

ECRI-004

SYNTAX III REVOLUTION Trial:

A randomized study to evaluate the feasibility of Heart-Team clinical decision making regarding the optimal (surgical or percutaneous based) revascularization strategy in patients with complex coronary artery disease, based on non-invasive coronary CT Angiography (CTA) imaging utilising high-definition GE RevolutionTM multi-slice CT and HeartFlow FFR_{CT} compared to the current standard of care with conventional invasive coronary angiography (CA)

Version 1.0, April 4th, 2016

Sponsor:
European Cardiovascular Research Institute (ECRI)
Westblaak 98
3012 KM Rotterdam
The Netherlands

CRO:
Cardialysis
Westblaak 98
3012 KM Rotterdam
The Netherlands

Protocol approval page

A randomized clinical study investigating utilising high-definition GE-Revolution scanning to streamline Heart Team decision-making on the most optimal revascularization modality in patients with complex coronary artery disease

Protocol version: 1.0, dated 04 April 2016

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

Patrick W. Serruys,
Prof. of Cardiology, Imperial College, London (UK)
Chairman Steering Committee

Date

Gerrit-Anne van Es
Managing Director, ECRI-Trials B.V.

Date

Protocol Signature page Site Principal Investigators

I have read this protocol and/or amendment and appendices and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the study.

I will conduct the study in accordance with the protocol and ISO 14155 guidelines, as well as local regulations. We, the undersigned, have read and approved the protocol specified above, and agree upon the contents.

Protocol version: 1.0, dated 04 April 2016

Principal Investigator

Principal Investigator (signature)

Date

Principal Investigator

Principal Investigator (signature)

Date

Principal Investigator

Principal Investigator (signature)

Date

Institution Name/Location

TABLE OF CONTENTS

1	PROTOCOL SYNOPSIS	6
2	INTRODUCTION	12
3	OBJECTIVE	22
4	STUDY DESIGN.....	23
5	ENDPOINTS	25
5.1	Primary Endpoint	25
5.2	Secondary endpoints	25
6	SUBJECT SELECTION	27
6.1	Inclusion Criteria	27
6.2	Exclusion Criteria	28
7	STUDY PROCEDURES	29
7.1	Screening.....	29
7.2	Patient Information and Informed Consent.....	29
7.3	Baseline evaluation prior to MSCT/ Heart Team discussion.....	29
7.4	MSCT.....	30
7.5	Anatomical SYNTAX Score, SYNTAX Score II and functional anatomy (FFR _{CT})....	30
7.6	Randomization	31
7.7	Heart Team meeting structure & organization.....	31
7.8	Data-flow	33
8	STATISTICAL DESIGN AND ANALYSIS	34
8.1	Introduction.....	34
8.2	Intent-To-Treat population.....	34
8.3	Sample size	34
8.4	Intend-to-Treat Analysis	35
8.5	Analysis of the Primary Endpoint.....	35
8.6	Analysis of the Secondary Endpoints	36
8.7	Descriptive statistical methodology.....	37
9	QUALITY CONTROL AND QUALITY ASSURANCE.....	39
9.1	Compliance to Standards and Regulations	39
9.2	Quality Assurance and Monitoring.....	39
9.3	Quality Assurance and Data management	39
9.4	On-site Audits	40
10	ORGANISATION	41
10.1	Sponsor.....	41
10.2	Steering Committee.....	41
10.3	Clinical Event Committee (CEC).....	41
10.4	Data Safety Monitoring Board (DSMB)	41
10.5	Data Management.....	41
10.6	Site Management and Monitoring.....	41
10.7	Safety Reporting.....	42
10.8	Statistical Analysis	42
11	DATA HANDLING AND RECORD KEEPING	43
11.1	Source Documentation (SD)	43
11.2	Case Report Form Completion.....	43

11.3	Record Retention	43
12	PUBLICATION POLICY	45
13	INVESTIGATOR RESPONSIBILITIES	46
13.1	Investigator Responsibility/Performance	46
13.2	Required Documents	46
13.3	Ethics Committee (EC) / Institutional Review Board (IRB) Approval.....	47
13.4	Informed Consent	47
13.5	Protocol Deviation.....	47
13.6	Reporting Requirements.....	48
13.7	Audits / Inspection.....	48
14	SPONSOR RESPONSIBILITIES	49
14.1	Role of ECRI	49
14.2	Supplemental Applications.....	50
14.3	Submitting Reports.....	50
14.4	Maintaining Records	50
14.5	Audit.....	51
14.6	Confidentiality.....	51
15	REFERENCES	52
16	APPENDIX I: SCHEDULE OF EVENTS	58
17	APPENDIX II: SYNTAX Score II.....	59
18	APPENDIX III: DEFINITIONS.....	61
19	APPENDIX IV: MSCT acquisition guidelines	64

1 PROTOCOL SYNOPSIS

Protocol Number	ECRI-004
Title	SYNTAX III REVOLUTION Trial: a randomized clinical study utilising high-definition GE-Revolution scanning and HeartFlow FFR _{CT} to streamline Heart Team decision-making on the most optimal revascularization modality in patients with complex coronary artery disease.
Study Hypothesis	Determination if a revascularization strategy for 3-vessel coronary artery disease based on non-invasive Revolution™ CT scanning and Heartflow FFR _{CT} will result in similar decisions as the conventional approach based on invasive coronary angiography.
Study design	<p>The SYNTAX III REVOLUTION Trial is a multicenter, all-comers trial (either isolated unprotected left-main or 3-vessel disease with or without left-main disease and candidate for either CABG or PCI treatment) aiming at randomizing two Heart Teams who would have to make a decision between surgical or percutaneous treatment according to either a conventional angiography or a multislice CT angiography assessment in approximately 223 patients in approximately 5-10 interventional cardiology centers in Europe. Patients with de novo 3-vessel disease or left-main disease (isolated or associated with 1, 2 or 3 vessel disease) will be eligible. In addition, the incremental value of FFR_{CT} in the decision making of the Heart Team arm allocated primarily to the assessment of the MSCT (CT first algorithm) will be a secondary endpoint.</p> <p>Patient study participation will end after final Heart Team treatment decision. The ultimate choice of treatment is up to the discretion of the physician/Heart Team.</p>
Objective	To compare a Heart Team clinical decision making strategy either based solely on non-invasive CT angiography (GE Revolution™) with and without adjunction of HeartFlow FFR _{CT} or based solely on conventional invasive angiography.
Secondary objectives	To evaluate in a population with multivessel disease, the outcomes <i>between</i> two strategies (non-invasive ‘CT first algorithm’ and invasive conventional ‘Angiography first algorithm’) and <i>within</i> these two strategies (based on differences in availability of sources of information).

	<p>The sources of information are:</p> <ul style="list-style-type: none"> - Invasive Angiography - Non-invasive GE Revolution CT - Functional anatomy by non-invasive FFR_{CT} (Heartflow) <p>The results to be compared are:</p> <ul style="list-style-type: none"> ○ Agreement on treatment recommendation ○ Agreement on treatment recommendation between different levels of available information ○ Agreement in coronary stenosis segments to be revascularized ○ Anatomical SYNTAX Score and the resulting SYNTAX Score II
Number of Patients	Approximately 223 patients in total.
Investigational Sites	Approximately 5-10 sites in Europe.
Follow-up	No follow-up assessment/visits. Study end after final Heart Team clinical decision making.
Primary Endpoint	Inter-rater agreement, as assessed by Cohen's Kappa, on revascularization strategy of two Heart Teams using an "Angio-first" algorithm (based on invasive SYNTAX Score II) or a "CT-first" algorithm (based on non-invasive SYNTAX Score II, without FFR _{CT}).
Secondary Endpoints	<ul style="list-style-type: none"> • Level of agreement in the decision making strategy based on CT only without functional assessment and the decision making strategy based on CT with functional assessment ("CT first" algorithm group). • Level of agreement in the decision making strategy based on CT only (with functional assessment) and the decision making strategy based on CT with functional assessment and conventional angiography ("CT first" algorithm group). • Level of agreement in the decision making strategy based on conventional angiography only and the decision making strategy based on CT with functional assessment and conventional angiography ("Angio first" algorithm group). • Inter-rater agreement on revascularization strategy (based on conventional angiography and CT with functional assessment) of two Heart Teams using an "Angio-first" algorithm or a "CT-first" algorithm. • Anatomical SYNTAX Score calculation based on non-invasive GE Revolution CT (visual by Heart Team involving an experienced coronary CT reader) and the resulting SYNTAX Score II.

	<ul style="list-style-type: none"> Anatomical SYNTAX Score calculation based on non-invasive GE Revolution CT (visual by Core Lab) and the resulting SYNTAX Score II. Anatomical SYNTAX Score calculation based on invasive Angiography (visual by Heart Team) and the resulting SYNTAX Score II. Anatomical SYNTAX Score calculation based on invasive Angiography (visual by Core Lab) and the resulting SYNTAX Score II. CT based functional anatomy (FFR_{CT} as assessed by Heartflow) Concordance in SYNTAX Score(s) between and within strategies Agreement in coronary stenosis segments to be revascularized between and within strategies.
Patient population	<p>i). Patients with left main (isolated, or associated with 1, 2 or 3 vessel disease) or de novo 3-vessel coronary artery disease (DS \geq 50%) who are able to undergo cardiac CT with a GE high-definition RevolutionTM multi-slice CT scanner.</p> <p>ii). Patients can be enrolled from a referral site, externally diagnosed and referred to the cardiologist and/or surgeon; or patients can be diagnosed internally. If the patient is diagnosed internally, the physician who performed the diagnosis should not be involved in the Heart-Team(s).</p> <p>iii). The enrolment criteria will be unrestrictive all anatomical SYNTAX Scores are eligible for initial screening similar to the SYNTAX I and II studies. As per the original SYNTAX Trial, prior CABG or PCI will be one of the few exclusion criteria.</p>
General Inclusion and Exclusion Criteria	<p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> Patients with at least 1 stenosis (angiographic, visually determined de novo lesions with \geq 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 with or without left main involvement; 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; Vessel size should be at least 1.5 mm in diameter as visually assessed in diagnostic angiogram; Patients with chronic stable angina or stabilized acute coronary syndromes (inclusion criteria of the SYNTAX I study): <ol style="list-style-type: none"> stable (Canadian Cardiovascular Society Class 1, 2, 3 or 4) angina

	<p>pectoris;</p> <p>b) or unstable (Braunwald class IB, IC, IIB, IIC, IIIB, IIIC) angina pectoris and ischemia with normal cardiac enzyme values prior to enrollment;</p> <p>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);</p> <p>5. <u>All</u> anatomical SYNTAX Scores are eligible;</p> <p>6. Patient amenable to a MSCT coronary angiography (e.g. no claustrophobia, high heartrate not amenable to beta-blockers, poor renal function, etc., up to discretion of investigator);</p> <p>7. 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;</p> <p><u>Exclusion Criteria:</u></p> <p>Candidates will be ineligible for enrolment in the study if any of the following conditions apply:</p> <ol style="list-style-type: none"> 1. Under the age of 18 years; 2. Unable to give Informed Consent; 3. 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; 4. Prior PCI or CABG; history of coronary stent implantation; 5. Evidence of evolving or ongoing acute myocardial infarction (AMI) in ECG and/or elevated cardiac biomarkers (according to local standard hospital practice) have not returned within normal limits at the time of enrollment; 6. Concomitant cardiac valve disease requiring surgical therapy (reconstruction or replacement); 7. Single or two-vessel disease (at time of Heart Team consensus); 8. Atrial fibrillation or significant arrhythmias; 9. Known allergy to iodinated contrast; 10. A Body Mass Index (BMI) of 35 or greater;
--	---

	11. Participation in another trial with an investigational drug or device.
Rationale for sample size calculation	<p>The SYNTAX III REVOLUTION Trial is a multicenter, all-comers trial aiming at randomizing two Heart Teams. Each patient will be assessed by two Heart Teams, the first Heart Team will perform a clinical decision based on SYNTAX Score II analysis with invasive angiography information (Angio first), the second Heart Team will perform a clinical decision based on SYNTAX Score II analysis with non-invasive MSCT information (CT first). For both strategies the Heart Team will lead to one of three treatment recommendations:</p> <p><i>CABG-only.</i></p> <p>1. CABG-only. Patient should be treated by CABG due to high 4-year mortality of PCI according to therapeutic recommendation of SYNTAX Score II.</p> <p><i>PCI-only/ Equipoise.</i></p> <p>1. <i>Equipoise.</i> Patient could be treated by either CABG or PCI, considering that the 4-year mortality prediction is similar between PCI and CABG.</p> <p>2. <i>PCI-only.</i> Patient should be treated by PCI due to high 4-year mortality of CABG according to therapeutic recommendation of SYNTAX Score II.</p> <p>The SYNTAX III REVOLUTION Trial is powered to show substantial inter-rater agreement between the Heart Team recommendation (“CABG only” or “PCI only/Equipoise”) based on the Angio first strategy and the Heart Team recommendation (“CABG only” or “PCI only/Equipoise”) based on the CT first strategy.</p> <p>The inter-rater agreement will be assessed by Cohen’s Kappa, a Kappa of 0.60 to 0.80 is considered to show substantial agreement.¹</p> <p>We expect the two Heart Team decisions to reach an almost perfect agreement (Kappa=0.80).¹</p> <p>Given these assumptions:</p> <ul style="list-style-type: none"> • Both the Angio first diagnostic algorithm and the CT first diagnostic algorithm will result in the “CABG-Only” treatment recommendation decision for 30% of the patients. • An almost perfect agreement (Kappa=0.80) • 90% power to show at least substantial agreement (Kappa>=0.60).¹ • 5% two-sided alpha <p>a sample size of 200 patients will be sufficient for achieving 90% power to reach a positive trial.² Assuming an attrition rate of maximum 10%, 223</p>

	patients will be included in the study.
Study organization/ Grant givers	SYNTAX III REVOLUTION Trial is an Investigator-Sponsored-Study (ISS). Sponsor: European Cardiovascular Research Institute (ECRI). Scientific Grant to ECRI from GE Healthcare and Heartflow.

2 INTRODUCTION

For the past 50 years revascularization associated with optimal medical therapy has been the cornerstone of coronary artery disease (CAD) treatment.³ Since the introduction of coronary artery bypass surgery (CABG) in 1964 and percutaneous coronary intervention (PCI) in 1977, revascularization procedures have undergone rapid technological advancements that have markedly improved their safety and efficacy, and have lead to their widespread clinical adoption across the world.^{4,5}

Since the introduction of invasive coronary angiography in the 1960s, it has to the present day remained the gold-standard diagnostic method to visualise the coronary anatomy and guide revascularization procedures. Invasive coronary angiography has however three major limitations; firstly is the marked inter- and intra- observer variability in its interpretation, secondly the lack of information regarding the functional significance of coronary lesions, and thirdly its invasive nature.⁶⁻⁹ It has long been recognised that the angiographic degree of a given coronary stenosis to be a poor tool to ascertain its physiological impact upon blood flow – with simple factors such as coronary lesion location and the amount of myocardium subtended shown to have a significant impact on whether the lesion will be ischaemic or not.¹⁰ Moreover, revascularisation of coronary stenoses based upon visual assessment (diameter stenosis) alone has been shown to lead to inappropriate revascularisation following PCI or CABG; conversely, functional driven revascularisation has been proven to reduce inappropriate revascularisation whilst simultaneously improving clinical outcomes.¹⁰⁻²⁰

Multislice Coronary Computed Tomography Angiography (coronary CTA)

In the last two decades, coronary CTA has been introduced as a non-invasive alternative for coronary anatomy assessment.²¹ Since its introduction, the technology has undergone rapid scientific advances with improvements in resolution, acquisition times, reduction in contrast volume and radiation doses, going from a eight-slice CT system in 2000, 16-slice CT in 2002, 64-slice CT systems in 2004, and more recently 128-slice and 256-slice CT systems. The current new generation GE RevolutionTM multi-slice 256-slice CT system, being utilised in the present study, provides best-in-class technology that will enable imaging of the entire heart in a single

heart beat, with the rapid speed of the scan facilitating a substantial reduction in both contrast volumes and radiation dosage.²²⁻²⁴

In the landmark multicentre CORE-64 study²⁵ – investigating the coronary CTA diagnostic ability utilising 64-row scanners compared to invasive angiography in 291 consecutive patients – coronary CTA (area under the receiver-operator curve [AUC] 0.84, 95% CI 0.79 to 0.88) was demonstrated to be similar to conventional invasive angiography (AUC 0.82, 95% CI 0.77 to 0.86) in its ability to identify patients who subsequently underwent revascularization. Further patient-based analyses demonstrated coronary CTA to be highly accurate for the diagnosis of patients with at least one coronary stenosis of 50% or more, as assessed by invasive quantitative coronary angiography (QCA), with an AUC 0.93 (95% confidence interval [CI], 0.90 to 0.96). In a vessel-based analysis, the AUC was 0.91 (95% confidence interval [CI], 0.88 to 0.93) demonstrating the good diagnostic capacity of 64-row coronary CTA.

More recently, the PROMISE²⁶ and SCOT-HEART²⁷ trials investigating over 14000 patients collectively, demonstrated the potential incremental value of coronary CTA over conventional practice in investigating patients with suspected angina due to coronary heart disease. In PROMISE, coronary CTA was shown to be non inferior to functional testing over a median follow up of 2 years, and allowed for better understanding of the coronary anatomy and presence of obstructive disease before the patient got to the catheterisation lab. This in turn was shown to reduce the likelihood of the patient undergoing invasive angiography demonstrating no obstructive CAD, as well as better directing of secondary prevention medication, such as statins. In SCOT-HEART, similar findings were shown to PROMISE, namely, that the addition of coronary CTA to standard medical therapy lead to an incremental benefit; in particular, for gaining an understanding of the presence of obstructive disease before the patient got to the catheterisation lab, thus reducing the likelihood of the patient undergoing invasive angiography demonstrating no obstructive CAD and allowing for the appropriate immediate targeting of revascularisation strategies and other secondary prevention care.

Anatomical SYNTAX Score, Functional SYNTAX Score and SYNTAX Score II

Decision-making between surgery and percutaneous based revascularisation

strategies in complex CAD has historically remained difficult.²⁸ To aid this process, European revascularisation guidelines currently advocate a multidisciplinary “Heart-Team” approach – consisting of at least a cardiologist and cardiac surgeon – and clinical tools, such as the anatomical SYNTAX Score and SYNTAX Score II, to objectively quantify CAD burden and clinical co-morbidity.^{7-9,29-38}

Anatomical SYNTAX Score

The anatomical SYNTAX Score (www.syntaxscore.com) was developed during the design of the SYNTAX Trial as a tool to force the interventional cardiologist and cardiac surgeon to systematically analyse the coronary angiogram and to specify the number of coronary lesions requiring treatment, their angiographic location and anatomical complexity.^{7,34-36,39-41} The anatomical SYNTAX Score combines the importance of a diseased coronary artery segment in terms of its severity (i.e. obstructive or occlusive), anatomical location and importance in supplying blood to the myocardium (‘vessel-segment weighting’ based on the Leaman Score⁴²), adverse characteristics of the coronary lesion for revascularisation (ACC/AHA lesion classification),^{43,44} the Medina Classification System for bifurcation lesions,⁴⁵ and total occlusion characteristics from the European TOTAL Surveillance Study⁴⁶ (**Fig. 1**). Each vessel segment, 1.5mm in diameter or greater (**Fig. 1**, labelled 1 through 16), with a $\geq 50\%$ diameter stenosis by visual estimation, is awarded a multiplication factor related to coronary lesion location and severity. Further characterisation of the coronary lesions leads to the addition of more points, which includes features of total occlusions (duration, length, blunt stump, presence of bridging collaterals or side branch), presence of bifurcation (based on the MEDINA classification⁴⁵) or trifurcation disease (number of diseased branches involved), side branch angulation, aorto-ostial lesion, severe tortuosity, lesion length >20 mm, heavy calcification, thrombus and diffuse or small vessel disease. An online SYNTAX Score algorithm⁴¹ automatically summates each of these features to calculate the final total SYNTAX Score.

Based primarily on the results of the SYNTAX Trial,^{40,47,48} both European and US guidelines on coronary revascularization now recommend the use of the anatomical SYNTAX score to aid cardiologists in selecting the most appropriate revascularization modality in patients with complex CAD.^{3,49,50} Specifically, current European revascularisation guidelines³² gives subjects

with 3VD and low SYNTAX Scores (0-22) a level of evidence of IA for CABG and IIa B for PCI. In subjects with ULMCA disease and low to intermediate SYNTAX Scores (<33), a level of evidence of IA is given for CABG and IIb B for PCI.

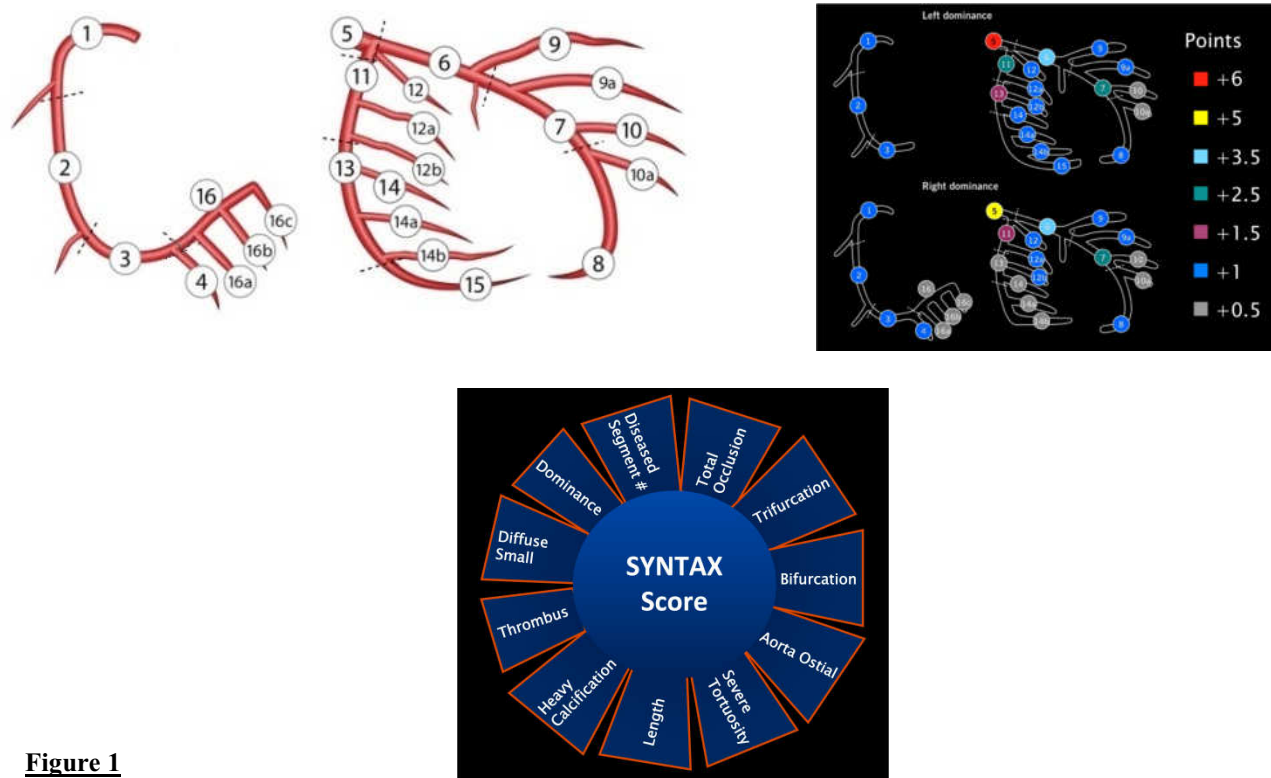


Figure 1

Coronary tree segments and their importance in supplying blood flow to the left ventricle (vessel segment weighting - Leaman score^{34,42}) based on the presence of a left or right dominant system (upper images). In a right dominant system, the right coronary artery (RCA) supplies approximately 16% and the left coronary system 84% of the flow to the left ventricle. Hence the left main has a weighting factor of x5, the left anterior descending (LAD) x3.5, the left circumflex (LCX) x1.5, and RCA x1. In a left dominant system, the RCA contribution of blood flow to the LV is supplied by the left circumflex, thus the left coronary system supplies 100% of the blood to the left ventricle (LAD 58%, LCX 42%). Thus the weighting factor for the left main is increased to x6, the LAD unaltered at x3.5, and LCX increased to x2.5. A multiplication factor of 2 is used for non-occlusive lesions (50-99% diameter stenosis) and 5 for occlusive (100% diameter stenosis) lesions. Other adverse lesion characteristics considered in the SYNTAX score have an additive value (lower image). Images used with permission from the SYNTAX Trial Investigators.

Functional SYNTAX Score

Percutaneous coronary intervention guided by the assessment of the functional significance of a lesion using fractional flow reserve (FFR) has been shown to reduce inappropriate revascularization whilst simultaneously improving clinical outcomes.^{10-20,51-53} The Functional SYNTAX Score uses the principle of the functional assessment of coronary lesions to

determine the SYNTAX Score, rather than the angiographic determination of the SYNTAX Score based upon visual assessment, as is undertaken in conventional anatomical SYNTAX Score calculations. In a retrospective sub-analysis of almost 500 patients (n=497) from the FFR-guided arm of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study, the primary benefit appeared in reclassifying higher-risk groups into lower risk categories without any adverse sequelae in terms of major adverse cardiac events (MACE) and death or myocardial infarction (MI) at 1 year.¹¹ It should be emphasized that subjects in the FAME Study had substantially less complex coronary artery disease (mean SYNTAX Score 14.8 ± 6.0) compared to the PCI arm of the SYNTAX Trial (mean SYNTAX Score 28.4 ± 11.5). Prospective validation of the functional SYNTAX Score in complex coronary artery disease is currently ongoing in the SYNTAX II (ClinicalTrials.gov Identifier: NCT02015832) and FAME III (ClinicalTrials.gov Identifier: NCT02100722) clinical trials.

SYNTAX Score II

The SYNTAX Score II combines anatomical and clinical characteristics to guide decision making between CABG and PCI.^{37,38} The European Society of Cardiology/European Association for Cardio-thoracic Surgery guidelines on myocardial revascularization²⁹ currently gives the SYNTAX Score II a recommendation of IIa (weight of evidence/opinion in favour of usefulness/efficacy – should be considered), level of evidence B.

During development of the SYNTAX Score II, it was hypothesised that the category based system of the anatomical SYNTAX Score (low <23 , intermediate $23-32$, high ≥ 33) was potentially concealing higher (or lower) risk patients in lower (or higher) risk groups.⁵⁴ The SYNTAX Score II was developed to overcome this limitation by allowing for individualised decision making, and was shown to identify subsets of patients in all tertiles (low [<23], intermediate [$23-32$], high [>32]) of the SYNTAX Score in which CABG or PCI would confer a long term mortality benefit or offer equipoise for long term prognosis.³⁷

In SYNTAX, the combination of the anatomical SYNTAX Score with ACEF (age, creatinine clearance and left ventricular ejection fraction) was shown to contain the bulk of the prognostic information in predicting mortality after CABG (excluding the anatomical SYNTAX

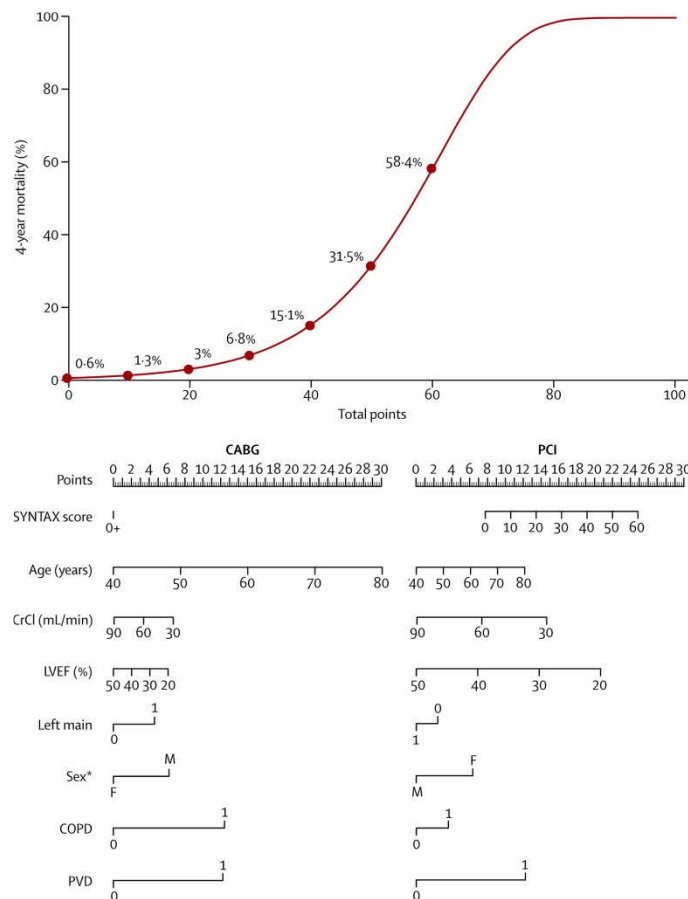
Score⁵⁴⁻⁵⁷) or PCI (including the anatomical SYNTAX Score⁵⁸). The SYNTAX Score II was therefore built on the ACEF ‘skeleton,’ with the addition of risk factors that were shown to directly affect decision making between CABG and PCI. Clinical factors that were shown to directly affect decision making between CABG and PCI were selected based on their ‘interaction effect,’ i.e. if a clinical factor was more predictive of mortality in patients undergoing PCI compared to CABG, or vice versa. For example, the anatomical SYNTAX Score aids decision-making between CABG and PCI because it is more predictive of clinical outcomes in patients undergoing PCI, compared to patients undergoing CABG (where it is not predictive).^{7,54} Based on this principle, younger age, female gender and reduced LVEF favoured CABG compared to PCI on long-term prognostic grounds. Thus, in such patients a LOWER anatomical SYNTAX Score would be required in order for the long-term mortality risk to be similar between CABG and PCI. By contrast, older age, chronic obstructive pulmonary disease or ULMCA disease favoured PCI compared to CABG and thus, in this type of patient, a HIGHER anatomical SYNTAX Score would be needed for the long-term mortality risks to be similar. A nomogram was developed (**Fig. 2**) that allowed for an accurate individualised prediction of 4-year mortality in patients proposing to undergo CABG or PCI to objectively aid decision making. The online version of the SYNTAX Score II will appear shortly after recruitment of patients in the ongoing SYNTAX II trial (ClinicalTrials.gov Identifier: NCT02015832) has been completed (www.syntaxscore.com).

The SYNTAX Score II was developed in 1800 patients from the randomised SYNTAX Trial. The design of SYNTAX was all-comers in order to reduce selection bias and therefore adds to the robustness of the SYNTAX Score II in application to contemporary clinical practice. External validation of the SYNTAX Score II³⁷ was performed in the multinational Drug Eluting stent for Left main coronary Artery disease (DELTA) Registry (14 centres in Europe, US and South Korea),⁵⁹ composed of subjects with ULMCA disease associated with or without multivessel disease (26% of the study population had 3 vessel disease [3VD]) (n=2891). Further retrospective validation of the SYNTAX Score II has recently been undertaken in 3,896 patients with 3-vessel and/or ULMCA disease undergoing PCI (n=2,190) or CABG (n=1,796) from the Japanese Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG multicenter registry.⁶⁰

Prospective validation of the SYNTAX Score II is currently occurring in 2 separate studies.

Firstly, in the international multicenter EXCEL Trial (Evaluation of XIENCE PRIME™ or XIENCE V® Everolimus Eluting Stent System Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) Trial (ClinicalTrials.gov Identifier: NCT01205776) having recently completed recruitment of patients. EXCEL recruited 1905 patients with ULMCA disease and investigator reported SYNTAX Scores <33, randomised to CABG (n=957) or PCI with contemporary stents (n=948). The Primary Endpoint is a composite measure of all-cause death, MI, or stroke at 3 years post revascularisation.⁶¹ As part of the prospective validation of the SYNTAX Score II in EXCEL, the SYNTAX Score II has been used to forecast and compare 4-year mortality in the PCI and CABG arms of EXCEL, and has predicted at least an equipoise for long-term mortality between CABG and PCI in subjects with ULMCA disease up to an intermediate anatomical complexity (anatomical SYNTAX Score <33).⁶²

Secondly in the ongoing SYNTAX II Trial (ClinicalTrials.gov Identifier: NCT02015832), where the SYNTAX Score II is being used as a clinical tool to recruit subjects with de novo three vessel disease (without left main involvement) on the grounds of patient safety, i.e. subjects with a similar long term mortality between CABG and PCI, in conjunction with the Heart Team. Notably subjects from all tertiles (low <23, intermediate 23-32, high ≥33) of the anatomical SYNTAX Score will be eligible. The PCI procedure will be guided by a functional assessment of all three vessels³⁷, a newer generation stent platform with a biodegradable polymer,¹¹ and intravascular ultrasound (IVUS) guided stent implantation.^{63,64} The PCI and CABG arms of the SYNTAX Trial^{48,65} will act as control arms.



Abbreviations: CABG coronary artery bypass graft surgery, PCI percutaneous coronary intervention; CrCl creatinine clearance (Cockcroft and Gault formula)²⁰; LVEF left ventricular ejection fraction; Left Main: unprotected left main coronary artery disease, COPD chronic obstructive pulmonary disease (long term use of bronchodilators or steroids for lung disease [EuroSCORE definition¹¹]); PVD peripheral vascular disease (aorta and arteries other than coronaries, with exercise related claudication, and/or revascularisation surgery and/or reduced or absent pulsation and/or angiographic stenosis of more than 50% [ARTS I definition¹⁹]).

Figure 2: The SYNTAX Score II nomogram for bedside application. 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 male with an anatomical SYNTAX Score of 30, ULMCA disease, CrCl 60 ml/min, a LVEF of 50%, and COPD, would have 41 points (predicted 4-year mortality: 16.3%) and 33 points (predicted 4-year mortality: 8.7%) to undergo CABG and 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.

**Due to the rarity of complex coronary artery disease in pre-menopausal women, mortality predictions in younger women are predominantly based on the linear relationship of age with mortality. The differences in mortality predictions in younger woman between CABG and PCI, will therefore be affected by larger 95% confidence intervals (CIs) but be equally valid.*

Courtesy of Farooq et al.³⁷

Non-invasive SYNTAX score

A limitation of the anatomical SYNTAX Score is the inter-observer variability in its calculation from the coronary angiogram, and the lack of information regarding the functional

significance of coronary lesions.⁶⁻⁹ Although appropriate training has been shown to improve the reproducibility of anatomical SYNTAX Score interpretation by clinicians, differences still persisted in the interpretation of several lesion types, in particular coronary bifurcations.⁶ The need to develop a more objective, rapidly calculated anatomical SYNTAX Score has become increasingly apparent.^{8,9} The development of a non-invasive anatomical SYNTAX Score will therefore potentially streamline the Heart Team process and allow for more objective decision-making by allowing for a non-invasive, less biased, anatomical and physiological assessment of the coronary anatomy in combination with clinical factors utilising the SYNTAX Score II.

Multislice Coronary CTA SYNTAX score

Papadopoulos et al⁶⁶ first described the feasibility and reproducibility of a MSCT-derived SYNTAX Score in 80 consecutive patients with symptomatic angina, using definitions of the angiographically defined SYNTAX Score adapted for the MSCT capabilities. The underlying concept being to allow for the anatomical SYNTAX Score to be calculated prior to the intervention, to potentially aid decision making and optimise patient management. Within this study, the MSCT SYNTAX Score was shown to be feasible, with results comparable to the anatomical SYNTAX Score calculated with conventional invasive coronary angiography. Whilst this study was shown to be highly reproducible,⁶⁶ a subsequent validation study of similar size numbers (n=104) was met with only fair agreement between MSCT and angiography derived SYNTAX Scores,⁶⁷ although this did improve substantially when analyses were restricted to good quality MSCT. Notably, both studies investigated subjects with predominantly less complex coronary artery disease (low SYNTAX Scores <23).^{66,67} Larger scale validation studies, particularly in more complex 'SYNTAX-like' patients, are awaited.

The addition of a non-invasive fractional flow reserve (FFR) component (Heartflow, Redwood City, California, USA) has the potential to allow for the non invasive calculation of a functional based MSCT SYNTAX Score. This technology is based upon utilizing computational fluid dynamic techniques applied to the MSCT angiography.⁶⁶ Validation data of the non-invasive FFR MSCT has been reported in the DISCOVER FLOW^{36,68} and multicentre DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography)⁶⁹ and NXT (Diagnostic performance of noninvasive fractional flow reserve

derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps)⁷⁰ trials.

As of present the MSCT substudy in the ongoing SYNTAX Trial II (ClinicalTrials.gov Identifier: NCT02015832) is currently developing a non invasive functional MSCT SYNTAX Score using the HeartFlow technology. It is expected that the present study will allow validation of the non invasive functional MSCT SYNTAX Score developed in SYNTAX II.

MSCT SYNTAX Score II

In the MSCT substudy of the ongoing SYNTAX II Trial, 68 patients had SYNTAX Score II calculations performed with both invasive coronary angiography and coronary CTA. The mean difference in SYNTAX score II PCI between ICA and coronary CTA was 0.5 ± 2.1 (limits of agreement -3.8 to 4.7). The intraclass correlation coefficient was 0.97 (95%CI 0.95 to 0.99) (unpublished data).

Purpose of Study

The purpose of the SYNTAX III trial is to investigate whether the Heart Team decision making regarding the choice of revascularization strategy based on non-invasive coronary CTA assessment of CAD (GE RevolutionTM) and non-invasive HeartFlow FFR_{CT} is at least comparable to the standard-of-care assessment based on invasive coronary angiography, in patients with complex CAD. The Heart Team decision making process will be compared between the two modalities of assessment (invasive vs. non-invasive) regarding the chosen revascularization strategy (PCI or CABG), the number of vessels requiring treatment and the coronary segments in need of revascularization.

3 OBJECTIVE

Primary Objective: to compare a Heart-Team *clinical decision making strategy* either based solely on non-invasive CT angiography (GE RevolutionTM) with and without adjunctive HeartFlow FFR_{CT} or based solely on conventional invasive angiography.

Secondary objectives:

To evaluate in a population with multivessel disease, the outcomes *between* two strategies (non-invasive ‘*CT first algorithm*’ and invasive conventional ‘*Angiography first algorithm*’) and *within* these two strategies (based on differences in availability of sources of information).

The sources of information are:

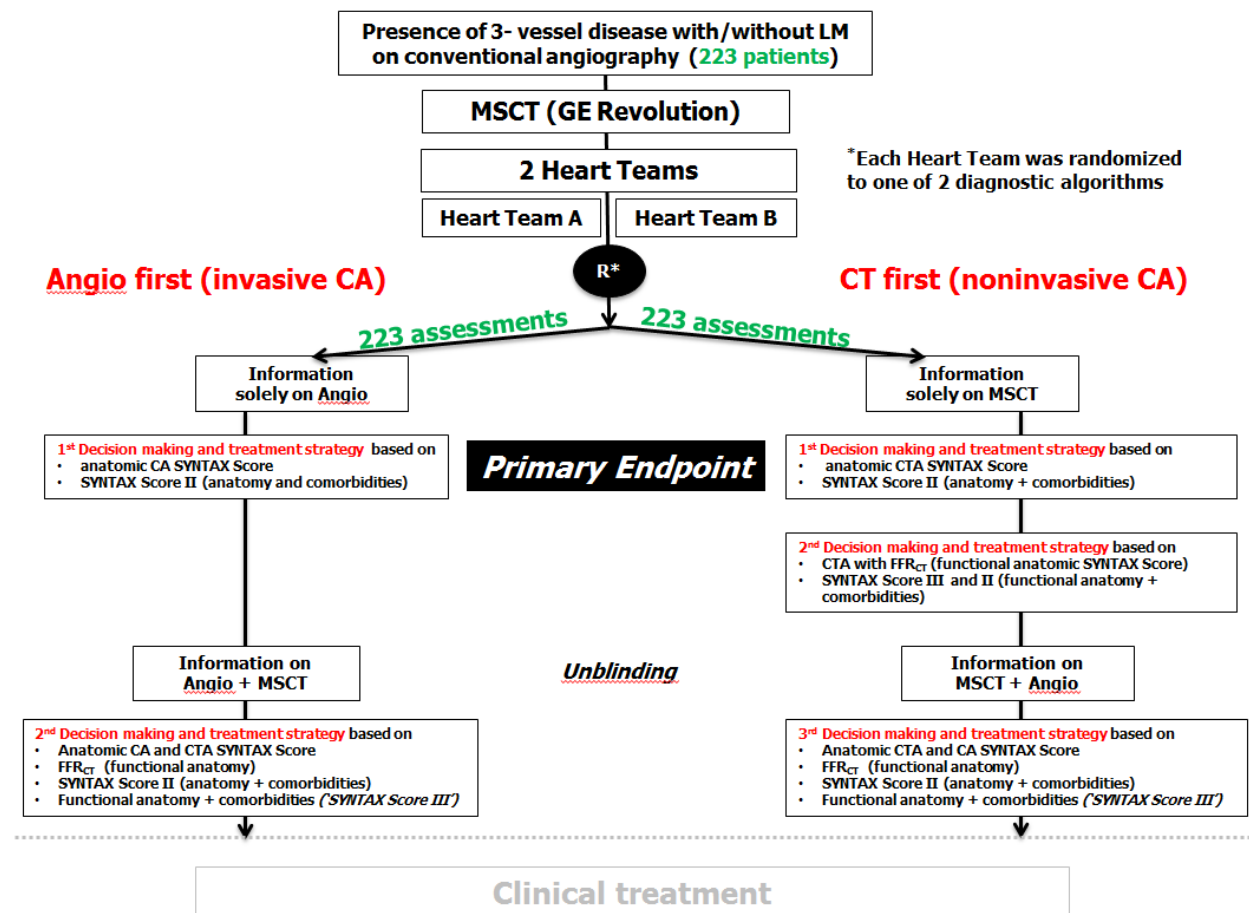
- Invasive Angiography
- Non-invasive GE Revolution CT
- Functional anatomy by non-invasive FFR_{CT} (Heartflow)

The results of information are:

- Agreement on treatment recommendation
- Agreement on treatment recommendation between different levels of available information
- Agreement in coronary stenosis segments to be revascularized
- Anatomical SYNTAX Score and the resulting SYNTAX Score II

4 STUDY DESIGN

The SYNTAX III REVOLUTION Trial is a multicenter, all-comers* trial aiming at randomizing two Heart Teams who would have to make a decision between surgical or percutaneous treatment according to either an invasive conventional angiography or a non-invasive multislice CT angiography assessment in approximately 223 patients in approximately 5-10 interventional cardiology centers in Europe. *Patients with de novo 3-vessel disease or left-main disease (isolated or associated with 1, 2 or 3 vessel disease) will be eligible.



For each given patient the Heart Team is randomly assigned to an “Angio-First” or a “CT-First” decision algorithm. There will be two (2) independent Heart Teams per hospital, and each patient will be assessed by both teams. The concordance or discordance of decision makings based on

either conventional angiography (Angio first algorithm) or MSCT angiography (CT first algorithm) will be assessed and constitute the primary endpoint of the trial. In addition, the incremental value of FFR_{CT} in the decision making of the Heart Team arm allocated primarily to the assessment of the MSCT (CT first algorithm) will be a secondary endpoint.

Patient study participation will end after final Heart Team treatment decision. The ultimate choice of treatment is up to the discretion of the physician/Heart Team.

5 ENDPOINTS

5.1 Primary Endpoint

Inter-rater agreement, as assessed by Cohen's Kappa, on revascularization strategy of two Heart Teams using an "Angio-first" algorithm (based on invasive SYNTAX Score II) or a "CT-first" algorithm (based on non-invasive SYNTAX Score II, without FFR_{CT}).

The Heart Team consensus on therapeutic strategy is made according to the following 3 options:

CABG-only.

1. *CABG-only.* Patient should be treated by CABG due to high 4-year mortality of PCI according to therapeutic recommendation of SYNTAX Score II.

PCI-only/ Equipoise.

1. *Equipoise.* Patient could be treated by either CABG or PCI, considering that the 4-year mortality prediction is similar between PCI and CABG.
2. *PCI-only.* Patient should be treated by PCI due to high 4-year mortality of CABG according to therapeutic recommendation of SYNTAX Score II

**The Heart Team can overrule the SYNTAX Score II therapeutic recommendation whenever the Heart Team identifies significant additional clinical risks which are not addressed in the SYNTAX Score II.*

5.2 Secondary endpoints

Secondary endpoints of this study are to assess:

- Level of agreement in the decision making strategy based on CT only without functional assessment and the decision making strategy based on CT with functional assessment ("CT first" algorithm group).
- Level of agreement in the decision making strategy based on CT only (with functional assessment) and the decision making strategy based on CT with functional assessment and conventional angiography ("CT first" algorithm group).

- Level of agreement in the decision making strategy based on conventional angiography only and the decision making strategy based on CT with functional assessment and conventional angiography (“Angio first” algorithm group).
- Inter-rater agreement on revascularization strategy (based on conventional angiography and CT with functional assessment) of two Heart Teams using an “Angio-first” algorithm or a “CT-first” algorithm.
- Anatomical SYNTAX Score calculation based on non-invasive GE Revolution CT (visual by Heart Team involving a radiologist) and the resulting SYNTAX Score II.
- Anatomical SYNTAX Score calculation based on non-invasive GE Revolution CT (visual by Core Lab) and the resulting SYNTAX Score II.
- Anatomical SYNTAX Score calculation based invasive Angiography (visual by Heart Team) and the resulting SYNTAX Score II.
- Anatomical SYNTAX Score calculation based on invasive Angiography (visual by Core Lab) and the resulting SYNTAX Score II.
- CT based functional SYNTAX Score (FFR_{CT} as assessed by Heartflow)
- Concordance in SYNTAX Score(s) between and within strategies
- Agreement in coronary stenosis segments to be revascularized between and within strategies.

6 SUBJECT SELECTION

i). Patients with left main (isolated, or associated with 1, 2 or 3 vessel disease) or de novo 3-vessel coronary artery disease (DS $\geq 50\%$) who are able to undergo cardiac CT with a GE high-definition RevolutionTM multi-slice CT scanner.

ii). Patients can be enrolled from a referral site, externally diagnosed and referred to the cardiologist and/or surgeon; or patients can be diagnosed internally. If the patient is diagnosed internally, the physician who performed the diagnosis should not be involved in the Heart-Team(s).

iii). The enrolment criteria will be unrestrictive all anatomical SYNTAX Scores are eligible for initial screening similar to the SYNTAX I and II studies. As per the original SYNTAX Trial, prior CABG or PCI will be one of the few exclusion criteria.

6.1 Inclusion Criteria

1. Patients with at least 1 stenosis (angiographic, visually determined de novo lesions with $\geq 50\%$ 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 with or without left main involvement;
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 chronic stable angina or stabilized acute coronary syndrome (inclusion criteria of the SYNTAX I study):
 - 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 with normal cardiac enzyme values prior to enrollment;

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;
6. Patient amenable to a MSCT coronary angiography (e.g. no claustrophobia, high heartrate not amenable to beta-blockers, poor renal function, etc., up to discretion of investigator);
7. 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;

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 18 years;
2. Unable to give Informed Consent;
3. 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;
4. Prior PCI or CABG; history of coronary stent implantation;
5. Evidence of evolving or ongoing acute myocardial infarction (AMI) in ECG and/or elevated cardiac biomarkers (according to local standard hospital practice) have not returned within normal limits at the time of enrollment;
6. Concomitant cardiac valve disease requiring surgical therapy (reconstruction or replacement);
7. Single or two-vessel disease (at time of Heart Team consensus);
8. Atrial fibrillation or significant arrhythmias;
9. Known allergy to iodinated contrast;
10. A Body Mass Index (BMI) of 35 or greater;
11. Participation in another trial with an investigational drug or device.

7 STUDY PROCEDURES

7.1 Screening

To assess the eligibility of the patient according to the inclusion/exclusion criteria, the presence of left main disease (isolated, or associated with 1, 2 or 3 vessel disease) or de novo 3-vessel coronary artery disease must be diagnosed on conventional angiography and/ or MSCT before randomization.

7.2 Patient Information and Informed Consent

If the eligibility of the patient is confirmed according to inclusion and exclusion criteria, patients must be consented prior to undergoing any study-specific procedures. Once the patient's general eligibility for the study is met, the background of the proposed study and the benefits and risks of the study must be explained to the patient prior to obtaining informed consent. Only those patients who sign the Ethics Committee approved informed consent form prior to any study-specific procedures (MSCT scanning with GE 256-slice REVOLUTION scanner) are candidates for actual enrolment in the study. Failure to provide written informed consent renders the patient 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.

7.3 Baseline evaluation prior to MSCT/ Heart Team discussion

As part of good clinical practice, the following routine laboratory tests must be performed prior to MSCT scanning/Heart Team randomization:

- creatinine clearance (Cockcroft-Gault⁷¹);

According to good routine local clinical practice, left ventricular ejection fraction (percentage) should be assessed quantitatively by either echo-cardiography, or conventional left ventriculography or other modalities. In addition, the history of chronic obstructive pulmonary disease, peripheral artery disease should be evaluated according to the EuroScore (I) definition.

7.4 MSCT

Prior to the Heart Team randomization, a MSCT scan must be obtained utilizing the 256-slice GE Revolution* CT scanner. Refer to Appendix IV for MSCT acquisition guidelines.

*A patient may be diagnosed/enrolled based on previously performed MSCT (but solely, if that CT was performed with the 256-slice GE Revolution CT scanner and within 1 month prior to patient enrolment.

FFR_{CT} will be used in the incremental process of Heart Team discussion (= secondary endpoint). The MSCT-derived FFR (FFR_{CT}) will only be disclosed after the first decision making has been concluded.

7.5 Anatomical SYNTAX Score, SYNTAX Score II and functional anatomy (FFR_{CT})

The baseline anatomical SYNTAX Score for angiography and for MSCT and SYNTAX Score II should be calculated prior to the start of the Heart Team meeting(s) and must be recorded in the eCRF.

The diagnostic angiograms and acquired and reconstructed MSCT images should be transferred automatically using AG Mednet to the independent Core Lab (Cardialysis, B.V., Rotterdam, NL) and to HeartFlow Inc. (Redwood city, California, USA) for the functional assessment derived from MSCT (FFR_{CT}).

Additionally, anatomical SYNTAX Score (angiography and CT) will be performed by the Core Laboratory. The site/Heart Team may consult the Core Lab SYNTAX Score (I and II) during the Heart Team meeting/treatment decision-making process.

The site/Heart Team may consult the Core Lab SYNTAX Score (I and II) during the Heart Team meeting/treatment decision-making process.

The site/Heart Team will also receive the functional anatomy (FFR_{CT}) for consultation.

7.6 Randomization

Before the start of enrolment, two Heart Teams (A and B) are formed and registered at each site, including at least one physician from each sub-speciality (i.e., radiologist, cardiac surgeon and interventional cardiologist). When a patient is enrolled, the algorithm of decision making is randomly allocated to two Heart Teams (i.e. Heart Team A: CT first, Heart Team B: Angiography first, or Heart Team A: Angiography first, Heart Team B: CT first) in order to ensure that the two Heart Teams experience both decision-making processes equally (e.g. CT based or Angio based). According to the allocated sequence, two Heart Teams discuss and make a treatment decision independently (blinded to the decision made by the other Heart Team).

In case any member of the Heart Team is not available due to logistical (e.g. on-call, congress, holiday) or other reasons (e.g. pre-exposure to angiography or MSCT) the site is allowed to have ‘back-up physicians’ for Heart Team A and Heart Team B. In other words, in order to prevent any delay in clinical decision making, the Heart Team can still proceed with the discussion as long as at least one physician from all three specialities is available.

7.7 Heart Team meeting structure & organization

The Heart Team should involve an interventional cardiologist, cardiac surgeon, radiologist (experienced coronary CT reader) and study coordinator.

It is recommended to execute the different levels of decision making during *one* Heart Team session. In other words, one should start the Heart Team meeting only when all information is available and accessible, i.e. anatomic SYNTAX Score by Angio and CT (by site and by Core Lab), SYNTAX Score II and functional anatomy (FFR_{CT}). Randomization is performed via the eCRF module. The *Heart Teams* are randomized to one of two groups (1:1) to either ‘Angio-first algorithm’ or ‘MSCT-first’ algorithm.

Angio first algorithm: Screen the patients first by means of conventional invasive angiography (i.e. anatomical SYNTAX Score [visual] and SYNTAX Score II) and record the first decision making on choice of revascularization (PCI or CABG), planning of revascularization measures (# of stents / # of grafts), and localization of diseased segments needing revascularization in the

eCRF. As an external reference, the independent Core Lab also provides anatomical SYNTAX Score for consultation. After the first decision making recording, the additional information of CT and the functional severity assessment is disclosed and the Heart Team completes the second decision based on information derived from both modalities.

CT first algorithm: Screen the patients first by means of non-invasive CT (i.e. anatomic SYNTAX Score [visual by experienced coronary CT reader/radiologist] and SYNTAX Score II and record the first decision making on choice of revascularization (PCI or CABG), planning of revascularization measures (# of stents / # of grafts), and localization of diseased segments needing revascularization in the eCRF. The radiologist of the Heart Team provides anatomical SYNTAX Score on MSCT, which is primarily used for decision making. As an external reference, the independent Core Lab also provides anatomical SYNTAX Score on MSCT for consultation.

After the first decision making recording the functional anatomy (FFR_{CT}) is disclosed to the Heart Team. The Heart Team recalculates the SYNTAX Score (I and II) by subtracting the (SYNTAX Score) points of non-flow limiting lesions (>0.80) and makes the second decision (incremental value FFR_{CT}). Next, the additional information of conventional angiography is disclosed and the Heart Team makes the third decision based on information derived from both modalities.

For the first, second and third decision making, the Heart Team records following items in the eCRF (as well as for the final/actual treatment):

- a. choice of revascularization mode: PCI/CABG;
- b. number of diseased vessels/diseased lesions;
- c. diseased segment numbers

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 whenever the Heart

Team identifies significant additional clinical risks which are not addressed in the SYNTAX Score II. Reasons for undertaking this should be clearly documented in the eCRF

Note: the Heart Team must co-sign and document in the eCRF (including date and time) each decision-making following the assigned algorithm prior to the unblinding with the complementary information (either Angio or MSCT, or functional anatomy).

Note: the physicians involved in the initial angiography/catherization or MSCT acquisition are not ‘blind’ for both imaging modalities and as a consequence cannot be part of the study Heart Team (randomisation).

7.8 Data-flow

The data-flow, the export of images, and the access to Core Lab SYNTAX Scores and FFR_{CT} will be described in a separate manual.

8 STATISTICAL DESIGN AND ANALYSIS

8.1 Introduction

The SYNTAX III REVOLUTION Trial is a multicenter, all-comers trial aiming at randomizing two Heart Teams. Each patient will be assessed by two Heart Teams, the first Heart Team will perform a clinical decision based on SYNTAX Score II analysis with angiographic information (Angio first), the second Heart Team will perform a clinical decision based on SYNTAX Score II analysis with MSCT information (CT first). For both strategies the Heart Team will lead to one of three treatment recommendations:

CABG-only.

1. *CABG-only.* Patient should be treated by CABG due to high 4-year mortality of PCI according to therapeutic recommendation of SYNTAX Score II.

PCI-only/ Equipoise.

1. *Equipoise.* Patient could be treated by either CABG or PCI, considering that the 4-year mortality prediction is similar between PCI and CABG.
2. *PCI-only.* Patient should be treated by PCI due to high 4-year mortality of CABG according to therapeutic recommendation of SYNTAX Score II.

8.2 Intent-To-Treat population

The ‘Intend-to-Treat’ population consists of all patients having a GE Revolution CT scan performed and for whom the Heart Team is randomly assigned to an “Angio-First” or a “CT-First” decision algorithm.

8.3 Sample size

The SYNTAX III REVOLUTION Trial is powered to show substantial inter-rater agreement between the Heart Team recommendation (“CABG only” or “PCI only/Equipoise”) based on the *Angio first* algorithm and the Heart Team recommendation (“CABG only” or “PCI only/Equipoise”) based on the *CT first* algorithm.

The inter-rater agreement will be assessed by Cohen's Kappa, on revascularization strategy of two Heart Teams using an "Angio-first" algorithm (based on invasive SYNTAX Score II) or a "CT-first" algorithm (based on non-invasive SYNTAX Score II, without FFRCT).

A Kappa of 0.60 to 0.80 is considered to show substantial agreement.¹ We expect the two Heart Team decisions to reach an almost perfect agreement (Kappa=0.80).¹

Given these assumptions:

- Both the *Angio first* diagnostic algorithm and the *CT first* diagnostic algorithm will result in the "CABG-Only" treatment decision for 30% of the patients,
- An almost perfect agreement (Kappa=0.80),
- 90% power to show at least substantial agreement (Kappa \geq 0.60)
- and a 5% two-sided alpha

a sample size of 200 patients will be sufficient for achieving 90% power to reach a positive trial.² Assuming an attrition rate of maximum 10%, 223 patients will be included in the study.

8.4 Intend-to-Treat Analysis

All analyses will be performed for the Intend-to-Treat population only.

8.5 Analysis of the Primary Endpoint

The inter-rater agreement will be assessed by Cohen's Kappa, on revascularization strategy of two Heart Teams using an "Angio-first" algorithm (based on invasive SYNTAX Score II) or a "CT-first" algorithm (based on non-invasive SYNTAX Score II, without FFR_{CT}). A 95% two-sided confidence interval will be calculated for Kappa, using the asymptotic variance of the Kappa coefficient and applying the standard normal distribution.⁷²

If the lower limit of this confidence interval is 0.6 or higher the trial is considered to be positive.

If the lower limit of this confidence interval is less than 0.6 the trial is considered to be negative.

8.6 Analysis of the Secondary Endpoints

No formal testing will take place for the secondary endpoints.

Secondary Endpoints measuring Inter-Rater agreement

Secondary Endpoints that measure inter-rater agreement are for the following situations:

- A comparison between the treatment recommendation between two diagnostic algorithms (*CT only* versus *Angio only*) at the same decision moment
- A comparison between the treatment recommendation for the same diagnostic algorithm (e.g. *CT only*) but for different levels of available information

Agreement is reached when both algorithms recommend “CABG only” or both algorithms recommend “PCI only/Equipoise”.

In both cases the inter-rater agreement will be measured by:

- 2*2 tables showing the treatment recommendations (“CABG only”/“PCI only/Equipoise”) for the compared situations.
- The percentage of patients with agreement between the algorithms and its 95% two-sided Confidence Interval (using the Clopper-Pearsons (Exact) approach).
- The inter-rater agreement as measured by Cohen’s Kappa and its 95% two-sided Confidence Interval for Kappa using the asymptotic variance of the Kappa coefficient and applying the standard normal distribution.⁷²

Additionally these endpoints measuring agreement will be reported.

- Concordance in SYNTAX Score(s) between and within strategies, measured as the difference in SYNTAX Score(s) points.
- Agreement in coronary stenosis segments to be revascularized between and within strategies (using AHA 16 segment model).^{73,74}
- An ad-hoc defined composite endpoint combining
 - Concordance in SYNTAX Score(s)
 - Agreement in coronary stenosis segments to be revascularized

-Agreement between treatment recommendation.

Continuous secondary endpoints

- Anatomical SYNTAX Score calculation based on non-invasive GE Revolution CT (visual by Heart Team involving a radiologist)
- Anatomical SYNTAX Score calculation based on non-invasive GE Revolution CT (visual by Core Lab)
- Anatomical SYNTAX Score calculation based on invasive Angiography (visual by Heart Team)
- Anatomical SYNTAX Score calculation based on invasive Angiography (visual by Core Lab)
- Functional SYNTAX Score by non-invasive FFR_{CT} (Heartflow)
- SYNTAX Score II derived from either conventional angiography (CA) or non-invasive angiography (CTA) by Heart Team

8.7 Descriptive statistical methodology

All statistical analyses will be done using the SAS System software, version 9.3 or above (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

Inter-rater agreement will be assessed by Cohen's Kappa. A 95% two-sided confidence interval will be calculated, using the asymptotic variance of the Kappa coefficient and applying the standard normal distribution.⁷²

Continuous endpoints will be summarized by their mean, standard deviation, number of observations, median, minimum, maximum and interquartile range. The variable means are evaluated by a paired t-test, the difference between treatments and its 95% confidence interval will be reported.

Categorical variables are summarized by frequencies and percentages. Baseline Characteristics

Demographics, medical history and other clinically relevant baseline variables will be tabulated. In principal patient oriented percentages refer to the proportion of patients with the characteristic present.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 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.

9.2 Quality Assurance and Monitoring

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

The study Sponsor, or designee, will monitor the study to ensure proper conduct and progress of the study including adequate protection of human subjects and the integrity of the clinical study data. It may include initiation and close-out visits. This will also include routine, periodic visits to study sites to confirm reported results are consistent with source documentation, appropriate subject enrollment, compliance with all applicable laws and regulations, and compliance with the protocol. Remote monitoring may also occur. The frequency of monitoring visits will be based upon enrollment, data integrity, and site compliance. A Monitoring Plan will be written for the study and will be kept separate from the protocol. Each study site will allow monitoring activities to be conducted at their site, including visits by the study Sponsor and/or their designee.

Therefore, access to the patients' files must be allowed as per the informed consent at the Investigator's site.

9.3 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, CTs, 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.

9.4 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.

10 ORGANISATION

10.1 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 14.

10.2 Steering Committee

The Steering Committee is responsible of the overall management of the study. The Steering Committee is comprised of a Chairman, PIs, co-PIs, and ECRI. Their names, roles and responsibilities are described in a separate Steering Committee Charter.

10.3 Clinical Event Committee (CEC)

Not applicable.

10.4 Data Safety Monitoring Board (DSMB)

Not applicable.

10.5 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).

10.6 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.

10.7 Safety Reporting

For the study patient, this study is ended after the MSCT acquisition has been performed. The clinical treatment decision-making and patient treatment is up to investigators' discretion and no follow-up investigation is implemented. Serious Adverse Events occurring between the moment the subject gave Informed Consent until the MSCT acquisition has been performed must be documented in the eCRF if considered related to study procedures within 24 hours. The investigator must inform Ethical Committee and manufacturers conform local practice.

10.8 Statistical Analysis

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

11 DATA HANDLING AND RECORD KEEPING

11.1 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;

11.2 Case Report Form Completion

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

11.3 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.

12 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 III REVOLUTION trial is an investigator-initiated and scientifically driven study nested within the European Cardiovascular Research Institute (ECRI) and set up in collaboration with GE Healthcare and Heartflow. All public presentations and manuscript generation and submissions will be led under the auspices of the Study Chairman 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.

13 INVESTIGATOR RESPONSIBILITIES

13.1 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.

13.2 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 Investigators participating in the Heart Team meetings (i.e. interventional cardiologists, radiologists and cardio-thoracic surgeons). These CVs should clearly show the investigator's 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.

13.3 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.

13.4 Informed Consent

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

13.5 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.

13.6 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.

Site responsibilities for submitting data and reports:

Type of CRF/Report	Completed by Site Within	Process
eCRF notification of study procedure related SAEs	24 hours	Enter eCRF pages within 24 hours of knowledge of event
eCRF (e.g. baseline assessments, SYNTAX Score, Heart Team decisions, final treatment (i.e. diseased vessels, segments)	Ongoing basis	Collected in the eCRF
Angiographic Films, MSCT scans.	Ongoing basis	Transferred to Core Lab using AG Mednet
Annual Reports	Forward as requested by EC/IRB	Copy provided by Sponsor to be send to EC/IRB (if required by national/local regulations)
Final Report	Forward within 3 months of study completion or termination	Copy provided by Sponsor to be send to EC/IRB (if required by national/local regulations)

13.7 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.

14 SPONSOR RESPONSIBILITIES

14.1 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 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 and Grant giver (GE) will select qualified investigators and facilities which have suitable equipment (GE 256-slice Revolution scanner) and 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
- Any statistical analyses and underlying supporting data
- Final report of the clinical investigation

14.2 Supplemental Applications

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

14.3 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.

14.4 Maintaining Records

The Sponsor will maintain copies of correspondence, data, 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.

14.5 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.

14.6 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 patients' 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.

15 REFERENCES

1. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159-174.
2. Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Phys Ther*. 2005;85(3):257-268.
3. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35(37):2541-2619.
4. Head SJ, Kieser TM, Falk V, Huysmans HA, Kappetein AP. Coronary artery bypass grafting: Part 1--the evolution over the first 50 years. *Eur Heart J*. 2013;34(37):2862-2872.
5. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet*. 1978;1(8058):263.
6. Genereux P, Palmerini T, Caixeta A, et al. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv*. 2011;4(6):553-561.
7. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention*. 2009;5(1):50-56.
8. Farooq V, Head SJ, Kappetein AP, Serruys PW. Widening clinical applications of the SYNTAX Score. *Heart*. 2014;100(4):276-287.
9. Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. *Heart*. 2014;100(2):169-177.
10. Wijns W, Bruyne B, Vanhoenacker P. What does the clinical cardiologist need from noninvasive cardiac imaging: Is it time to adjust practices to meet evolving demands? *Journal of Nuclear Cardiology*. 2007;14(3):366-370.
11. Nam CW, Mangiacapra F, Entjes R, et al. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol*. 2011;58(12):1211-1218.
12. Farooq V, Giris C, Magro M, et al. The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy. *EuroIntervention*. 2013;8(11):1277-1285.
13. Toth G, De Bruyne B, Casselman F, et al. Fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. *Circulation*. 2013;128(13):1405-1411.
14. Layland J, Oldroyd KG, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J*. 2015;36(2):100-111.
15. Nijjer SS, Sen S, Petraco R, Davies JE. Advances in Coronary Physiology. *Circ J*. 2015.
16. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371(13):1208-1217.

17. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367(11):991-1001.
18. Toth GG, Toth B, Johnson NP, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. *Circ Cardiovasc Interv*. 2014;7(6):751-759.
19. McDaniel MC, Eshtehardi P, Sawaya FJ, Douglas JS, Samady H. Contemporary clinical applications of coronary intravascular ultrasound. *JACC Cardiovasc Interv*. 2011;4(11):1155-1167.
20. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334(26):1703-1708.
21. Nieman K, Cademartiri F, Lemos PA, Raaijmakers R, Pattynama PM, de Feyter PJ. Reliable noninvasive coronary angiography with fast submillimeter multislice spiral computed tomography. *Circulation*. 2002;106(16):2051-2054.
22. Mollet NR, Cademartiri F, de Feyter PJ. Non-invasive multislice CT coronary imaging. *Heart*. 2005;91(3):401-407.
23. Hoffmann U, Ferencik M, Cury RC, Pena AJ. Coronary CT angiography. *J Nucl Med*. 2006;47(5):797-806.
24. Arbab-Zadeh A, Hoe J. Quantification of coronary arterial stenoses by multidetector CT angiography in comparison with conventional angiography methods, caveats, and implications. *JACC Cardiovasc Imaging*. 2011;4(2):191-202.
25. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359(22):2324-2336.
26. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372(14):1291-1300.
27. investigators S-H. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015.
28. 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):1966-1975.
29. Authors/Task Force m, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35(37):2541-2619.
30. Hillis LD, Smith PK, Anderson JL, et al. 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.
31. Levine GN, Bates ER, Blankenship JC, et al. 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.
32. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31(20):2501-2555.
 33. Head SJ, Kaul S, Mack MJ, et al. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. *Eur Heart J*. 2013;34(32):2510-2518.
 34. Sianos G, Morel MA, A.P. K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005 1:219-227. Europa Edition 2005. All rights reservedEuroPCRonline.com.
 35. Farooq V, Brugaletta S, Serruys PW. The SYNTAX score and SYNTAX-based clinical risk scores. *Semin Thorac Cardiovasc Surg*. 2011;23(2):99-105.
 36. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. *Heart*. 2011;97(23):1902-1913.
 37. Farooq V, van Klaveren D, Steyerberg EW, et al. 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):639-650.
 38. Farooq V, van Klaveren D, Steyerberg EW, Serruys PW. SYNTAX score II - Authors' reply. *Lancet*. 2013;381(9881):1899-1900.
 39. Head SJ, Farooq V, Serruys PW, Kappetein AP. The SYNTAX score and its clinical implications. *Heart*. 2013.
 40. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360(10):961-972.
 41. SYNTAX score calculator: <http://www.syntaxscore.com>. SYNTAX working-group. Launched 19th May 2009.
 42. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation*. 1981;63(2):285-299.
 43. Smith SC, Jr., Feldman TE, Hirshfeld JW, Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47(1):e1-121.
 44. Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation*. 1999;99(17):2345-2357.
 45. Medina A, Suarez de Lezo J, Pan M. [A new classification of coronary bifurcation lesions]. *Rev Esp Cardiol*. 2006;59(2):183.

46. Hamburger JN, Serruys PW, Scabra-Gomes R, et al. Recanalization of total coronary occlusions using a laser guidewire (the European TOTAL Surveillance Study). *Am J Cardiol.* 1997;80(11):1419-1423.
47. Kappetein AP, Feldman TE, Mack MJ, et al. 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):2125-2134.
48. Mohr FW, Morice MC, Kappetein AP, et al. 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):629-638.
49. Levine GN, Bates ER, Blankenship JC, et al. 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. *Circulation.* 2011;124(23):e574-651.
50. Hillis LD, Smith PK, Anderson JL, et al. 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.
51. Tonino PA, Fearon WF, De Bruyne B, et al. 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):2816-2821.
52. Pijls NH, Fearon WF, Tonino PA, et al. 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):177-184.
53. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360(3):213-224.
54. Serruys PW, Farooq V, Vranckx P, et al. 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):606-617.
55. Ranucci M, Castelvechio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation.* 2009;119(24):3053-3061.
56. Ranucci M, Castelvechio S, Conte M, et al. The easier, the better: age, creatinine, ejection fraction score for operative mortality risk stratification in a series of 29,659 patients undergoing elective cardiac surgery. *J Thorac Cardiovasc Surg.* 2011;142(3):581-586.
57. Ranucci M, Castelvechio S. The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs. *EuroIntervention.* 2010;6(5):549-553.

58. Farooq V, Vergouwe Y, Raber L, et al. 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):3098-3104.
59. Chieffo A, Meliga E, Latib A, et al. 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):718-727.
60. Campos CM, van Klaveren D, Iqbal J, et al. Predictive Performance of SYNTAX Score II in Patients With Left Main and Multivessel Coronary Artery Disease. *Circ J*. 2014;78(8):1942-1949.
61. 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.
62. Campos CM, van Klaveren D, Farooq V, et al. Long-term forecasting and comparison of mortality in the Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial: prospective validation of the SYNTAX Score II. *Eur Heart J*. 2015.
63. 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):250-257.
64. Meredith IT, Verheye S, Dubois CL, et al. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. *J Am Coll Cardiol*. 2012;59(15):1362-1370.
65. Zhang Y, Farooq V, Garcia-Garcia HM, et al. 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):855-865.
66. Papadopoulou SL, Girasis C, Dharampal A, et al. CT-SYNTAX score: a feasibility and reproducibility Study. *JACC Cardiovasc Imaging*. 2013;6(3):413-415.
67. Kerner A, Abadi S, Abergel E, et al. Direct comparison between coronary computed tomography and invasive angiography for calculation of SYNTAX score. *EuroIntervention (In Press)*. 2013.
68. Serruys PW, Girasis C, Papadopoulou SL, Onuma Y. Non-invasive fractional flow reserve: scientific basis, methods and perspectives. *EuroIntervention*. 2012;8(4):511-519.
69. Koo BK, Erglis A, Doh JH, et al. 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):1989-1997.
70. Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol*. 2014;63(12):1145-1155.

71. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
72. Fleiss JL, Cohen J, Everitt BS. Large sample standard errors of kappa and weighted kappa. *Psychological Bulletin*. 1969;72(5):323-327.
73. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51(4 Suppl):5-40.
74. Serruys PW, Unger F, van Hout BA, et al. The ARTS study (Arterial Revascularization Therapies Study). *Semin Interv Cardiol*. 1999;4(4):209-219.
75. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *European heart journal*. 2003;24(9):881-882.
76. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *The New England journal of medicine*. 2001;344(15):1117-1124.

16 APPENDIX I: SCHEDULE OF EVENTS

EVENT	SCREENING	ENROLMENT	HEART TEAM Preparation	HEART TEAM Meeting
Diagnostic Angiography ¹	X			
Cardiac history and anginal status	X			
Informed Consent	X			
GE Revolution MSCT		X		
Heart Team Randomization		X		
Anatomical SYNTAX Score by Angio ^{2 3}			X	
Anatomical SYNTAX Score by MSCT ^{2 3}			X	
SYNTAX Score II by Angio ^{2 3}			X	
SYNTAX Score II by MSCT ^{2 3}			X	
Functional Anatomy (FFR _{CT}) ^{2 4}			X	
Consult combined information modality 1				X
Document treatment recommendation 1 Heart Team				X
Consult combined information modality 2				X
Document treatment recommendation 2 Heart Team				X
Consult combined information modality 3				X
Document final Heart Team treatment recommendation				X

¹ 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.

² Collect and forward to central Core Lab.

³ By site and Core Lab

⁴ By HeartFlow

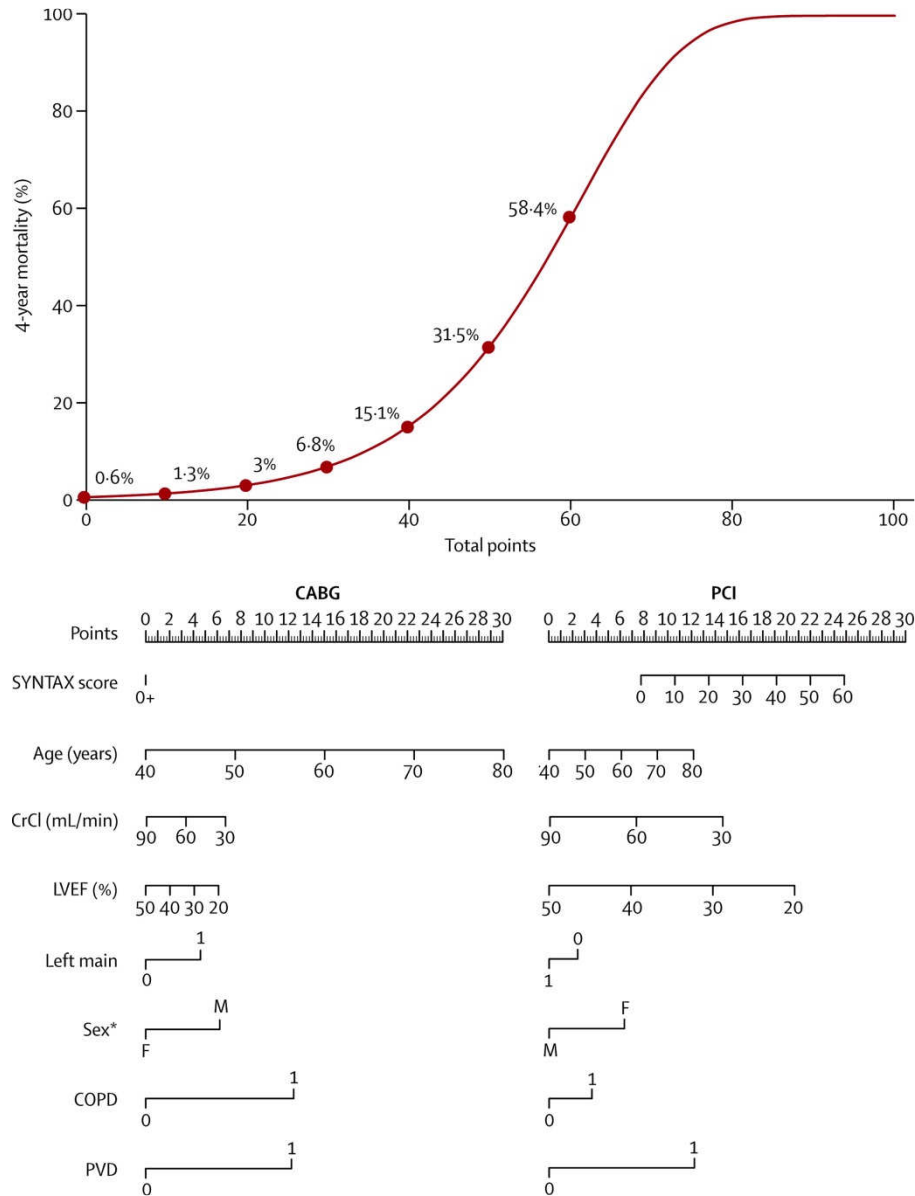
17 APPENDIX II: SYNTAX SCORE II

SYNTAX Score II nomogram for bedside application. An online version will be made available online at the original SYNTAX Score website (www.syntaxscore.com).⁴¹

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,⁷⁵ long-term use of bronchodilators or steroids for lung disease. PVD defined according to ARTS I definition,⁷⁶ 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.³⁷



*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.

18 APPENDIX III: DEFINITIONS

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.

Relationship of Adverse Event to the investigational treatment and/or procedure

- Certain: Event or laboratory test abnormality, with plausible time relationship to treatment and/or procedure. It cannot be explained by disease or other drugs.
- Probable: Event or laboratory test abnormality, with plausible time relationship to treatment and/or procedure. Unlikely to be attributed to disease or other drugs.
- Possible: Event or laboratory test abnormality, with plausible time relationship treatment and/or procedure. Could also be explained by disease or other drugs.

- Unlikely: Event or laboratory test abnormality, with a time to treatment and/or procedure that makes a relationship improbable (but not impossible).
- Unassessable: Event or laboratory test abnormality, more data is needed for proper assessment.

ANGINA PECTORIS

Braunwald Classification of Unstable Angina:

Severity		Clinical Circumstances		
		A	B	C
		Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary UA)	Develops in the absence of extracardiac condition (primary UA)	Develops within 2 weeks after acute myocardial infarction (postinfarction UA)
I	New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	IIA	IIB	IIC
III	Angina at rest within 48 hr (angina at rest, acute)	IIIA	IIIB Troponin negative IIIB Troponin positive	IIIC

Canadian Cardiovascular Society (CCS) Classification of Stable Angina:

CLASS	
0	Asymptomatic
I	Angina with strenuous exercise (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	Angina with moderate exertion (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	Angina with mild exertion (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	Angina at any level of physical exertion (inability to carry on any physical activity without discomfort - angina syndrome may be present at rest).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

[EuroScore definition]

Long term use of bronchodilators or steroids for lung disease.

PERIPHERAL VASCULAR DISEASE (PVD)

[EuroScore definition]

Aorta and other arteries than coronary arteries, with exercise related claudication, or reduced or absent pulsation, or angiographic stenosis of more than 50%.

19 APPENDIX IV: MSCT ACQUISITION GUIDELINES

Introduction

- Utilize **256-slice GE Revolution CT Scanner**.
- Imaging the **entire coronary tree** allows for the most accurate FFR_{CT} computation.

Preparation

- Assess heart rate and rhythm. Heart rate control (below 65 beats per minute) reduces 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 5 times.
 - Contraindications: conduction delays, hypotension, severe asthma, allergy to betablockers, reduced left ventricle ejection fraction.
 - Consider ivabradin for patients with contra-indications to betablockers (in case of ivabradine the dosage suggested is 5 mg twice a day for at least 3-4 days before the scan)
- 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
 - 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).

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 5 ml/sec

Data acquisition:

- 1) Overview/scout of the entire chest.
- 2) Contrast enhancement:
 - ≥300 g/L iodine contrast medium.
 - Injection rate: 5-6 ml/s.
 - Total amount depends on the patient size, the scan mode and the scan duration.
 - Contrast-scan timing:
 - **Test/Timing Bolus:** 15-20 ml of contrast is injected, preferably followed by a bolus chaser. Place the localizer line one centimeter below the carina and just

above the base of the heart, the optimal location to find the ascending aorta for a timed contrast injection. The time of (maximum) enhancement is used as the delay of the data acquisition after start of contrast injection.

- *Bolus tracking/Smart Prep*: arrival of the (entire) bolus is monitored by using a 4-chamber view.
 - A saline bolus of ≈ 50 ml is injected after the contrast medium at the same rate.
- 3) Scan mode :
- ECG-triggered one-beat scan mode should be used. For HR <65, 75% of the R-R cycle is appropriate. For HR >65 or variable heart rates, 40-80% of the R-R cycle is appropriate with ECG mA modulation. Consider use of Auto-Gating functionality on the system.
- 4) Acquisition parameters:
- Thinnest detector width.
 - For patients acquired in standard mode we suggest 100 kVp/500 mA for BMI <25; 100 kVp/550 mA for BMI included between 25 and 30 and 120 kVp/600 mA for BMI >30; for HD mode we suggest 100 kVp for BMI <25, together with 550 mA
 - Scan range: from 1-2 cm below the carina until the caudal border of the heart.
 - High Definition Mode should be used preferably **except** in patients with BMI > 25

Alternate Data Acquisition protocols may be applicable based on local experience and expertise. These alternative protocols will be reviewed and approved by the Steering Committee including potential review of sample clinical cases.

Image reconstruction (appropriately labelled):

- 0.625mm slice thickness
- ASIR-V 50% in all cases should be provided. Additional ASIR-V levels may be provided if ASIR-V 50% is inadequate.
- Field-of-view enclosing the **entire heart** (cover inferior carina to lower heart border) (approx. 18 x 18 cm).
- Standard kernel 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.
- Additional high-definition reconstructions should be provided at the optimal phase(s). If High Definition mode was not performed, then Detail kernel reconstructions should be provided
- If motion artifacts persist in the optimal phase images, the standard and high definition (or detail) reconstructions should be done with “Temporal Enhanced” enabled and SnapShot Freeze processing should be performed on the Advantage Workstation.

DVD/USB recording:

- Scout images
- ECG trace
- Standard kernel reconstructions for at least one (or the same) optimal phase for each diseased coronary segment, preferably three or more datasets including both systolic and

diastolic phases. SnapShot Freeze processed images should be provided if any motion persists in the optimal phases (the accuracy of FFR-CT need to be evaluated for images reconstructed with SSF).

- HD or Detail reconstructions for at least one (or the same) optimal phase for each diseased segment. SnapShot Freeze processed images should be provided if any motion persists in the optimal phases (the accuracy of FFR-CT need to be evaluated for images reconstructed with SSF).