Supplementary Material

Coronary Computed Tomography Angiography for Heart Team Decision-making in Multivessel Coronary Artery Disease.

Carlos Collet MD, Yoshinobu Onuma MD, PhD, Daniele Andreini MD, PhD, Jeroen Sonck MD, Giulio Pompilio MD, PhD, Saima Mushtaq MD, Mark La Meir MD, PhD, Yosuke Miyazaki MD, PhD, Johan de Mey MD, PhD, Oliver Gaemperli MD, PhD, Ahmed Ouda, MD, PhD, Juan Pablo Maureira MD, PhD Damien Mandry MD, PhD, Edoardo Camenzind MD, PhD, Laurent Macron MD, PhD, Torsten Doenst MD, PhD, Ulf Teichgräber MD, PhD, Holger Sigusch MD, PhD, PhD, Taku Asano MD, Yuki Katagiri MD, Marie-angele Morel MsC, Gianluca Pontone MD, PhD, Thomas F. Lüscher MD, PhD , Antonio L. Bartorelli MD , Patrick W. Serruys MD, PhD for the SYNTAX III REVOLUTION investigators

Table of contents

Steering committee

Patrick W. Serruys: Chairman of the Steering Committee. Gerrit-Anne van Es: Sponsor European Cardiovascular Research Institute. Daniele Andreini: Centro Cardiologico Monzino. Antonio Bartorelli: Centro Cardiologico Monzino. Giulio Pompilio: Centro Cardiologico Monzino. Thomas Lüscher: University Hospital Zurich. Jeroen Sonck: University Hospital Brussels. Mark La Meir: University Hospital Brussels. Johan de Mey: University Hospital Brussels.

Academic Research Organization

Cardialysis, Rotterdam, The Netherlands: Gerrit- Anne van Es (Director);

Data Management

Cardialysis, Rotterdam, The Netherlands: Ingrid Leal. Ton de Vries.

Biostatistics and Data Analysis

Cardialysis, Rotterdam, The Netherlands: Ton de Vries, Wietze Lindeboom, Marco Bressers, Carlos Collet, Gerrit-Anne van Es.

Coronary Computed Tomography Angiography and Fractional Flow Reserve derived from CT Core Laboratory Analysis

Cardialysis, Rotterdam, The Netherlands: Yoshinobu Onuma (Director), Yosuke Miyazaki, Carlos Collet.

Coronary Angiography Core Laboratory Analysis

Cardialysis, Rotterdam, The Netherlands: Yoshinobu Onuma (Director), Taku Asano, Yuki Kataguiri.

List of Investigators

Centro Cardiologico Monzino: Daniele Andreini, Antonio Bartorelli, Francesco Alamanni, Gianluca Pontone, Stefano De Martini, Giulio Pompilio. Centre Cardiologique du Nord: Philippe Guyon, Jean-Louis Sablayrolles, Patrick Mesnildrey, Laurent Macron, Franck Digne, Nicolas Bonnet, University Hospital Nancy: Juan Pablo Maureira, Xavier Orry, Pierre-Adrien Metzdorf, Damien Mandry, Edoardo Camezind, Thierry Folliguet. University Hospital of Jena: Ioannis Diamantis, Gloria Färber, Marc Schönweirb, Ulf Teichgräber, Torsten Doenst, Holger Sigusch. University Hospital Zurich: Oliver Gaemperli, Philipp Kaufmann, Thomas Lüscher, Jasmina Alibegovic, Christian Templin, Robert Manka, Ronny Büchel, Francesco Maisano, André Plass, Christine Hager, Valerie Treyer, Simone Wijnand, Ulrike Sänger, Verena Weichselbaumer, Slayman Obeid, Andrea Thesenvitz, Patrick Siegrist, Diana Reser, Ahmed Ouda, Devdas Inderbitzin, Aju Pazhenkottil, Hector Rodriguez, Maurizio Taramasso, Andreas Giannopoulos Nooraldaem Yousif. UZ Brussel: Jeroen Sonck, Johan De Mey, Mark La Meir, Dries Belsack, Jens Czapla, Danny Schoors.

Table S1. Inclusion and exclusion criteria

Inclusion Criteria

1. Patients with at least 1 stenosis (angiographic, visually determined de novo lesions with ≥50% DS) in all 3 major epicardial territories (LAD and/or side branch, CX and/or side branch, RCA and/or side branch) supplying viable myocardium 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;

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.

Table S2. Coronary computed tomography angiography acquisition protocol

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).

Table S3. Primary and secondary end points
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 FFRCT). 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.
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 (FFRCT 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.

Table S4. Primary diagnostic method used for assessment of eligibility.

Modality	Number (%)
Coronary CTA	60 (27)
Conventional angiography	163 (73)

Table S5. Agreement of the SYNTAX score Tertiles between Coronary computed tomography angiography and conventional angiography.

	Anatomical SYNTAX score tertiles derived from Coronary Computed Tomography Angiography			
Anatomical SYNTAX score tertiles derived from Conventional Angiography	**≤ 22**	**22 - 32**	**> 32**	**Total**
≤ 22	9.9% (22/222)	9.0% (20/222)	8.6% (19/222)	27.5% (61/222)
22 – 32	5.4% (12/222)	12.2% (27/222)	14.9% (33/222)	32.5% (72/222)
> 32	2.3% (5/222)	7.2% (16/222)	30.6% (68/222)	40.1% (89/222)
Total	17.6% (39/222)	28.4% (63/222)	54.1% (120/222)	100% (222/222)