of a lesion in the LAD and CX territories may be included in the trial as a 3VD equivalent;
3. Vessel size should be at least 1.5 mm in diameter as visually assessed in diagnostic angiogram;
4. Patients with
   a) stable (Canadian Cardiovascular Society Class 1, 2, 3 or 4) angina pectoris;
   b) or unstable (Braunwald class IB, IC, IIB, IIC, IIIB, IIIC) angina pectoris and ischemia;
   c) or patients with atypical chest pain or those who are asymptomatic provided they have myocardial ischemia (e.g. treadmill exercise test, radionuclide scintigraphy, stress echocardiography);
5. All anatomical SYNTAX Scores are eligible for initial screening with the SYNTAX Score II;
6. Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethical Committee of the respective clinical site;
7. Signed Heart Team Decision Form between local cardiologist and surgeon that the selected case meets all of the inclusion and exclusion criteria;

6.2 Exclusion Criteria

Candidates will be ineligible for enrolment in the study if any of the following conditions apply:

1. Under the age of 21 years;
2. Known pregnancy at time of enrolment. Female of childbearing potential (and last menstruation within the last 12 months), who are not taking adequate contraceptives. Female who is breastfeeding at time of enrolment;
3. Prior PCI or CABG;
4. Patients with ongoing acute myocardial infarction and enzymes CKMB >2x upper limit of normal;
5. Concomitant cardiac valve disease requiring surgical therapy (reconstruction or replacement);
6. Single or two-vessel disease at the time of Heart Team consensus;
7. Participation or planned participation in another cardiovascular clinical study before one year follow up is completed;
8. Mental condition (psychiatric or organ cerebral disease) rendering the subject unable to understand the nature, scope, and possible consequences of the study or mental retardation or language barrier such that the patient is unable to give informed consent and potential for non-compliance towards the requirement in the study protocol.

7 STUDY PROCEDURES

7.1 Patient Information and Informed Consent

All potential subjects must be consented prior to undergoing any study-specific procedures. 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 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.

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 ISO14155, EC requirements and country specific regulations.

7.2 Baseline evaluation

The following routine tests will be performed:

a) Routine laboratory tests prior to the procedure according to local hospital practice. Creatinine and creatinine clearance (Cockcroft and Gault[63]) are mandated to be performed prior to procedure. Cardiac enzymes must be sampled prior to the PCI procedure in order to detect acute myocardial infarction (AMI) patients. Prior to the PCI procedure the cardiac enzymes (CK-MB or Troponin) must be less than 2-times the upper limit of normal (<ULN).
b) 12-lead electrocardiogram pre, and post procedure and at discharge

7.3 Anatomical, residual and functional SYNTAX Scores

The baseline anatomical SYNTAX Score and SYNTAX Score II will be recorded in the eCRF. All procedural coronary angiograms will be collected and allowances made for the export of this data to Cardialysis, Rotterdam. No analyses will be performed by the Core Laboratory. At a later stage post hoc analysis of the baseline anatomical SYNTAX Score, residual SYNTAX Score[52, 53] and functional SYNTAX Score[40] will be undertaken (academic research).

7.3.1 EuroSCORE and EuroSCORE II

EuroSCORE and EuroSCORE II will be collected and recorded in the eCRF.

7.4 Patient Allocation

Calculation of the SYNTAX Score II and prognostic outcomes (mortality predictions) following CABG or PCI will be determined at 4 years using the SYNTAX Score II online calculator. Individual mortality predictions for CABG and PCI that can be separated with 95% confidence (ie, that can be statistically separated, p<0•05) will have a treatment recommendation for either CABG alone or PCI alone. Individual mortality predictions for CABG and PCI that cannot be separated with 95% confidence (i.e., could not be statistically separated, p>0•05) will have a treatment recommendation for either CABG or PCI.

Comparisons of 4 year mortality predictions will be undertaken using the SYNTAX Score II online calculator, which will incorporate statistical comparisons of mortality predictions for CABG and PCI (as previously highlighted). The online calculator will provide the heart team with an objective treatment recommendation, namely, CABG is recommended, PCI is recommended, or either CABG or PCI is recommended. Final decision of treatment recommendation will be left at the discretion of the heart team after formal dialogue with the patient and provision of the prognostic information. The heart team may overrule the treatment recommendation made by the online calculator. Reasons for undertaking this should be clearly documented in the eCRF.

Having established that the patient could be potentially recruited based on the SYNTAX Score II on the grounds of patient safety, subjects will be assessed by the heart team as to whether *"equivalent anatomical revascularization"* could be potentially achieved between CABG and PCI. Secondly, the heart team must clearly establish that both CABG and PCI would be equally offered to the patient. If the patient fulfils both criteria then the patient may be recruited in the SYNTAX II Trial.

The decision for the subject's inclusion into SYNTAX II will be documented and *'signed off'* by both members of the local Heart Team (Heart Team Worksheet) - subsequently investigator will receive patient allocation number.

7.5 MSCT

After Heart Team consensus, but prior to the planned PCI procedure, a MSCT scan should be obtained (documentary only). Refer to Appendix VI for MSCT acquisition protocol. The MSCT results and results of MSCT-derived FFR will only become available after completion of the SYNTAX II study, and therefore investigators will be blinded to its results during the study. Furthermore, the analysis of MSCT and FFR_{CT} will be performed by analysts blinded to iFR/FFR and angiographic data.

7.5.1 MSCT and angiographic SYNTAX Score: Exploratory Endpoint

- To prospectively examine the value of an objective anatomic SYNTAX Score based on non-invasive MSCT imaging - compared to conventional angiographic SYNTAX Score as visually assessed by the Heart Team.

7.5.2 MSCT and non-invasive FFR_{CT}: Exploratory Endpoints

- To prospectively compare, in a population of patients with multi-vessel disease, functional stenosis severity assessed with non-invasive FFR_{CT} with invasive functional assessment with iFR/FFR, using per-vessel comparisons. Per vessel analysis will be performed to calculate the percentage of vessels properly classified by MSCT-FFR, in terms of haemodynamic stenosis severity, compared to invasive iFR/FFR measurements.
- To prospectively compare, in a population of patients with multi-vessel disease, functional SYNTAX scores calculated from a) multi-slice computed tomography coronary angiography and non-invasive FFR, and b) conventional angiography and iFR/FFR. In both a) and b), functional SYNTAX score is defined as anatomical SYNTAX scoring limited to vessels with haemodynamically significant stenoses (as estimated by HeartFlow [non-invasive functional SYNTAX score] or iFR/FFR [invasive functional SYNTAX score])

7.6 Index Procedure

7.6.1 iFR/FFR

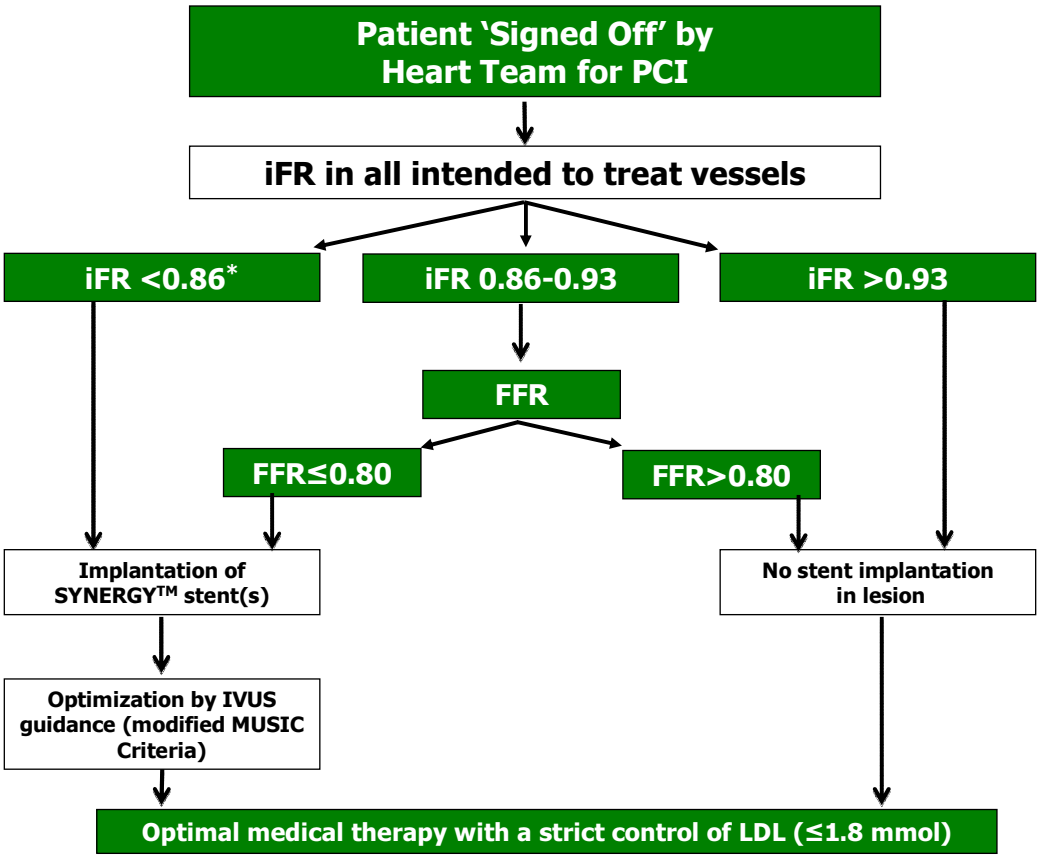
All centres must be experienced in PCI of complex coronary artery disease, utilizing functional (iFR/FFR) and IVUS guidance.

iFR is a recently introduced pressure-derived index for the assessment of coronary stenosis severity that, at difference to FFR, does not require adenosine administration and provides an estimation of stenosis severity a few seconds after crossing the stenosis with the pressure guide-wire.[41] These characteristics make iFR a more ideal method to apply ischemia driven revascularisation in patients with 3VD, in whom multiple measurements are required.

The subject will undergo invasive adenosine-free iFR® assessment of all 3 major epicardial vessels. All lesions intended to be treated should be interrogated, including side-branches. Total occlusions and culprit lesions of acute coronary syndromes[64-66] preclude iFR measurements. iFR values will be collected with the PrimeWire Prestige Plus with Accuesense™ technology. In

place of the PrimeWire Prestige Plus wire, the Verrata™ wire will be permitted to be used in the study once the wire has received an expected CE-mark.

In SYNTAX II ischemia driven revascularisation will be performed following a hybrid decision-making strategy of coronary revascularisation with iFR and FFR.[67] The use of a hybrid iFR/FFR approach, currently undergoing testing in the ADVISE II study (ClinicalTrials.gov Identifier: NCT01740895) has the potential of significantly reducing the need for adenosine administration, whilst maintaining a 95% classification agreement to the FFR-only strategy.[67]



**** Consider FFR pullback with sequential lesions***

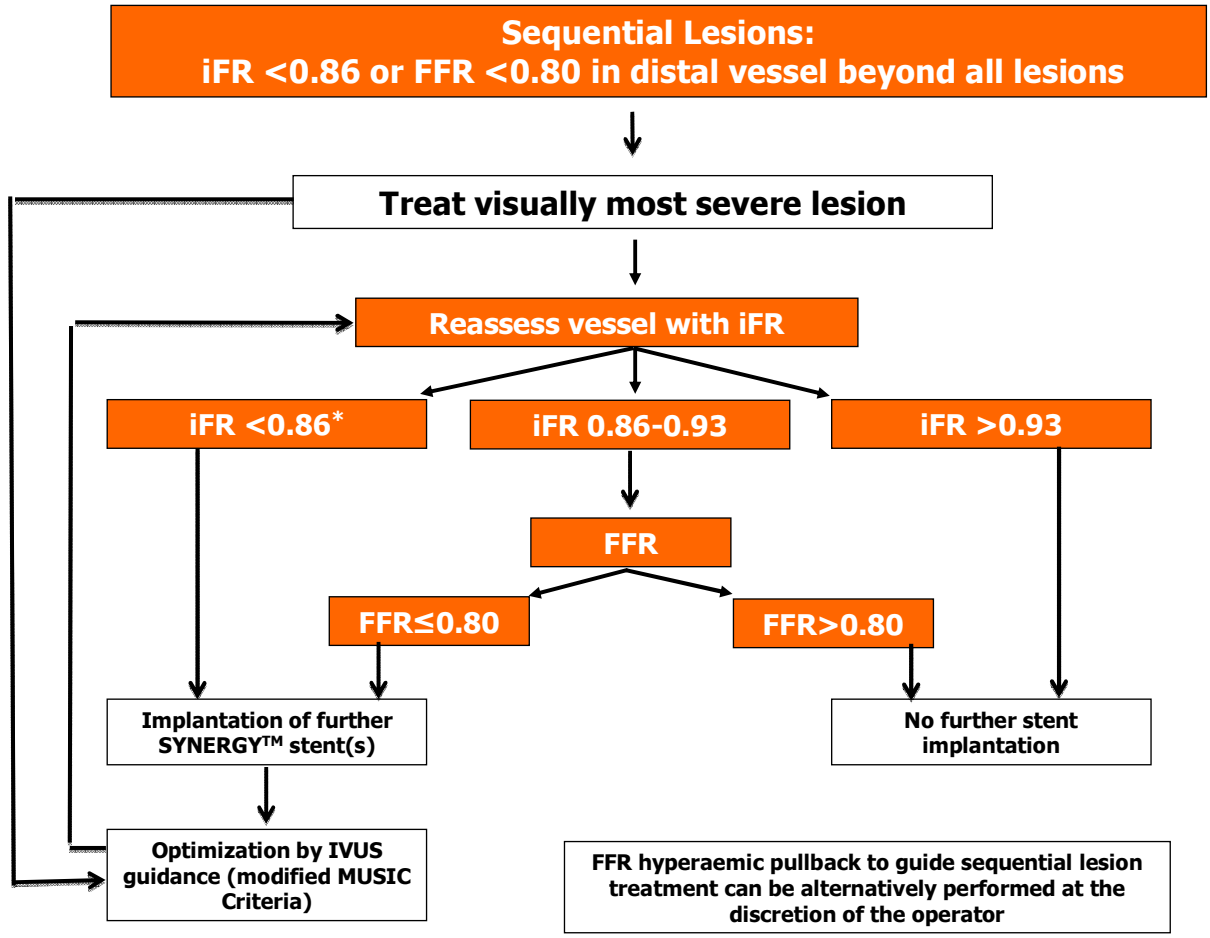
Study Flowchart: Part-2: PCI procedure

iFR values will be collected with the PrimeWire Prestige Plus (or Verrata™ wire) with Accusense™ technology.

In case of iFR <0.86 the lesion will be treated by PCI. If iFR is ≥0.86 and ≤0.93, FFR is mandated to be measured using i.v. or i.c. adenosine, and the decision to treat will be based on an FFR cutoff of 0.80. iFR >0.93 the stenosis should not be treated.

In subjects with contraindications to adenosine administration, revascularisation will be performed using iFR as a dichotomous index, using most recently reported cutoff value of iFR <0.89 for haemodynamic significance.[67]

In case of sequential lesions, the procedure depicted in the flowchart should be followed.



Study Flowchart: Part-2a: PCI procedure (sequential lesions)

iFR/FFR values will be recorded in the eCRF. No analysis will be performed by the core laboratory. Export of recordings to Cardialysis will be performed for post hoc analysis at a later stage (academic research).

7.6.2 Stent implantation

Stent implantation will be performed according to routine local clinical practice using the femoral, brachial or radial approach with the intention of achieving equivalent anatomical revascularization to CABG. The radial approach, although not mandated, will be strongly recommended.[68]

Patients will exclusively be implanted with the SYNERGY™ stent.[50, 51] Stenting should be attempted for each lesion in a vessel with a >1.5 mm in diameter as assessed on the diagnostic angiogram and agreed to be revascularised by the Heart Team in order to achieve equivalent anatomical revascularization.

IVUS use at pre-PCI is left to the discretion of the investigator. IVUS assessment post stent implantation for optimisation of stent deployment is mandated (see part 7.5.3).

If the implantation of the SYNERGY stent was not successful, the reason should be recorded in the CRF.

7.6.2.1 Treatment of Bifurcations

All types of bifurcation may need stenting of the main vessel, and/or the side branch, followed by kissing balloon post-implantation if a two stent approach is adopted. The treatment goal is to avoid gaps whenever more than one stent is used. Bifurcation techniques will be selected depending on the anatomy and morphology, although it is expected that most lesions would require a simple (provisional) approach, in keeping with recommendations from the European Bifurcation Club.[69, 70]

Stent sizing in bifurcation stenoses should take into account vessel diameter mismatch between mother and daughter vessels, following the recommendations of the European Bifurcation Club[69, 70] (see also Appendix V for detailed treatment of bifurcations – mandated and recommended strategies).

7.6.2.2 Treatment of Total Occlusions

It has recently been shown that the presence of a total occlusion (TO) to be the strongest independent predictor of incomplete revascularisation in the PCI arm of the SYNTAX Trial.[32, 33] Operator skill and use of specific techniques and devices are key determinants PCI success in CTOs.[34] A dedicated chronic total occlusion (CTO) operator is recommended to be made available in all participating centres. Staging of the revascularisation procedure should be encouraged, to ensure CTOs are appropriately revascularised. CTO recanalization can be performed using the antegrade or retrograde approach, as well as using specific re-entry techniques such as the StingRay device [71] Selection of stent length can be based on IVUS imaging. Viability assessment of total occlusions will be left at the discretion of the operator.[72-77] A tolerant attitude, refraining stenting towards moderate stenoses located distal to the occluded segment should be followed, on the grounds of important vessel diameter shift after vessel recanalization.[78]

7.6.3 Intravascular Ultrasound (IVUS)

In SYNTAX II Trial, mechanical IVUS catheters (Revolution® Rotational Imaging Catheter / Volcano Therapeutics or Atlantis™ SR Pro or SR Pro2 Imaging Catheter or Opticross™ / Boston Scientific Corp) or phase array IVUS catheters (EagleEye® Platinum Digital IVUS Catheter / Volcano Therapeutics) will be used to guide SYNERGY implantation. Use of either motorised or manual IVUS pullback will be allowed, although motorised pullback is recommended.

Both Boston and Volcano IVUS consoles have incorporated simplified software algorithms into their consoles to allow for the operator to undertake these calculations, and allow export of the data for post hoc analysis at a later stage. The following are the recommendations made on the grounds of evidence collected in the DES era:

- **Plaque preparation based on pre-procedural IVUS.** Rotational atherectomy or cutting balloon should be considered if a >270° arc of superficial calcium is evident in IVUS.[79] Pre-procedural IVUS is left to the discretion of the investigator (not mandatory).
- **Selection of SYNERGY dimensions.** Separate recommendations are given for selecting SYNERGY stent diameter in bifurcation and non-bifurcation stenoses.
    - In ***non-bifurcation*** stenoses: stent diameter matching distal vessel diameter or area (See table in **Appendix IV**).
    - In ***bifurcation*** stenoses: stent diameter matching distal (daughter) branch, with mandatory post-dilation of the proximal (mother) segment and polygon of confluence (POC) with a larger balloon size according to IVUS imaging. Regarding stent length, IVUS can be useful in outlining the presence of significant neighbour stenoses that might cause in-flow or out-flow narrowing after DES implantation, a very common finding in cases of DES thrombosis that is believed to be causative.
    - **Incomplete stent *expansion*:** See IVUS criteria **Appendix IV**.
    - **Incomplete stent *apposition*.** A non-compliant balloon sized with IVUS to vessel luminal diameter or area will be used in segments with malapposition (See table in Appendix IV)

No analyses will be performed by the Core Laboratory. However, allowances will be made for export of IVUS data to Cardialysis, Rotterdam for potential post hoc analysis at later stage (academic research).

The operator will record the numerical values of the IVUS targets in the eCRF.

7.6.4 Staged procedures

Staged procedures are permitted, and will be encouraged for more complex cases – e.g. revascularization of total occlusions – to increase the likelihood of complete revascularization and to decrease the risk of contrast induced nephropathy.

The recommended timing of a planned elective staged second PCI procedure is within 2 weeks post index procedure (with an upper limit allowed for 4 weeks in exceptional circumstances). The need for staging, and all specific lesions planned to be treated during the staged procedure should be captured beforehand in the eCRF. Staged procedures are only allowed in non-target vessels. Stented index segments or immediately adjacent segment(s), including adjacent branch segment(s) should not be manipulated again. The staged procedures will not affect the original follow-up schedule. Staged procedures should be performed in the exact same manner as the index procedure, including iRF/FFR, IVUS, medications, etc.

7.7 Concomitant Medications

Optimal medical therapy will be mandated in all patients and will be assessed at clinical follow-up visits.

7.7.1 Anti-Platelet Medication

Dual antiplatelet (aspirin + clopidogrel/ticagrelor/prasugrel) will be mandated for at least 6 months, aspirin indefinitely. Ticagrelor therapy will be encouraged to be continued in patients already receiving this therapy, based on this regime having been shown to have the best safety to efficacy ratio.[80, 81]

Loading dose:

- All patients must receive aspirin ≥300 mg/day starting 12-24 hours prior to the procedure (even if the subject is on chronic aspirin therapy).
- Clopidogrel loading dose must be 600 mg, starting 12-24 hours prior to the procedure (even if the subject is on chronic clopidogrel therapy).

On the rare occasion of a patient not receiving aspirin or clopidogrel as outlined above, the procedure is to be deferred until appropriate administration of antiplatelet therapy has been attained. Loading of antiplatelet therapy immediately prior to PCI should be discouraged, since lack of pre-procedural anti-platelet therapy was linked to creatine kinase (CK) cardiac enzyme rises >2 x upper limit of normal post PCI and adverse mortality in the SYNTAX Trial.[28, 82]

Alternatively:

- Prasugrel 60 mg >1 hr before PCI; or
- Ticagrelor 180 mg >1 hr before PCI if approved by the local regulatory authorities during the enrolment period of this protocol.

Maintenance dose:

Starting from the day after the procedure, aspirin 75-100 mg per will be prescribed to all patients indefinitely.

Additionally, all patients must receive platelet aggregation inhibition therapy for at least 6 months as currently recommended by the ESC/AHA/ACC guidelines which includes:

- Clopidogrel 75 mg once daily.

Alternatively:

- Prasugrel 10 mg once daily; or
  (The dose of prasugrel may be decreased to 5mg od in patients with a weight <60 kg or age >75 years).
- Ticagrelor (90 mg bid)

7.7.2 Other medication

- Unless contraindicated, peri-procedural IIb/IIIa inhibitor will be given according to the guidelines.[11-13]
- The use of other medications (e.g. beta-blockers, ACE inhibitors) should be given in accordance to the guidelines.[11-13]

7.7.3 PCI Statin therapy

Optimal medical therapy with strict control of LDL (target of ≤1.8 mmol/l) is strongly recommended, along with optimization of all medical therapy – rosuvastatin/atorvastatin (according to the guidelines). Strict control of LDL levels is recommended aiming for a target of ≤1.8 mmol.

Several randomized trials have demonstrated that high dose statin therapy decreases PCI-related myonecrosis in subjects undergoing stent implantation, whether or not the subject is already taking chronic statin therapy.[83-87] Therefore, in the absence of absolute contraindications to statin use (e.g. severe allergy with prior use), one of the following statin regimens must be administered at least 12 hours (at least one dose) before the PCI, regardless of LDL level and history of prior statin use.

- atorvastatin 80 mg daily
- rosuvastatin 40 mg daily

Risk Factor Modification

Tight control of risk factors will be mandated in line with the European and US revascularisation guidelines.[11-13] Cholesterol reduction, with a LDL ≤1.8, will be an additional protocol defined target the operator will be recommended to record and control.

In summary, patients (de novo 3VD) will be treated according to ACC/AHA/ESC guidelines, i.e. Heart Team discussion (Ia); functional evaluation for diagnosis in absence of objective evidence of ischemia (Ia); and LDL levels ≤1.8mmol (Ia).

7.8 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 CRO.

7.9 Follow-up Period

7.9.1 Hospital visits at 1 month (± 7 days), 6 months (± 14 days) and 1 year (± 30 days) post-procedure

An assessment of the angina status, cardiovascular drug use and any Serious Adverse Events will be recorded during clinical follow-up visits.

An anonymised copy of the ECG (showing patient ID and recording date) should be sent to the CRO.

7.9.2 Telephone contacts at 2 years (± 30 days), 3 years (± 30 days), 4 years (± 30 days) and 5 years (± 30 days)

During these telephone contacts information from the patient will be gathered on any Major Adverse Cardiac or Cerebrovascular Events (MACCE). Patients will also be asked for angina status and cardiovascular drug use.

7.10 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.

All subjects should be encouraged to remain in the study until he/she has completed the protocol requirements during the 5-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.

8 STATISTICAL DESIGN AND ANALYSIS

8.1 Introduction

This trial is a non-randomized single arm study that aims to perform a comparative analysis with historical controls. Patient recruitment in the current trial will be using the SYNTAX Score II, and the historical control will be with similarly selected patients from the randomised SYNTAX Trial.

The analytical plan will be split into two sections:

1. Descriptive statistical methodology: to describe the results of the current trial by itself.
2. Comparative statistical methodology: to describe the comparison between the SYNERGY™ Everolimus Eluting Stent (EES) results of this trial and similar selected patients from the PCI and CABG cohorts of the randomised SYNTAX Trial.

8.2 Patient Selection

Patients will be prospectively recruited in the current trial with the SYNTAX Score II. Similarly selected subjects (using the SYNTAX Score II) will be undertaken from the PCI and CABG cohorts of the randomised SYNTAX Trial and will act as control groups for the current trial.

The study populations of SYNTAX II and the de-novo 3-vessel disease patients of SYNTAX I will be 'matched' based on the SYNTAX Score II. During the recruitment of the SYNTAX II study it will be monitored whether the populations sufficiently overlap.

No reference data for multivessel disease can be found in the published literature for the SYNERGY EES; thus the data is inferred from the Italian EXECUTIVE Pilot Trial (Ribichini et al)[88] in which the XIENCE EES was compared to the Taxus Liberte (paclitaxel eluting stent [PES]) in multivessel coronary disease. In the current trial, EES will be compared to the selected PES arm (superiority) and the selected CABG arm (non inferiority) of the SYNTAX Trial.

8.3 Assumptions for comparative analysis

In the EXECUTIVE Trial, the PES arm had an event rate for MACE (major adverse cardiac events) at 1 year of 16.5%, and 11.1% for the EES arm. This implies a ratio of 11.1/16.5 i.e. 0.67.

We assume the same ratio as the margin of effect of the new device in the current trial. We assume the incidence of stroke will be low and unchanged in the current trial as compared to the SYNTAX Trial, therefore the outcome of major adverse cardiac and cerebrovascular events (MACCE) will be assessed in order to allow comparisons with the CABG arm. The incidence of MACCE at 1 year for the selected PES arm was 17.1%; assuming a ratio of 0.67, we estimate 11.5% as the incidence of MACCE in the current trial. The incidence of MACCE at 1 year for the selected CABG arm was 10.8%. In our assumptions - as factor of benefit - we only considered the hazard ratio of Synergy vs. Taxus. We did not introduce reduction in the hazard ratio due to functional/IVUS assessment.

SYNTAX II will not consider CABG as a separate arm and therefore we need to define the uncertainty margins in advance. The point estimate of 10.8% for the selected CABG arm is accompanied with a 95% confidence interval of 7.7-14.6% (Clopper-Pearson Exact Test). It is assumed that there have been minimal changes of CABG over the time since the recruitment of the SYNTAX Trial.

8.4 Sample size

8.4.1 Superiority testing (PCI) for the primary endpoint

A sample size of 416 patients will guarantee a power of 90% to show superiority of the EES arm of the current trial to the historical PES control group. The assumptions used are:

1) a 5% 2-sided level of significance (alpha)
2) a 11.5% MACCE rate at 360 days for the EES arm, compared to the historical control of 17.1% in the selected patients from the PES arm of the SYNTAX Trial.

8.4.2 Non-inferiority testing (CABG) for the exploratory endpoint

A sample size of 416 patients will guarantee a power of 80% to show non-inferiority of the EES arm of the current trial to the historical CABG control group. The assumptions used are:

1) a 5% 1-sided level of significance (alpha)
2) a 11.5% MACCE rate at 360 days for the EES arm, compared to the historical control of 10.8% in the selected patients from the CABG arm of the SYNTAX Trial
3) a non-inferiority margin of 5%, as was used in the SYNTAX Trial.

8.4.3 Sample size justification

For the comparison with the selected PCI arm a sample size of 450 patients is chosen to obtain a power of at least 90%.

8.5 Analytical plan

The primary analysis will be based on the intention-to-treat principle. More details will be described in the statistical analysis plan.
All statistical analyses will be done using the SAS System software, version 9.2 or above (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

8.5.1 Descriptive statistical methodology

Continuous variables will be presented using mean, standard deviation, median, minimum and maximum. Discrete variables will be presented in terms of frequencies and percentages.

8.5.2 Comparative statistical methodology

For the primary endpoint (MACCE at 360 days) the log rank test will be applied to compare the SYNTAX II with the historical control of the selected PCI arm.

For the comparison to the selected CABG arm a 90% CI for the incidence of MACCE at 360 days will be constructed. If the upper limit of 90% CI in the current trial is less than 15.8%, the SYNERGY EES will be declared non-inferior to the selected CABG arm.

For the current trial day 0 will be the day of patient allocation, i.e. the day of patient "signed off" by the Heart Team.

8.6 Validation of SYNTAX Score II

Prospective validation of the SYNTAX Score II for all-cause death at 1, 2 and 5 year will be undertaken.

9 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 patient has signed Informed Consent.

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

9.1 Serious Adverse Events (SAEs) Definitions

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

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).

9.2 Anticipated Adverse Device Effects

Anticipated adverse device effects for Synergy, IVUS, iFR/FFR procedures are described in the Instructions For Use (IFU).

If the investigator observes device malfunctions that led or might have led to a death or serious deterioration in health of a patient, user or other person or has complaints with regard to defects in the medical devices, the investigator shall, within 24 hours of such observation, report such device malfunction or complaint to the device company. Company shall be responsible for handling all complaints and reported device malfunctions in respect of the quality of medical devices, for determining the measures to be taken due to such observations or complaints and for ensuring that all necessary actions are taken including, but not limited to, any necessary action in connection with the recall of the medical devices or the reporting of incidents to competent authorities if deemed appropriate by the Company. Discussions regarding such device malfunction or complaints will be held between the Company and the Participating Site.

9.3 Reporting to Ethics Committee (EC)

Safety reporting to local ECs will be in accordance with the “guidelines on a medical device vigilance system” by the European Commission (MEDDEV2.12 rev 6, Dec 2009) and in compliance with local country law.

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. At the time the event is reported in the eCRF, no event-supporting source documentation needs to be sent. Event supporting source documents will be requested by the sponsor (via monitoring organisation and/or CRO) for the purpose of clinical event adjudication.

Clinical study staf must report device malfunctions directly to the manufacturer, who will then perform vigilance reporting to Competent Authorities, if applicable.

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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 local ethics committees, as well as to the Data Safety Monitoring Board (DSMB).

9.4 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. 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.

9.5 Risk Analysis

There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures and it is expected that the procedural risks in this study and existing stenting procedure will not be significantly different. Known adverse events that may result from stent intervention (incorporating IVUS/FFR assessments) include but may not be limited to:

- Allergic reaction or hypersensitivity to device material and its degredants (everolimus, platinum, chromium, poly-lactide-co-glycolide (PLGA))
- Shortness of breath/dyspnea
- Distal embolism (air, tissue, or thrombotic)
- Nausea/Vomiting
- Coronary and stent thrombosis
- Coronary and stent embolism
- Coronary dissection
- Total coronary occlusion
- Abrupt coronary closure/threatened abrupt closure
- Coronary injury
- Coronary spasm
- Coronary perforation
- Coronary rupture
- Pseudoaneurysm
- Angina (stable or unstable)
- Urgent or non-urgent coronary artery bypass graft surgery
- Vascular complications including at the entry site which may require vessel repair and vessel dissection
- Hematoma
- Respiration cease
- Hypertension
- Death

- Bleeding
- Bleeding complication (that may require transfusion)
- Shock
- Myocardial ischemia
- Cardiac enzyme level elevation
- Myocardial infarction
- Cardiac tamponade
- Cardiac arrest
- ECG change
- Heart failure
- Renal failure
- Stent implanted in unintended location
- Restenosis of lesion/vessel treated with stent
- Access site infection or pain
- Access site hematoma or bleeding
- Cerebral stroke/cerebral vascular accident (CVA)
- Hypotension
- Palpitation
- Aneurysm
- Arteriovenous fistula
- Pulmonary edema
- Fever
- Arrhythmia (atrial or ventricular)
- Peripheral ischemia (due to vascular injury)
- Adverse reaction to drug (to everolimus, antiplatelets or contrast agent)

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 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). The study will be performed in accordance with the Declaration of Helsinki 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.

10.2 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.

10.3 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).

A baseline monitoring visit will be scheduled when first patients have been enrolled and data 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, iFR, IVUS recordings and per protocol required 12-lead ECGs.

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. On a regular basis, the monitoring organisation will contact each site to discuss the progress of the study with respect to patient enrolment, timely attendance of patients to their follow-up visits and other relevant study aspects such as data query resolution.

Each participating clinic will receive a close-out visit to resolve any outstanding issues and to perform the final source data verification.

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

10.4 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 incomplete, inconsistent or missing data.

10.5 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.

11 ORGANISATION

11.1 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.

11.2 Steering Committee

The Steering Committee is responsible of the overall management of the study at the highest level. The Steering Committee is comprised of a Chairman, Deputy Study Chair, PIs, Co-PIs, ECRI). Their names, roles and responsibilities are described in a separate Steering Committee Charter.

11.3 Clinical Event Committee (CEC)

The composition, events to be adjudicated, the minimum amount of data required, and the algorithm followed in order to classify the events are described in a separate CEC Charter.

11.4 Data Safety Monitoring Board (DSMB)

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

11.5 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).

11.6 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.

11.7 Safety Reporting

Sites are responsible for reporting of incidents, including device malfunctions, to the manufactures. Manufacturers are responsible for vigilance reporting of device malfunctions to competent authorities according to the "guidelines on medical devices vigilance system" by the European Commission (MEDDEV2.12 rev 6, Dec 2009).

No expedited safety reporting is foreseen.

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for event reporting to the EC/IRB according to local and national requirements.

11.8 Statistical Analysis

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for the statistical analysis.

12 DATA HANDLING AND RECORD KEEPING

12.1 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;
- Study patient's condition upon completion of or withdrawal from the study.

12.2 Case Report Form Completion

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

12.3 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 according to the national requirements 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.

13 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 SYNTAX II trial is an investigator-initiated and scientifically driven study nested within the European Cardiovascular Research Institute (ECRI) and set up in collaboration with Boston Scientific and Volcano. All public presentations and manuscript generation and submissions will be led under the auspices of the 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 Principal Investigators. All 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.

14 INVESTIGATOR RESPONSIBILITIES

14.1 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.

14.2 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.

14.3 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.

14.4 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.

14.5 Protocol Deviation

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

14.6 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**
Serious Adverse Event Notification eCRF (including death, MACE)	24 hours	Enter eCRF pages within 24 hours of knowledge of event
eCRF (Baseline, In-hospital summary, Follow-up, Patient Withdrawal)	Ongoing basis	Collected in the eCRF
Angiographic Films, ECGs, IVUS and iFR/FFR recordings. MSCT scans (if applicable).	Ongoing basis	Collected by site and shipped to Core lab within 7 days
Device malfunctions	Ongoing basis	Collected by site and provided to manufacturer
Annual Reports	Forward as requested by EC/IRB	Copy provided by Sponsor to be send to EC/IRB
Final Report	Forward within 3 months of study completion or termination	Copy provided by Sponsor to be send to EC/IRB

14.7 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.

15 SPONSOR RESPONSIBILITIES

15.1 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 together with the Steering Committee 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.

Documentation

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

- All study relevant documents (protocol, EC/IRB approval and comments, patient information and informed consent template, relevant correspondence, etc.)
- Signed and dated Case Report Form
- Records of 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

15.2 Supplemental Applications

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

15.3 Submitting Reports

The Sponsor will submit the appropriate reports identified by the regulations. This includes withdrawal of any EC/IRB approval, interim (if any) and final reports.

15.4 Maintaining Records

The Sponsor will maintain copies of correspondence, data, 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 ISO14155.

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

15.5 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.

15.6 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.

16 REFERENCES

1. SYNTAX score calculator: www.syntaxscore.com. SYNTAX working-group. Launched 19th May 2009.
2. Sianos G, Morel MA, A.P. K, Morice MC, Colombo A, Dawkins K, van den Brand M, Dyck NV, Russell ME, Mohr FW, Serruys PW. (2005) The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*.
3. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. American heart journal 2006;**151**(6):1194-204.
4. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;**360**(10):961-72.
5. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. EuroIntervention 2009;**5**(1):50-6.
6. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation 2010;**121**(24):2645-53.
7. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. Eur Heart J 2011;**32**(17):2125-34.
8. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. Heart 2011;**97**(23):1902-13.
9. Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. Heart 2013.
10. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Jr., Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;**381**(9867):629-38.
11. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. Eur Heart J 2010;**31**(20):2501-55.
12. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID,

Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;**58**(24):e44-122.
13. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM, Jr., Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011;**58**(24):e123-210.
14. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, CarriÈ D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, K‰hler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. The Lancet 2009;**373**(9670):1190-1197.
15. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. Journal of the American College of Cardiology 2003;**41**(8):1293-304.
16. Farooq V, Serruys PW. "Cherry-picking" patients for randomized, controlled trials-reliving the past. J Am Coll Cardiol 2013;**61**(24):2492.
17. Taggart DP. Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. Ann Thorac Surg 2006;**82**(6):1966-75.
18. Farkouh ME, Dangas G, Leon MB, Smith C, Nesto R, Buse JB, Cohen DJ, Mahoney E, Sleeper L, King S, 3rd, Domanski M, McKinlay S, Fuster V. Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) Trial. Am Heart J 2008;**155**(2):215-23.
19. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S, 3rd, Bertrand M, Fuster V. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;**367**(25):2375-84.
20. Serruys PW, Farooq V. Revascularization strategies in patients with diabetes. N Engl J Med 2013;**368**(15):1454-5.
21. Banning AP, Westaby S, Morice MC, Kappetein AP, Mohr FW, Berti S, Glauber M, Kellett MA, Kramer RS, Leadley K, Dawkins KD, Serruys PW. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. Journal of the American College of Cardiology 2010;**55**(11):1067-75.
22. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, Dawkins KD, Mack MJ. Treatment of complex coronary artery disease in patients with diabetes: 5-year results

comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. Eur J Cardiothorac Surg 2013;**43**(5):1006-13.
23. Farooq V, Serruys PW, Stone GW, Virmani R, Chieffo A, Fajadet J. Left main coronary artery disease. Percutaneous Interventional Cardiovascular Medicine. The PCR-EAPCI Textbook. PCR publishing / EUROPA EDITION, Toulouse, France, 2012: Part 3, Chapter 12: 407-445.
24. Serruys PW, Farooq V, Vranckx P, Girasis C, Brugaletta S, Garcia-Garcia HM, Holmes DR, Jr., Kappetein AP, Mack MJ, Feldman T, Morice MC, Stahle E, James S, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. JACC Cardiovasc Interv 2012;**5**(6):606-17.
25. Farooq V, Vergouwe Y, Raber L, Vranckx P, Garcia-Garcia H, Diletti R, Kappetein AP, Morel MA, de Vries T, Swart M, Valgimigli M, Dawkins KD, Windecker S, Steyerberg EW, Serruys PW. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score. Eur Heart J 2012;**33**(24):3098-104.
26. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Jr., Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;**381**(9867):639-50.
27. Farooq V, van Klaveren D, Steyerberg EW, Serruys PW. SYNTAX score II - Authors' reply. Lancet 2013;**381**(9881):1899-900.
28. Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Stahle E. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. Eur Heart J 2012;**33**(24):3105-13.
29. Chieffo A, Meliga E, Latib A, Park SJ, Onuma Y, Capranzano P, Valgimigli M, Jegere S, Makkar RR, Palacios IF, Kim YH, Buszman PE, Chakravarty T, Sheiban I, Mehran R, Naber C, Margey R, Agnihotri A, Marra S, Capodanno D, Leon MB, Moses JW, Fajadet J, Lefevre T, Morice MC, Erglis A, Tamburino C, Alfieri O, Serruys PW, Colombo A. Drug-Eluting Stent for Left Main Coronary Artery Disease: The DELTA Registry: A Multicenter Registry Evaluating Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Treatment. JACC Cardiovasc Interv 2012;**5**(7):718-27.
30. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen CP, Nelson RG. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;**380**(9854):1662-73.
31. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, James MT, Hemmelgarn BR. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012;**380**(9844):807-14.

32. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, Mack M, Feldman T, Morice MC, Stahle E, James S, Colombo A, Diletti R, Papafaklis MI, de Vries T, Morel MA, van Es GA, Mohr FW, Dawkins KD, Kappetein AP, Sianos G, Boersma E. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol 2013;**61**(3):282-94.
33. Head SJ, Mack MJ, Holmes DR, Jr., Mohr FW, Morice MC, Serruys PW, Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. Eur J Cardiothorac Surg 2012;**41**(3):535-41.
34. Thompson CA, Jayne JE, Robb JF, Friedman BJ, Kaplan AV, Hettleman BD, Niles NW, Lombardi WL. Retrograde techniques and the impact of operator volume on percutaneous intervention for coronary chronic total occlusions an early U.S. experience. JACC Cardiovasc Interv 2009;**2**(9):834-42.
35. Whitlow PL, Burke MN, Lombardi WL, Wyman RM, Moses JW, Brilakis ES, Heuser RR, Rihal CS, Lansky AJ, Thompson CA. Use of a novel crossing and re-entry system in coronary chronic total occlusions that have failed standard crossing techniques: results of the FAST-CTOs (Facilitated Antegrade Steering Technique in Chronic Total Occlusions) trial. JACC Cardiovasc Interv 2012;**5**(4):393-401.
36. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. Journal of the American College of Cardiology 2010;**55**(25):2816-21.
37. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. Journal of the American College of Cardiology 2010;**56**(3):177-84.
38. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;**367**(11):991-1001.
39. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;**360**(3):213-24.
40. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, De Bruyne B, Pijls NH, Fearon WF. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. J Am Coll Cardiol 2011;**58**(12):1211-8.
41. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J, Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-

intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;**59**(15):1392-402.
42. Zhang Y, Farooq V, Garcia-Garcia HM, Bourantas CV, Tian N, Dong S, Li M, Yang S, Serruys PW, Chen SL. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. EuroIntervention 2012;**8**(7):855-65.
43. Zhang YJ, Garcia-Garcia HM, Farooq V, Bourantas CV, Serruys PW, Chen SL. Revisiting: "Comparison of intravascular ultrasound versus angiography guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients". EuroIntervention 2013.
44. Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol 2010;**56**(10 Suppl):S43-78.
45. Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol 2010;**56**(10 Suppl):S1-42.
46. Stefanini GG, Holmes DR, Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;**368**(3):254-65.
47. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabate M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;**379**(9824):1393-402.
48. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, Feit F, Bhatt DL, Slater J. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation 2012;**125**(23):2873-91.
49. Farooq V, Gogas BD, Serruys PW. Restenosis: delineating the numerous causes of drug-eluting stent restenosis. Circulation. Cardiovascular interventions 2011;**4**(2):195-205.
50. Wilson GJ, Huibregtse BA, Pennington DE, Dawkins KD. Comparison of the SYNERGY with the PROMUS (XIENCE V) and bare metal and polymer-only Element control stents in porcine coronary arteries. EuroIntervention 2012;**8**(2):250-7.
51. Meredith IT, Verheye S, Dubois CL, Dens J, Fajadet J, Carrié D, Walsh S, Oldroyd KG, Varenne O, El-Jack S, Moreno R, Joshi AA, Allocco DJ, Dawkins KD. Primary Endpoint Results of the EVOLVE TrialA Randomized Evaluation of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent. Journal of the American College of Cardiology 2012;**59**(15):1362-1370.
52. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of Incomplete Revascularization and its Association With Five-Year Mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Trial Validation of the Residual SYNTAX Score * Clinical Perspective. Circulation 2013;**128**(2):141-51.
53. Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW, Stone GW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. J Am Coll Cardiol 2012;**59**(24):2165-74.

54. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;**24**(9):881-2.
55. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;**16**(1):9-13.
56. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;**15**(6):816-22; discussion 822-3.
57. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. Eur J Cardiothorac Surg 2012;**41**(4):734-44; discussion 744-5.
58. Takkenberg JJ, Kappetein AP, Steyerberg EW. The role of EuroSCORE II in 21st century cardiac surgery practice. Eur J Cardiothorac Surg 2013;**43**(1):32-3.
59. Serruys PW, Girasis C, Papadopoulou SL, Onuma Y. Non-invasive fractional flow reserve: scientific basis, methods and perspectives. EuroIntervention 2012;**8**(4):511-9.
60. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, DeFrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;**58**(19):1989-97.
61. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, Erglis A, Lin FY, Dunning AM, Apruzzese P, Budoff MJ, Cole JH, Jaffer FA, Leon MB, Malpeso J, Mancini GB, Park SJ, Schwartz RS, Shaw LJ, Mauri L. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;**308**(12):1237-45.
62. Farooq V, Head SJ, Kappetein AP, Serruys PW. Widening clinical applications of the SYNTAX Score. Heart 2013.
63. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;**16**(1):31-41.
64. Samady H, Lepper W, Powers ER, Wei K, Ragosta M, Bishop GG, Sarembock IJ, Gimple L, Watson DD, Beller GA, Barringhaus KG. Fractional flow reserve of infarct-related arteries identifies reversible defects on noninvasive myocardial perfusion imaging early after myocardial infarction. J Am Coll Cardiol 2006;**47**(11):2187-93.
65. Leesar MA, Abdul-Baki T, Akkus NI, Sharma A, Kannan T, Bolli R. Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina. Effect on duration of hospitalization, cost, procedural characteristics, and clinical outcome. J Am Coll Cardiol 2003;**41**(7):1115-21.
66. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. JACC Cardiovasc Interv 2010;**3**(12):1274-81.
67. Petraco R, Park JJ, Sen S, Nijjer SS, Malik IS, Echavarria-Pinto M, Asrress KN, Nam CW, Macias E, Foale RA, Sethi A, Mikhail GW, Kaprielian R, Baker CS, Lefroy D, Bellamy M, Al-Bustami M, Khan MA, Gonzalo N, Hughes AD, Francis DP, Mayet J, Di Mario C, Redwood

S, Escaned J, Koo BK, Davies JE. Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation. EuroIntervention 2013;**8**(10):1157-65.
68. Rao SV, Cohen MG, Kandzari DE, Bertrand OF, Gilchrist IC. The transradial approach to percutaneous coronary intervention: historical perspective, current concepts, and future directions. J Am Coll Cardiol 2010;**55**(20):2187-95.
69. Hildick-Smith D, Lassen JF, Albiero R, Lefevre T, Darremont O, Pan M, Ferenc M, Stankovic G, Louvard Y. Consensus from the 5th European Bifurcation Club meeting. EuroIntervention 2010;**6**(1):34-8.
70. Stankovic G, Lefevre T, Chieffo A, Hildick-Smith D, Lassen JF, Pan M, Darremont O, Albiero R, Ferenc M, Finet G, Adriaenssens T, Koo BK, Burzotta F, Louvard Y. Consensus from the 7th European Bifurcation Club meeting. EuroIntervention 2013;**9**(1):36-45.
71. Werner GS, Schofer J, Sievert H, Kugler C, Reifart NJ. Multicentre experience with the BridgePoint devices to facilitate recanalisation of chronic total coronary occlusions through controlled subintimal re-entry. EuroIntervention 2011;**7**(2):192-200.
72. Baks T, van Geuns RJ, Duncker DJ, Cademartiri F, Mollet NR, Krestin GP, Serruys PW, de Feyter PJ. Prediction of left ventricular function after drug-eluting stent implantation for chronic total coronary occlusions. Journal of the American College of Cardiology 2006;**47**(4):721-5.
73. Kwon DH, Hachamovitch R, Popovic ZB, Starling RC, Desai MY, Flamm SD, Lytle BW, Marwick TH. Survival in patients with severe ischemic cardiomyopathy undergoing revascularization versus medical therapy: association with end-systolic volume and viability. Circulation 2012;**126**(11 Suppl 1):S3-8.
74. Gerber BL, Rousseau MF, Ahn SA, le Polain de Waroux JB, Pouleur AC, Phlips T, Vancraeynest D, Pasquet A, Vanoverschelde JL. Prognostic value of myocardial viability by delayed-enhanced magnetic resonance in patients with coronary artery disease and low ejection fraction: impact of revascularization therapy. J Am Coll Cardiol 2012;**59**(9):825-35.
75. Camici PG, Wijns W, Borgers M, De Silva R, Ferrari R, Knuuti J, Lammertsma AA, Liedtke AJ, Paternostro G, Vatner SF. Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). Circulation 1997;**96**(9):3205-14.
76. Fiocchi F, Sgura F, Di Girolamo A, Ligabue G, Ferraresi S, Rossi R, D'Amico R, Modena MG, Torricelli P. Chronic total coronary occlusion in patients with intermediate viability: value of low-dose dobutamine and contrast-enhanced 3-T MRI in predicting functional recovery in patients undergoing percutaneous revascularisation with drug-eluting stent. Radiol Med 2009;**114**(5):692-704.
77. Kirschbaum SW, Baks T, van den Ent M, Sianos G, Krestin GP, Serruys PW, de Feyter PJ, van Geuns RJ. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. Am J Cardiol 2008;**101**(2):179-85.
78. Galassi AR, Tomasello SD, Crea F, Costanzo L, Campisano MB, Marza F, Tamburino C. Transient impairment of vasomotion function after successful chronic total occlusion recanalization. J Am Coll Cardiol 2012;**59**(8):711-8.
79. Mosseri M, Satler LF, Pichard AD, Waksman R. Impact of vessel calcification on outcomes after coronary stenting. Cardiovasc Revasc Med 2005;**6**(4):147-53.

80. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;**361**(11):1045-57.
81. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009;**120**(25):2577-85.
82. Farooq V, Serruys PW, Holmes DR, Kappetein AP, Mack M, Feldman T, Dawkins KD, Mohr FW, James S, Ståhle E. Abstract: The long term (4-year) prognostic significance of abnormal cardiac enzyme rises in patients treated with surgical or percutaneous revascularisation: a substudy from the SYNTAX Trial. Presented at: Congress of the European-Society-of-Cardiology (ESC), AUG 25-29, 2012, Munchen, GERMANY. European Heart Journal 2012;**33**(suppl 1):500.
83. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. Circulation 2004;**110**(6):674-8.
84. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G, Montinaro A, Di Sciascio G. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. J Am Coll Cardiol 2007;**49**(12):1272-8.
85. Di Sciascio G, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. J Am Coll Cardiol 2009;**54**(6):558-65.
86. Briguori C, Visconti G, Focaccio A, Golia B, Chieffo A, Castelli A, Mussardo M, Montorfano M, Ricciardelli B, Colombo A. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. J Am Coll Cardiol 2009;**54**(23):2157-63.
87. Briguori C, Colombo A, Airoldi F, Violante A, Focaccio A, Balestrieri P, Paolo Elia P, Golia B, Lepore S, Riviezzo G, Scarpato P, Librera M, Bonizzoni E, Ricciardelli B. Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction. Eur Heart J 2004;**25**(20):1822-8.
88. Ribichini I, Romano M, Rosiello R, Vecchia LL, Cabianca E, Caramanno G, Milazzo D, Loschiavo P, Rigattieri S, Musarò S, Pironi B, Fiscella A, Amico F, Indolfi C, Spaccarotella C, Bartorelli A, Trabattoni D, Rovere FD, Rolandi A, Beqaraj F, Belli R, Sangiorgio P, Villani R, Berni A, Sheiban I, Quijada MJL, Cappi B, Ribaldi L, Vassanelli C. A Clinical and Angiographic Study of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with Multi-Vessel Coronary Artery Disease. The EXECUTIVE Trial. JACC Interventions (In Press) 2013.
89. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-

artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;**344**(15):1117-24.
90. de Jaegere P, Mudra H, Figulla H, Almagor Y, Doucet S, Penn I, Colombo A, Hamm C, Bartorelli A, Rothman M, Nobuyoshi M, Yamaguchi T, Voudris V, DiMario C, Makovski S, Hausmann D, Rowe S, Rabinovich S, Sunamura M, van Es GA. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). Eur Heart J 1998;**19**(8):1214-23.

17 APPENDIX I: SCHEDULE OF EVENTS

Event	**Screen**	**Procedure**	**Post - Procedure to Hospital D/c**	**1 Mo** ±7 days	**6 Mo** ±14 days	**1 Yrs** ±30 days	**2-5Yrs** ±30 days
Type of contact				***Visit***	***Visit***	***Visit***	***Phone***
Local Heart Team conference - Inclusion/ exclusion Criteria - SYNTAX Score II - EuroSCORE - EuroSCORE II	X						
Informed consent	X						
Physical examination	X						
Medical and Cardiac history	X						
Anginal Status	X		X	X	X	X	X
[1]CBC, blood chemistry, lipids	X						
CK-MB	X[2]		X[3]				
Troponin	X[2]		X[3]				
12 lead ECG[7]	X[4]		X[5]	X	X	X	
Medication regimen	X	X	X	X	X	X	X
Angiography[6, 7]		X					
IVUS[7]		X					
FFR/(iFR)[7]		X					
MSCT[7]	X						
Serious Adverse Event monitoring		X	X	X	X	X	X

[1] within 7 days prior to procedure

[2] CK-MB/Troponin is drawn at least 24 hours prior to PCI.

[3] CK-MB/Troponin is determined pre-discharge or within 48 hours whatever comes first

[4] ECG at time of screening should be at least 24 hours prior to PCI

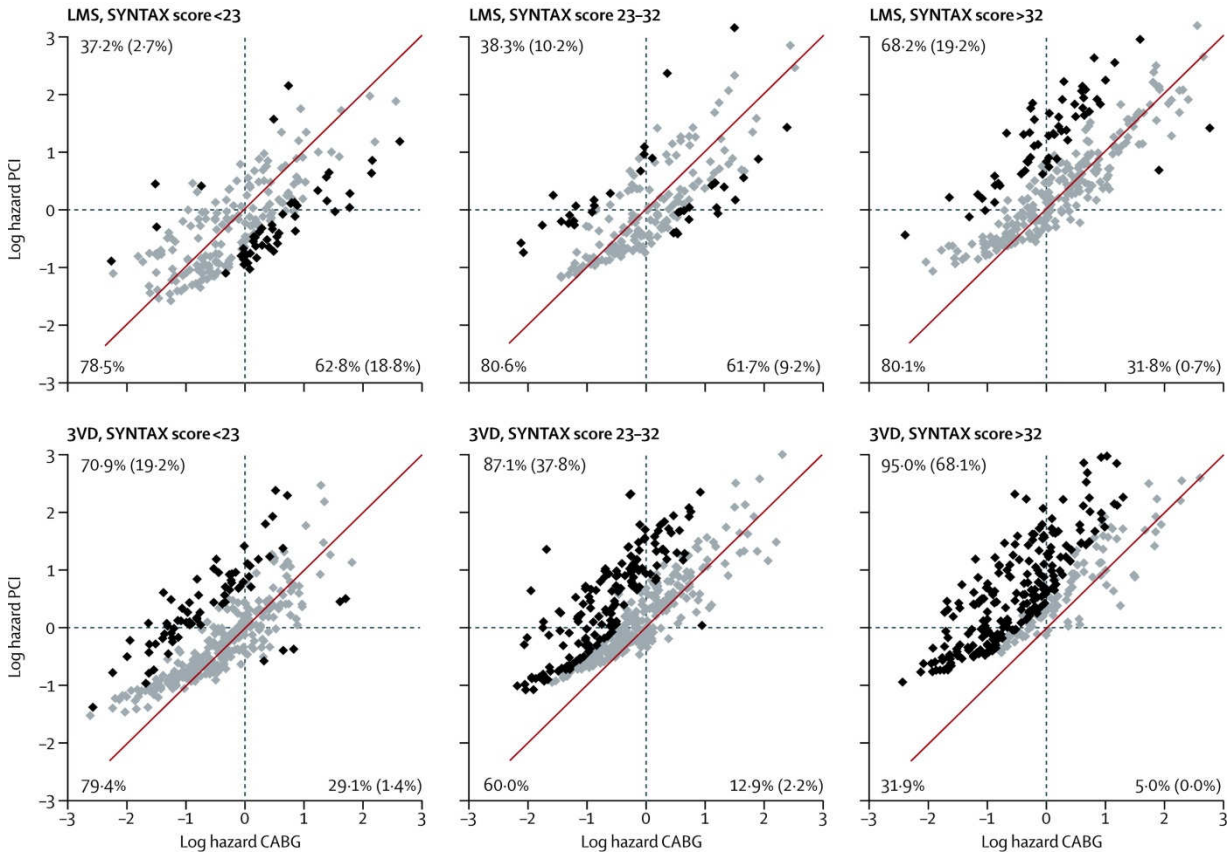
[5] within 24 hours post-procedure or at discharge, whichever comes first

[6] In index angiograms for anatomical SYNTAX Score assessment both the right coronary artery (RCA) and left coronary artery (LCA, incl. LAD and LCX) must be imaged.

[7] Collect and forward to central Core Lab (material collection only).

18 APPENDIX II: PROPORTION OF 3VD PATIENTS SUITABLE FOR PCI

Mortality predictions for CABG versus PCI for each individual patient in the randomised SYNTAX trial (n=1800). Scatter plots illustrating mortality predictions for the left main (upper panel) and 3VD (lower panel) cohorts separated by conventional tertiles of the SYNTAX Score. The diagonal line represents identical mortality predictions for CABG and PCI. Individual predictions plotted to the left of the diagonal line favour CABG (actual percentages shown in top left corner), and to the right favour PCI (actual percentages shown in bottom right corner). Individual mortality predictions for CABG or PCI that could be separated with 95% confidence ($p<0\cdot05$) are coloured black (actual percentage shown in parentheses in respective corners). Mortality predictions that could not be separated with 95% confidence ($p>0\cdot05$) are highlighted in grey, and identify patients with similar 4-year mortality. Percentages of patients in each category are shown. CABG=coronary artery bypass surgery. PCI=percutaneous coronary intervention. LMS=left main stem. 3VD=three-vessel disease. Adapted and reproduced from Farooq et al.[26]



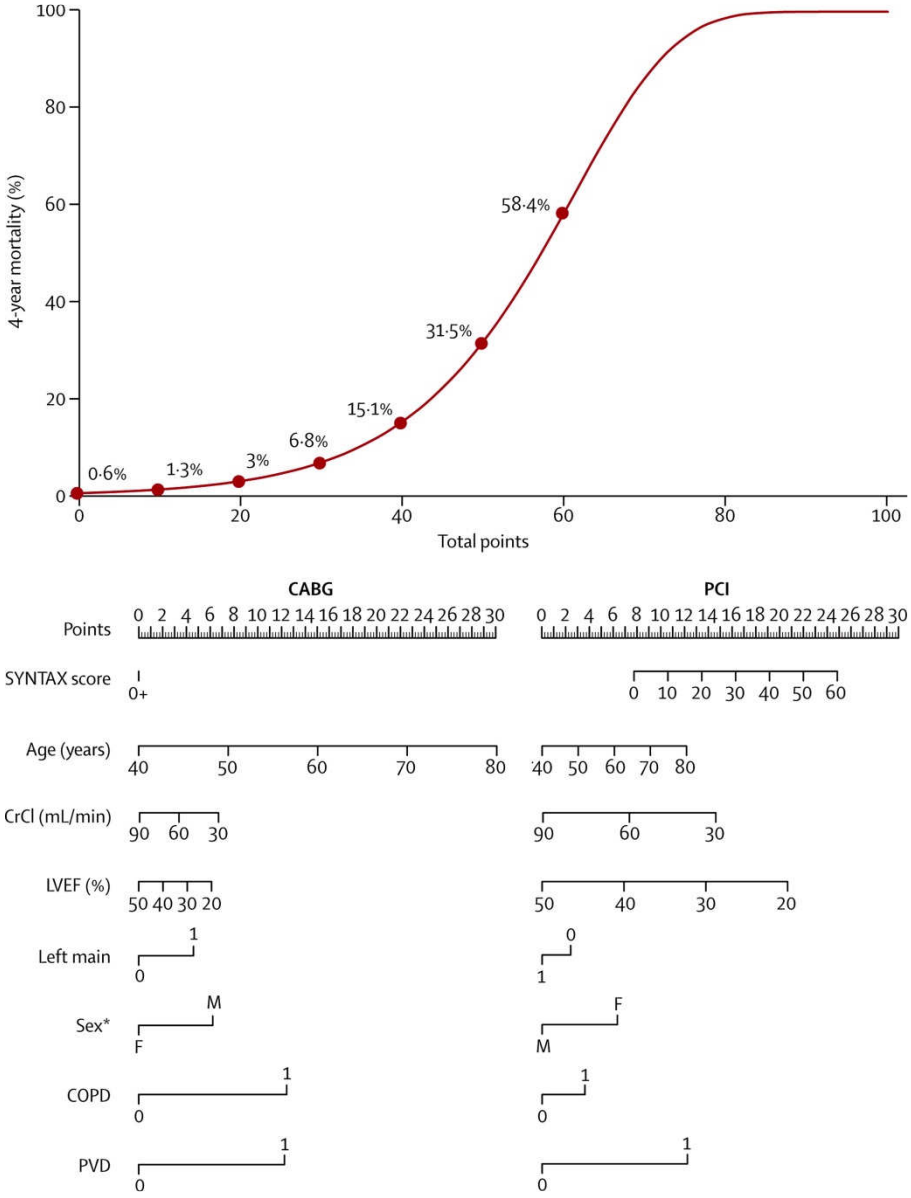
19 APPENDIX III: SYNTAX SCORE II

SYNTAX Score II nomogram for bedside application. An online version will be made available online at the original SYNTAX Score website (www.syntaxscore.com).[1]

Total number of points for 8 factors can be used to accurately predict 4-year mortality for the individual patient proposing to undergo for CABG or PCI. For example, a 60 year old man with an anatomical SYNTAX score of 30, unprotected left main coronary artery disease, creatinine clearance of 60 mL/min, an LVEF of 50%, and COPD, would have 41 points (predicted 4-year mortality 16·3%) to undergo CABG and 33 points (predicted 4-year mortality 8·7%) to undergo PCI respectively. The same example without COPD included would lead to identical points (29 points) and 4-year mortality predictions (6·3%) for CABG and PCI.

COPD defined with EuroSCORE definition,[54] long-term use of bronchodilators or steroids for lung disease. PVD defined according to ARTS I definition,[89] aorta and arteries other than coronaries, with exercise-related claudication, or revascularisation surgery, or reduced or absent pulsation, or angiographic stenosis of more than 50%, or combinations of these characteristics.

Adapted from Farooq et al.[26]



*Because of the rarity of complex coronary artery disease in premenopausal women, mortality predictions in younger women are predominantly based on the linear relation of age with mortality. The differences in mortality predictions in younger women between CABG and PCI will therefore be affected by larger 95% CIs than those in older women.

20 APPENDIX IV: IVUS CRITERIA

IVUS Criteria (**Modified MUSIC Criteria**[90]): for evaluation of appropriate stent apposition:

1). Complete apposition against the vessel wall of the entire stent *AND*

2). a) ≥90% of the average reference lumen area or ≥100% of lumen area of the reference segment with the lowest lumen area; *or*

b) MLA >between 5.5 mm^2; *or*

c) MLA ≥80% of the average reference lumen area or ≥90% of lumen area of the reference segment with the lowest lumen area. AND

3). Symmetric stent expansion.

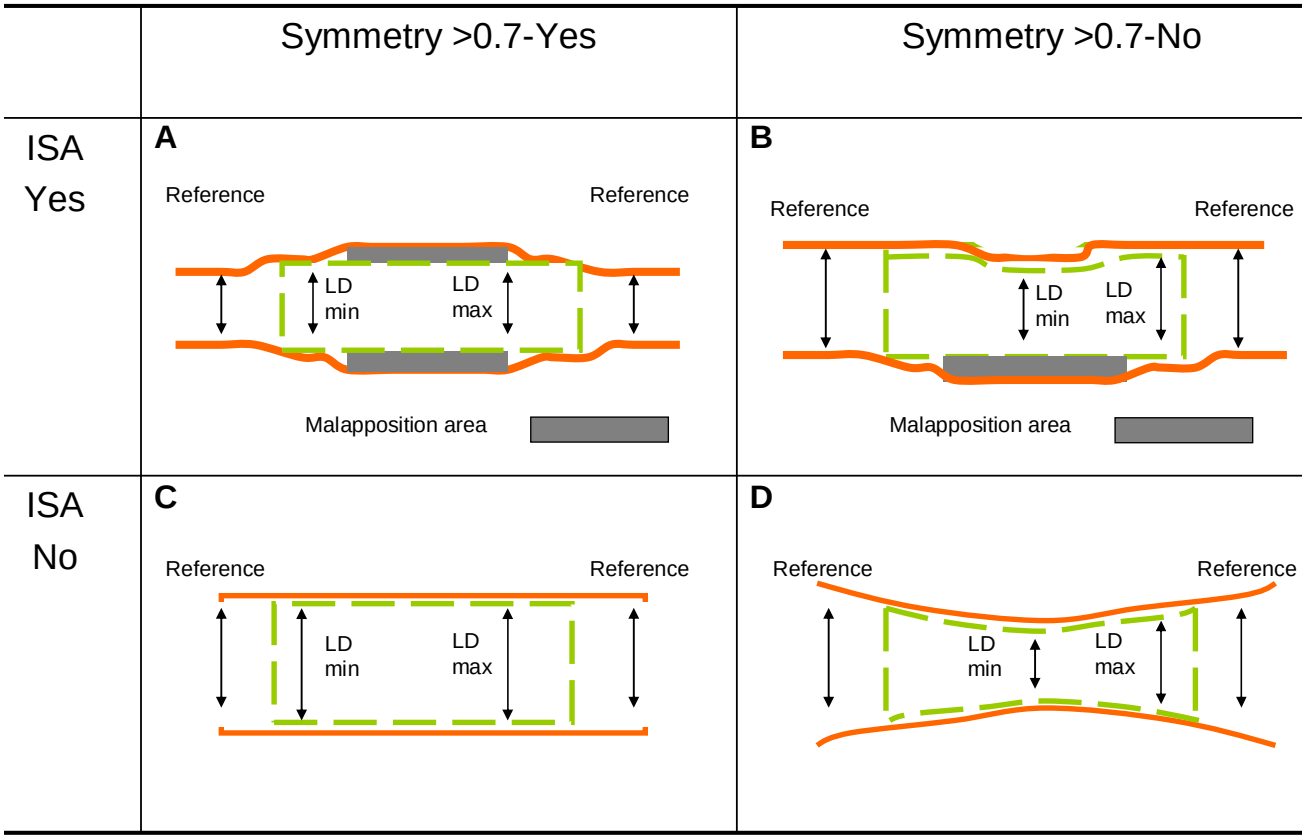


Figure: Stent Symmetry, Expansion and Apposition

ISA: Incomplete Stent Apposition

A. Symmetry check: LD min/LD max is close to 1, thus is symmetric; Expansion check: The minimum lumen area within the stent should be compared to that of the reference segments; Apposition check: there is a space behind the struts, thus the stent is not lying on the vessel luminal wall and therefore is not well apposed. **We recommend postdilation, preferably with a non compliant balloon according the inflation chart.**

B. Symmetry check: LD min/LD max is far from 1, thus is asymmetric. **We recommend postdilation preferably with a non compliant balloon according the inflation chart**; Expansion check: The minimum lumen area within the stent should be compared to that of the reference segments; Apposition check: there is a space behind the struts, thus the stent is not lying on the vessel luminal wall and therefore is not well apposed. **We recommend postdilation, preferably with a non compliant balloon according the inflation chart.**

C. Symmetry check: LD min/LD max is 1, thus is symmetric; Expansion check: The minimum lumen area within the stent should be compared to that of the reference segments; Apposition check: there is NO space behind the struts, thus the stent is lying on the vessel luminal wall and therefore is well apposed and therefore no extra actions are needed.

D. Symmetry check: LD min/LD max is far from 1, thus is asymmetric. **We recommend postdilation, preferably with a non compliant balloon according the inflation chart.**; Expansion check: The minimum lumen area within the stent should be compared to that of the reference segments; Apposition check: there is NO space behind the struts, thus the stent is lying on the vessel luminal wall and therefore is well apposed and therefore no extra actions are needed.

21 APPENDIX V: BIFURCATION MANAGEMENT CRITERIA

Principals - consistent with European Bifurcation club

1) Provisional T is preferred strategy
2) 2 wires from the outset are *recommended* when branch is of sufficient size for the lesion to be considered a bifurcation and it has some disease
3) Probable 2 stents (operators choice of technique) when disease is in a suitably sized side branch and branch disease extends >5mm
4) When 2 stents are used kissing balloon post dilatation is *mandatory* at completion
5) When 1 stent used- kissing balloon post dilatation is not mandatory at completion
6) Large side branch with proximal disease and very challenging access should be stented once accessed - (no iFR/FFR required of branch before treatment) - these are exceptional cases.

Performance/technique- pre stent

7) Plan to perform iFR/FFR to main vessel prior to PCI – *mandatory*
8) When performing elective 2 stents strategy- iFR/FFR to main vessel prior to PCI – *mandatory* and branch iFR/FFR *at operators discretion*
9) Plan to perform provisional approach and branch appears diseased and may require stenting – iFR/FFR of branch *recommended*
10) In 0,0,1 lesion iFR/FFR of main vessel *mandatory* and branch *recommended*

Performance/technique- post stent

11) Post stent deployment in main vessel iFR/FFR *recommended of main vessel*
12) Post stent deployment in main vessel – treatment of branch vessel
    a. Normal flow in branch with discrete pinched ostium – *operators discretion* either leave it or iFR/FFR prior to stenting – *mandatory*
    b. Reduced flow / dissection in significant branch - *bail out strategy at operators discretion- can do iFR/FFR at completion at operators discretion. If 2 stents placed final kissing is mandatory.*

Angiographically 1,1,0 LAD D1 bifurcation
iFR/FFR of the LAD confirms need for stent
stent placed, discrete ostial pinch of D1 but normal flow
iFR/FFR mandatory if further stent to D1 considered
iFR/FFR of LAD at completion

Angiographically 1,1,0 LAD D1 bifurcation
iFR/FFR of the LAD confirms need for stent
LAD stent placed , but TIMI II flow in D1
wire with any wire chosen by operator and proceed as per usual practice including additional stent if considered necessary
iFR/FFR of LAD at completion and D1 if possible

Angiographically 1,0,1 LAD D1 bifurcation
iFR/FFR of the LAD confirms need for stent
unable to comment on D1 ostium in presence of proximal stenosis using iFR/FFR
if disease >5mm in D1- 2 stent strategy of operators choice with kissing to complete procedure
if disease <5mm in D1- stent LAD and then iFR/FFR of D1 is further stent considered
iFR/FFR of LAD at completion

Angiographically 0,0,1 LAD D1 bifurcation
iFR/FFR of the LAD confirms no requirement for LAD stent
iFR/FFR of the D1 confirms requirement for stent (unusual)
stent strategy of operators choice
iFR/FFR of LAD and D1 at completion

Angiographically 0, 1, 0 LAD D1 bifurcation
iFR/FFR of the LAD confirms requirement for LAD stent
stent to LAD – will usually cover bifurcation
stent strategy of operators choice
discrete ostial pinch of D1 but normal flow iFR/FFR mandatory if further stent to D1 considered
iFR/FFR of LAD and ideally D1 at completion

22 APPENDIX VI: DEFINITIONS

I. According to SYNTAX I Trial, MACCE is defined as:

- All cause death
- Cerebrovascular event (stroke)
- Documented myocardial infarction
- Repeat revascularization (PCI and/or CABG).

DEATH

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

Cardiac Death: any death due to immediate cardiac causes (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death.

Vascular Cause death: death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-Cardiovascular death: any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

STROKE

A focal neurological deficit of central origin lasting more than 72 hours and results in irreversible brain damage or permanent body impairment. Type and severity of symptoms is dependent on the location and extent of brain tissue whose circulation has been involved. Strokes will be further classified as ischemic or hemorrhagic based on imaging studies. When blood flow to the brain is interrupted because of rupture of a vessel causing bleeding into or around the brain, it is considered hemorrhagic. When a vessel that supplies the brain is blocked, the event is considered ischemic.

MYOCARDIAL INFARCTION

A myocardial infarction will be considered whether it occurred spontaneously or in association with angioplasty or coronary bypass graft surgery procedures. A definite diagnosis of myocardial infarction is made:

Definition I: Within the first 7 days post intervention:
New Q-waves (*) and one plasma level of CKMB 5x upper limit for normal.

Definition II: At least 7 days after any intervention procedure:
Either a. New Q-waves (*)
Or one plasma level of CKMB 5x upper limit for normal

(*) development of new abnormal Q-waves not present on the patient's baseline (i.e. before allocation) ECG. The Minnesota Code for pathological Q-waves will be used.
(*) In cases of ECG diagnosis of MI in the presence of a complete left bundle branch block, peak CKMB levels should be obtained locally.

TLR

Target Lesion Revascularization is defined as any ischemia-driven repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel due to any of the following:

1. the patient had a positive functional study corresponding to the area served by the target lesion.
2. ischemic ECG changes at rest in a distribution consistent with the target vessel
3. ischemic symptoms referable to the target lesion.

TVR

Target Vessel Revascularization is defined as any ischemia-driven repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel due to any of the following:

1. the patient had a positive functional study corresponding to the area served by the target vessel
2. ischemic ECG changes at rest in a distribution consistent with the target vessel
3. ischemic symptoms referable to the target lesion.

II. Contemporary definitions

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

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

- **Cardiac death:**
  Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all study procedure related deaths including those related to concomitant treatment.

- **Vascular death:**
  Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

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

Stroke

1. Duration of a focal/global neurological deficit ≥24 hours or<24 hours if any of the following conditions exist:
   i. at least one of the following therapeutic interventions:
      a. Pharmacologic (i.e., thrombolytic drug administration)
      b. Non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty)
   ii. Available brain imaging clearly documents a new hemorrhage or infarct
   iii. The neurological deficit results in death
2. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, other metabolic abnormality, peripheral lesion, or drug side effect). Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
3. Confirmation of the diagnosis by a neurology or neurosurgical specialist and at least one of the following:
   a. Brain imaging procedure (at least one of the following):
      i. CT scan
      ii. MRI scan
      iii. Cerebral vessel angiography
   b. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

A. If the acute focal signs represent a worsening of a previous deficit, these signs must have either
   1. Persisted for more than one week, or
   2. Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

B. Strokes may be sub-classified as follows:
   1. Ischemic (Non-hemorrhagic): a stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology.
   2. Hemorrhagic: a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma,* and primary subarachnoid hemorrhage.
      *All subdural hematomas that develop during the clinical trial should be recorded and classified as either traumatic versus nontraumatic.
   3. Unknown: the stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

C. Stroke Disability

All strokes with stroke disability of Modified Rankin Scale (mRS) ≥1 will be included in the primary endpoint. All diagnosed strokes (even with mRS 0) will also be tabulated. Stroke disability will be classified using an adaptation of the modified Rankin Scale.

Scale	Disability
0	No stroke symptoms at all. (May have other complaints)
1	No significant disability; symptoms present but no physical or other limitations.
2	Slight disability; limitations in participation in usual social roles, but independent for activities of daily living (ADL)
3	some need for assistance but able to walk without assistance
4	Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care
5	Severe disability requiring constant nursing care and attention.
Stroke: Modified Rankin score ≥1 and increase by ≥1 from baseline	

D. Transient Ischemic Attack (as compared to stroke) is defined as:

- New focal neurologic deficit with rapid symptom resolution, usually 1-2 hours, always within 24 hours
- Neuroimaging without tissue injury

Myocardial Infarction

New Universal Definition 2012

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: Myocardial infarction secondary to an ischemic imbalance
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, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic 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 ($\leq 99^{th}$ 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 ischemia, or (ii) new ischemic 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 ischemia 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 grafting (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.

Revascularization

The revascularizations will be adjudicated per the ARC definition.

- **Location of Revascularization:**

  - **Target Lesion Revascularization (TLR)**
    TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

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

  - **Non Target Lesion Revascularization (Non-TLR)**
    Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.

  - **Non Target Vessel Revascularization (Non-TVR)**
    Revascularization of the vessel identified and treated as the non-target vessel at the time of the index procedure.

Stent Thrombosis (Per ARC Circulation 2007; 115: 2344-2351)

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the subject left the catheterization lab.

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

  * Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0 - 30 days) - this definition is currently used in the community.
  † Including “primary” as well as “secondary” late stent thrombosis; “secondary” late stent thrombosis is a stent thrombosis after a target segment revascularization.

- **Categories:**
  - Definite
  - Probable
  - Possible

Definitions of each category are as follows.

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

  Angiographic confirmation of stent thrombosis*
  The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one 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 elevation or depression in cardiac biomarkers (refer to definition of spontaneous MI)
    - Nonocclusive thrombosis
      - Thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
    - Occlusive thrombus
      - TIMI 0 or TIMI 1 in-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

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

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

- **Probable stent thrombosis**
  Either of the following occurred after stent implantation will be considered a probable stent thrombosis:
    - Any unexplained death within the first 30 days
    - Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

- **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.

III. Other definitions

ACUTE SUCCESS DEFINITIONS

Clinical Device Success (Lesion Basis)

Successful delivery and deployment of the assigned device at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of < 30% by QCA (by visual estimation if QCA unavailable).

Clinical Procedure Success (Patient Basis)

Achievement of final in-stent residual stenosis of < 30% by QCA (by visual estimation if QCA unavailable) with successful delivery and deployment of the assigned device at the intended target lesion and successful withdrawal of the delivery system without the occurrence of MACCE during the hospital stay (maximum of 7 days), and with or without use of other therapeutic device.

In multiple target lesion setting all lesions must meet clinical procedure success criteria to have a patient level procedure success.

ADVERSE EVENT DEFINITIONS

Adverse Event (AE)

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

Serious Adverse Event (SAE)

If an adverse event meets any of the criteria below, it is regarded as a serious adverse event (SAE).

- 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.

Adverse Device Effect

Adverse device effects include issues related to its specifications, product experiences and device malfunctions, insufficient contents of instruction for use and adverse device effects. It also includes inevitable adverse events potentially occurs even if a device is properly used. This means that an adverse device effect is defined as any adverse event that is related to the study device, or whose relationship to the study device is unknown.

Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is an adverse device effect (including infection that is suspected to relate to use of the device) of which occurrence and the occurrence trend such as number and frequency of the occurrences, and conditions on the occurrence cannot be predicted from the Investigator's Brochure of the investigational device.

Angina Pectoris

- **Braunwald Classification of Unstable Angina:**
  - I. New onset of severe or accelerated angina. Patients with new onset (≤ 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.
  - II. Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.
  - III. Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

- **Canadian Cardiovascular Society [CCS] Classification of Stable Angina:**
  - I. Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.
  - II. Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
  - III. Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.
  - IV. Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

TIMI (Thrombosis in Myocardial Infarction) Flow Grades

0. No contrast flow through the stenosis.
1. A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
2. Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
3. Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.

23 APPENDIX VI: MSCT ACQUISITION GUIDELINES

[Optimizing Imaging Quality for MSCT and FFR_{CT}]

Introduction

- Please utilize **64 Slice CT** Scanner.
- Imaging the **entire coronary tree** allows for the most accurate FFRCT computation.

Preparation

- Assess heart rate and rhythm. Heart rate control (below 60 beats per minute) reduces misregistration and motion artifacts.
- Heart rate modulation for heart rates >60/min during breath holding.
    - Oral: metoprolol tartrate 100 mg, one hour before the exam.
      atenolol 50 mg, one hour before the exam.
    - IV: metoprolol 5 mg, repeated up to 3 times.
    - Contraindications: conduction delays, hypotension, severe asthma, allergy to betablockers.
    - Consider ivabradin or calcium antagonist for patients with contra-indications to betablockers.
- Full explanation of exam, and practice breath hold. Ensure breath hold time will be sufficient for scan time. Evaluate impact of breath holds on heart rate.

Nitrates and FFR_{CT}.

• use NTG preferably 3 minutes prior to CT image acquisition;
• use 1-2 sprays (0.4mg-0.8mg)
• use beta-blocker with it to avoid reflex tachycardia/vasoconstriction
• ask patients not to take any nitrates 12-14 hours prior to CT acquisition
• additional Beta blockade may be given after nitroglycerin to counteract the reflex tachycardia

- Confirm absence of allergy to contrast media (consider prophylaxis for patients with doubtful or mild reactions to contrast in the past).
- No caffeine (coffee, tea, energy drinks, and most soda) products <12h pre-scan.
- No smoking 5 minutes prior to scan.

Patient installation

- Attach ECG leads, avoid respiratory muscles, check signal stability during breath hold.
- Placement of an IV catheter that allows a flow of at least 4 ml/s.

Data acquisition

- Overview/scout of the entire chest.
- Contrast enhancement:
  - ≥300 g/L iodine contrast medium.
  - Injection rate: 4-6 ml/s.
  - Total amount depends on the patient size, the scan mode and the scan duration.
  - Contrast-scan timing:
  - Test bolus acquisition: 15-20 ml of contrast is injected, preferably followed by a bolus chaser. The time of (maximum) enhancement is used as the delay of the data acquisition after start of contrast injection.
  - Bolus tracking: arrival of the (entire) bolus is monitored in the ascending aorta. To avoid premature triggering of the scan the ROI should be sufficiently large and placed away form the superior vena cava.
  - A saline bolus of ≈50 ml is injected after the contrast medium at the same rate.
- Scan mode (depending on the available CT equipment and local experience):
  - ECG-gated spiral scan mode. ECG-triggered tube modulation: use and nominal output width depending on the heart rate and rate stability. Full-output window wider, to include both end-systolic and diastolic phase, for heart rates >70/min.
  - ECG-triggered sequential (step-and-shoot) scan mode can be used by experienced sites for patients with a modest heart rate (<70-75/min) without rhythm irregularities. Scan window preferably widened to allow reconstruction of more phases, wider for faster heart rates (>65/min).
  - High-pitch spiral scans (Definition Flash®) not recommended.
- Acquisition parameters:
  - Thinnest detector width.
  - Tube current (mA), depending on the size of the patient.
  - Tube voltage 120 kV, 100 kV can be considered for (very) small patients (<70 kg).
  - Scan range: from 1-2 cm below the carina until the caudal border of the heart.

Image reconstruction (appropriately labelled):

1) Standard reconstructions:

- Standard medium-sharp convolution kernel.
- ECG-editing, if necessary.
- Field-of-view enclosing the entire heart (cover inferior carina to lower heart border) (approx. 18 x 18 cm).
- Reconstructed slice thickness equal or slightly wider than the individual detector width. In case of noisy images (obesity), thicker-slice reconstructions may be added.
- Reconstructions of at least three different phases. Depending on the scan protocol both diastolic and systolic reconstructions should be performed.

- Reconstructions should be optimized for the segments of interest (ROI). In case of suboptimal image quality other phases should be explored.
- In case of slab artifacts at the level of the lesions/segments of interest, ECG editing may improve image quality.

2) Sharp-kernel reconstructions:

- Thinnest slice thickness
- One or two reconstructions at the best phase for each of the one or two stented segments, based on the standard reconstructions.

DVD recording:

- Topogram.
- ECG file.
- Scan protocol file containing: scan mode, mA, kV, DLP, etc.
- Standard kernel reconstructions, at least one (or the same) optimal phase for each diseased coronary segment, preferably three or more datasets including both systolic and diastolic phases.
- Sharp kernel reconstructions (dedicated stent reconstruction), at least one (or the same) optimal phase for each diseased segment.

Summary

• FFR_{CT} is derived from precise modelling of the coronary tree, not just areas of disease

• cCTA best practices = best practices for FFR_{CT} data
J Cardiovasc Comput Tomogr. 2009 May-Jun;3(3):190-204

• Scan optimization is essential in unlocking the potential of FFR_{CT}