Impact of coronary calcification assessed by coronary CT angiography on treatment decision in patients with three-vessel CAD: insights from SYNTAX III trial

Daniele Andreini\textsuperscript{a,b,*}, Kuniaki Takahashi\textsuperscript{c}, Saima Mushtaq\textsuperscript{a}, Edoardo Conte\textsuperscript{a}, Rodrigo Modolo\textsuperscript{c,d}, Jeroen Sonck\textsuperscript{e}, Johan De Mey\textsuperscript{f}, Paolo Ravagnani\textsuperscript{a}, Danny Schoors\textsuperscript{g}, Francesco Maisano\textsuperscript{g}, Philipp Kaufmann\textsuperscript{g}, Wietze Lindeboom\textsuperscript{h}, Marie-angele Morel\textsuperscript{h}, Torsten Dosen\textsuperscript{i}, Ulf Teichgräber\textsuperscript{i}, Gianluca Pontone\textsuperscript{a,}, Giulio Pompilio\textsuperscript{a,b}, Antonio Bartorelli\textsuperscript{a,j}, Yoshinobu Onuma\textsuperscript{k} and Patrick W. Serruys\textsuperscript{l}, on behalf of the Syntax III Revolution Investigators

\textsuperscript{a} Department of Cardiovascular Imaging, Centro Cardiologico Monzino, IRCCS, Milan, Italy
\textsuperscript{b} Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
\textsuperscript{c} Department of Cardiology, Amsterdam University Medical Center, Amsterdam, Netherlands
\textsuperscript{d} Cardiology Division, Department of Internal Medicine, Hospital de Clinicas, University of Campinas, Campinas, São Paulo, Brazil
\textsuperscript{e} Cardiovascular Center Aalst, OLV Hospital, Aalst, Belgium
\textsuperscript{f} Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussel, Belgium
\textsuperscript{g} University of Zurich, Zurich, Switzerland
\textsuperscript{h} Cardialysis BV, Rotterdam, Netherlands
\textsuperscript{i} Jena University Hospital, Friedrich-Schiller-University of Jena, Jena, Germany
\textsuperscript{j} Department of Biomedical and Clinical Sciences “Luigi Sacco”, University of Milan, Milan, Italy
\textsuperscript{k} Thoraxcenter, Erasmus MC, Rotterdam, Netherlands
\textsuperscript{l} Department of Cardiology, Royal Brompton and Harefield Hospitals, Imperial College London, London, UK

\textsuperscript{*} Corresponding author. Centro Cardiologico Monzino, IRCCS, Via Parea 4, 20138 Milan, Italy. Tel: +39-02-58002577; e-mail: daniele.andreini@ccfm.it (D. Andreini).

Received 21 April 2021; received in revised form 13 July 2021; accepted 13 August 2021
Abstract

OBJECTIVES: The aim of this study was to determine Syntax scores based on coronary computed tomography angiography (CCTA) and invasive coronary angiography (ICA) and to assess whether heavy coronary calcification significantly limits the CCTA evaluation and the impact of severe calcification on heart team’s treatment decision and procedural planning in patients with three-vessel coronary artery disease (CAD) with or without left main disease.

METHODS: SYNTAX III was a multicentre, international study that included patients with three-vessel CAD with or without left main disease. The heart teams were randomized to either assess coronary arteries with coronary CCTA or ICA. We stratified the patients based on the presence of at least 1 lesion with heavy calcification defined as arc of calcium >180° within the lesion using CCTA. Agreement on the anatomical SYNTAX score and treatment decision was compared between patients with and without heavy calcifications.

RESULTS: Overall, 222 patients with available CCTA and ICA were included in this trial subanalysis (104 with heavy calcification, 118 without heavy calcification). The mean difference in the anatomical SYNTAX score (CCTA derived—ICA derived) was lower in patients without heavy calcifications [mean (-1.96 SD; +1.96 SD) = 1.5 (-19.3; 22.4) vs 5.9 (-17.5; +29.3), P = 0.004]. The agreement on treatment decision did not differ between patients with (Cohen’s kappa 0.79) or without coronary calcifications (Cohen’s kappa 0.84). The agreement on the treatment planning did not differ between patients with (concordance 80.3%) or without coronary calcifications (concordance 82.8%).

CONCLUSIONS: An overall good correlation between CCTA- and ICA-derived Syntax score was found. The presence of heavy coronary calcification moderately influenced the agreement between CCTA and ICA on the anatomical SYNTAX score. However, agreement on the treatment decision and planning was high and irrespective of the presence of calcified lesions.

Keywords: Coronary calcification • Coronary computed tomography angiography • Heart team

ABBREVIATIONS

| Abbreviation | Description                        |
|--------------|------------------------------------|
| CAD          | Coronary artery disease            |
| CCTA         | Coronary computed tomography angiography |
| CI           | Confidence interval                 |
| CTA          | Computed tomography angiography    |
| DECT         | Dual-energy computed tomography    |
| FFRCT        | Fractional flow reserve derived from CTA |
| HT           | Heart team                         |
| ICA          | Invasive coronary angiography      |
| PCI          | Percutaneous coronary intervention |

INTRODUCTION

Severe calcifications of vessel wall and atherosclerotic plaque hamper visual assessment of coronary arteries with coronary computed tomography angiography (CCTA) due to blooming artefacts. This drawback may explain the discrepancy that has been observed between non-invasive and invasive luminal evaluation [1]. Although scanners with improved spatial resolution and/or dual-energy technology may overcome most of the beam-hardening artefacts [2, 3], assessment of coronary arteries with a high calcific burden is still a weakness of this non-invasive imaging modality. Moreover, severe calcifications, which are easily detectable with CCTA, may influence treatment decision-making and planning particularly in patients with multivessel coronary artery disease (CAD). The SYNTAX III Revolution trial showed that the treatment decision-making based on CCTA in patients with three-vessel CAD is in high agreement (Cohen’s kappa 0.82) with the decision derived from invasive coronary angiography (ICA) [4]. However, the influence of coronary calcifications on treatment decision-making and selection of vessels to be revascularized remains to be investigated. Thus, the present study sought to determine the impact of heavy coronary calcifications on heart team’s treatment decision and procedural planning in patients with three-vessel CAD.

METHODS

Study design

Date and number of the IRB approval are as follows: 05 August 2016 and CCM441 (trial registration number: NCT02813473).

The present study reports a predefined subanalysis of the SYNTAX III REVOLUTION trial. The design of the SYNTAX III REVOLUTION trial has been reported previously [5]. The trial was an international, multicentre study in which 2 heart teams (HTs) composed of an interventional cardiologist, a cardiac surgeon and a cardiac radiologist were randomized to assess and characterize CAD with either CCTA or ICA in patients with three-vessel CAD with or without left main coronary artery involvement, although all patients underwent both CCTA and ICA. The results of the primary end point represented by the agreement between the 2 HTs on the revascularization strategy have been recently published and showed a very high agreement [Cohen’s kappa 0.82; 95% confidence interval (CI) 0.74–0.91], suggesting the potential feasibility of a treatment decision-making and planning based solely on this non-invasive imaging modality [4]. For the present analysis, patients were stratified based on the presence of at least 1 coronary lesion with heavy calcification defined as an arc of calcium >180° within the lesion using CCTA. Agreement on the anatomical SYNTAX score and treatment decision was compared between patients with and without heavy calcifications. The study was approved by the investigational review board and ethics committee at each participating centre.

Enrolment and randomization

Patients with three-vessel CAD diagnosed with either CCTA or ICA and candidates for either percutaneous coronary intervention (PCI) or CABG were assessed for eligibility. Patients were consented to undergo CCTA using a whole-heart coverage, high-definition CT scanner (Revolution CT, GE Healthcare, Chicago, IL, USA) and to participate in a randomized trial of decision-making between PCI and CABG performed by the local heart team and
Image acquisition and analysis

CCTA was performed using the GE Revolution CT scanner with a spatial resolution of 230 μm along the X–Y planes, a Z-axis resolution of 625 μm, a rotational speed of 0.28 s and a Z-plane coverage of 16 cm enabling to image the heart in 1 heartbeat [6]. The imaging acquisition guidelines are detailed in the Supplementary Material, Table S1. The protocol mandated the use of nitrates prior to CCTA acquisition and beta-blockers in cases of heart rate higher than 65 bpm. The 2 local heart teams signed off their decision on the choice of revascularization mode based on the anatomical assessment alone. The anatomic SYNTAX scores were also calculated by an independent core lab based on the anatomical assessment alone. The anatomic SYNTAX score was eligible for screening and the 4-year mortality prediction is similar between them. Any anatomical SYNTAX score was signed off their decision on the choice of revascularization mode assigned to their specific heart team (CCTA or ICA). Each HT calculated the anatomic SYNTAX score based only on their allocated imaging modality and subsequently integrated the clinical information to compute the SYNTAX score II providing a treatment recommendation, i.e. CABG, PCI or equipoise between CABG and PCI. In particular, the HT’s treatment recommendation led to 1 of 3 decisions according to the SYNTAX score II and other anatomical and clinical information including coronary calcification: (i) CABG only, patients should be treated by CABG due to a higher 4-year mortality with PCI; (ii) PCI only, patients should be treated by PCI due to a higher 4-year mortality with CABG; and (iii) equipoise between CABG and PCI, patients could be treated by either approach, considering that the 4-year mortality prediction is similar between them. The power calculation of the sample size of the SYNTAX III REVOLUTION trial has been previously described [5]. However, for the present subanalysis, 2 subsamples of 118 and 104 subjects provided 80% power to deem as significant (alpha = 0.05) a difference of at least 0.25 between the 2 kappa values (for instance, 0.89 vs 0.64). Continuous variables were compared with the Student’s t-test for normally distributed or the Wilcoxon rank-sum test for non-normally distributed data, respectively. Differences in categorical variables were assessed with the χ² test or, in case of values below 5 in any cells of contingency tables, Fisher’s exact test. These criteria were prespecified. Agreement between SYNTAX II recommendation strategy derived from ICA only versus derived from ICA and CCTA was assessed with the concordance coefficient of kappa. Briefly, the Cohen’s kappa coefficient (k) is used to measure inter-rater reliability (and also intrarater reliability) for qualitative (categorical) items. The agreement on the SYNTAX score between the 2 imaging modalities was assessed by the Pearson correlation and Bland–Altman or Passing Bablok method [7, 8]. A two-sided P-value of 0.05 or less was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

From 29 June 2016 to 8 February 2018, 223 patients with three-vessel CAD were enrolled in 6 centres from 5 European countries. Baseline clinical characteristics and CCTA acquisition data of the entire SYNTAX III population are shown in Supplementary Material, Table S2. CCTA assessment was feasible in 222/223 (99%) patients. Baseline clinical characteristics and CCTA acquisition data in patients with (n = 118) or without (n = 104) heavy calcifications are reported in Table 1. Patients with heavy calcification were significantly older (mean age 69.5 ± 7.9 vs 65.9 ± 9.4, P = 0.002) and more often had diabetes (46.2% vs 30.5%, P = 0.016). No other significant differences were found between the 2 groups. As previously reported, in the entire population, the mean anatomical SYNTAX score derived from CCTA was 33.9 ± 13.0, whereas that derived from ICA was 30.3 ± 12.2, with a mean difference between them of 3.58 (-1.96; +1.96 SD = -18.8; 25.9, respectively) and a correlation coefficient of 0.59 (P < 0.001) [4]. In patients with heavy calcification, the mean computed tomography angiography (CTA)-derived anatomical SYNTAX score was 38.6 ± 12.7, whereas the mean SYNTAX score derived from ICA was 32.7 ± 12.9, with a mean difference between them of 5.9 (-1.96; +1.96 SD = -17.5; 29.3, respectively) and a correlation coefficient of 0.56 (P < 0.001) (y = 0.553 x + 20.53) (Fig. 1). In patients without heavy calcification, the mean CTA-derived anatomical SYNTAX score was 29.7 ± 11.9, whereas that derived from ICA was 28.2 ± 11.3, with a mean difference between them of 1.5 (-1.96; +1.96 SD = -19.3; 22.4) and a correlation coefficient of 0.58 (P < 0.001) (y = 0.615 x + 12.395) (Fig. 1). The mean difference in the anatomical SYNTAX score was significantly lower in patients without heavy calcifications compared to those with heavy calcifications (P = 0.004). CCTA-Syntax score and ICA-Syntax score were significantly different only in patients with heavy calcifications, as shown in Table 2. Figures 2 and 3 show 2 case examples of heavily calcified coronary lesions with (Fig. 2) and without (Fig. 3) discrepancy between the anatomical SYNTAX scores derived from CCTA and ICA.
Primary end point: differences in treatment decision

As previously reported, in the whole population the agreement concerning HT’s treatment recommendation between CCTA and ICA was very high (93%), according to the statistical nomenclature of Cohen’s kappa, with a coefficient of 0.82 (95% CI 0.73–0.90) [4]. In patients with heavy calcification, the agreement concerning HT’s treatment recommendation between the 2 imaging modalities was also very high (91.3%), with a kappa coefficient of 0.79 (95% CI 0.66–0.92). In patients without heavy calcification, similar results in terms of agreement in the HT’s treatment recommendation (94%) and related Cohen’s kappa coefficient (0.84, 95% CI 0.73–0.96) were found.

Secondary end point: differences in procedural planning

Overall, the heart teams agreed on the coronary vessels to be revascularized in 81.1% of the cases [4]. The agreement on treatment planning did not differ between patients with heavy vessel calcifications [concordance ranged between 94.2% (left anterior descending artery) and 66.3% (left circumflex artery), overall vessels’ concordance of 82.8% (586/708 vessels)] (Table 4).

SYNTAX score II and heart team’s treatment recommendation based on computed tomography angiography-Syntax score and invasive coronary angiography-Syntax score

Differences between patients with and without heavy vessel calcifications regarding the final revascularization strategy based on the Syntax II scores and the clinical evaluation are reported in Table 5.

DISCUSSION

The main findings of the present study can be summarized as follows: (i) as expected, heavy coronary calcifications affected the capability of CCTA to accurately assess the anatomical SYNTAX score. Indeed, we found a significantly higher difference between the CCTA-derived anatomical SYNTAX score compared with that derived from ICA in patients with heavy calcifications versus those without heavy calcifications (difference of 5.9 vs 1.5 points, respectively, \( P = 0.004 \)); (ii) despite the discrepancy in the anatomical SYNTAX score assessment, the agreement on the HT’s treatment decision did not differ in patients with (Cohen’s kappa

Table 1: Baseline clinical characteristics of patients with and without heavy calcification

| Characteristics                              | Patients with heavy calcifications (n = 104) | Patients without heavy calcifications (n = 118) | P-value |
|----------------------------------------------|--------------------------------------------|-----------------------------------------------|---------|
| Demographics                                |                                            |                                               |         |
| Age (years), mean ± SD                      | 69.5 ± 7.9                                 | 65.9 ± 9.4                                    | 0.002   |
| Male gender, % (n)                          | 86.5 (90/104)                              | 82.2 (97/118)                                 | 0.376   |
| CAD risk factors, % (n)                     |                                            |                                               |         |
| Current smoking                             | 17.3 (17/98)                               | 27.4 (31/113)                                 | 0.081   |
| Diabetes mellitus                           | 46.2 (48/104)                              | 30.5 (36/118)                                 | 0.016   |
| Treatment for diabetes                      |                                            |                                               |         |
| Insulin                                     | 13.5 (14/104)                              | 7.6 (9/118)                                   | 0.109   |
| Medication                                  | 29.8 (31/104)                              | 22 (26/118)                                   |         |
| Diet                                        | 1.9 (2/104)                                | 0 (0/118)                                    |         |
| Hypertension                                | 76.9 (80/104)                              | 72.9 (86/118)                                 | 0.489   |
| Hyperlipidaemia                             | 70.9 (73/104)                              | 69 (80/116)                                   | 0.759   |
| Family history of CAD                       | 34.9 (30/86)                               | 35.6 (36/101)                                 | 0.914   |
| Medical history, % (n)                      |                                            |                                               |         |
| Previous stroke                             | 8.7 (9/104)                                | 7.6 (9/118)                                   | 0.78    |
| Previous myocardial infarction              | 2 (2/102)                                  | 0 (0/118)                                    | 0.128   |
| COPD                                        | 13.5 (14/104)                              | 12.7 (15/118)                                 | 0.869   |
| PVD                                         | 20.2 (21/104)                              | 15.3 (18/118)                                 | 0.335   |
| Clinical presentation                       |                                            |                                               | 0.898   |
| Silent ischaemia, % (n)                     | 43.3 (45/104)                              | 41.5 (49/118)                                 |         |
| Unstable angina, % (n)                      | 9.6 (10/104)                               | 8.5 (10/118)                                  |         |
| Stable angina, % (n)                        | 47.1 (49/104)                              | 50 (59/118)                                   |         |
| BMI (kg/m²), mean ± SD                      | 26.7 ± 3.8                                 | 26.4 ± 3.7                                    | 0.545   |
| Creatinine clearance (ml/min), mean ± SD    | 79.6 ± 26.9                                | 83.4 ± 28.1                                   | 0.298   |
| LVEF (%), mean ± SD                         | 54.3 ± 11.2                                | 54.9 ± 10.9                                   | 0.706   |
| CCTA data, mean ± SD                        |                                            |                                               |         |
| Heart rate during CCTA acquisition          | 62.7 ± 8.2                                 | 61.7 ± 8.9                                    | 0.401   |
| CCTA effective dose (mSv)                   | 4.9 ± 2.6                                  | 5.2 ± 3.4                                     | 0.473   |

BMI: body mass index; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; COPD: chronic obstructive pulmonary disease; LVEF: left ventricle ejection fraction; mSv: milliSievert; PVD: peripheral vascular disease; SD: standard deviation.
Anatomical SYNTAX Score

Figure 1: Anatomical SYNTAX score. Correlations (upper panels) and differences (bottom panels) between anatomical Syntax score derived from CCTA and ICA in patients with (left panels) and without (right panels) heavy coronary calcifications. CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography.

Table 2: CCTA-Syntax score and ICA-Syntax scores in patients with or without heavy calcification

|                      | CCTA-Syntax score | ICA-Syntax score | P-value |
|----------------------|-------------------|------------------|--------|
| Patients with heavy calcification | 38.6 ± 12.7       | 32.7 ± 12.9      | <0.001 |
| Patients without heavy calcification | 29.7 ± 11.9       | 28.2 ± 11.3      | 0.119  |

CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography.

The results of the SYNTAX III REVOLUTION trial suggest the potential feasibility of a treatment decision-making and planning in patients with complex and multivessel CAD based solely on a non-invasive approach represented by CCTA. However, some concerns remain on the capability of CCTA to serve as decision-making tool in patients with a high calcific coronary burden, a frequent condition in complex and diffuse CAD, particularly in elderly and diabetic patients. Indeed, CCTA images are less accurate and interpretable in these settings, often leading to the overestimation of lesion severity with a negative impact on the specificity and accuracy of the method [1, 9]. On the other hand, in comparison with ICA, CCTA offers not only the possibility for assessing calcium distribution but also a roadmap along coronary arteries. Moreover, compared to invasive optical coherence tomography, CCTA provides similar information, despite a systematic overestimation of calcific plaque volume [10]. In our subanalysis of the SYNTAX III REVOLUTION trial, patients with heavily calcified lesions were significantly older (mean age 69.5 ± 7.9 vs 65.9 ± 9.4) and more often had diabetes (46.2% vs 30.5%). Of note, despite these unfavourable clinical conditions and a higher SYNTAX score (38.6 ± 12.7), the correlation between CCTA-derived and ICA-derived SYNTAX scores was also high in patients without calcifications (r = 0.56, P < 0.001) and similar to that obtained in patients without calcifications (r = 0.58, P < 0.001). Accordingly, the main finding of this study was that the presence of heavily calcified lesions did not affect the capability of CCTA to guide treatment decision-making (Cohen’s K of 0.79 for CCTA versus ICA) and treatment planning, with a concordance that was 80.3% for all vessels. These remarkable results are likely due, at
least in part, to the innovative technology with improved spatial resolution (0.23 mm) of the CT scanner used in this trial. Indeed, this scanner demonstrated to be more accurate in patients with high pretest likelihood of CAD and atherosclerotic burden [3]. Another potential reason why the overall quality of CCTA images was high is the low heart rate achieved during scanning (62.7 ± 8.2 and 61.7 ± 8.9 bpm in patients with and without coronary calcifications, respectively) due to a strict adherence to the protocol acquisition guidelines. Indeed, the protocol recommended heart rate modulation by beta-blockers in patients with >60 bpm during breath holding. Although the overall positive findings, some concerns remain on the relatively low concordance between heart team’s treatment recommendation based on the 2 imaging modalities for left circumflex artery (concordance in about the two-third of patients in both groups) and diagonal branches (concordance in 66% of patients in the group with heavy calcification). These findings may be related to the weakness of CCTA in the assessment of small vessels, such as the mid-distal portion of left circumflex artery and the diagonals, particularly in portions with the presence of large calcific plaques, where the beam-hardening artefacts might hinder the right residual lumen assessment. However, it is important to note that the concordance for the main and large vessels as left anterior descending artery and right coronary artery was also very high (94.2% and 87.5%, respectively) in patients with heavy calcific lesions. In summary, our study demonstrates that even in patients with heavy coronary calcifications, high atherosclerotic burden and diffuse CAD, in whom the appropriateness of CCTA is considered quite low, this non-invasive imaging tool showed to be suitable for treatment decision-making. This novel use of CCTA may be additional to the proven ability of the method to predict cardiac events in patients with non-

Figure 2: Calcified coronary lesion with Syntax score discrepancy. A case of a heavily calcified lesion leading to discrepancy between CCTA-derived (A) and ICA-derived (B) SYNTAX scores. CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography; LAD: left anterior descending; LCX: left circumflex.

Figure 3: Calcified coronary lesion without Syntax score discrepancy. A case of a heavily calcified lesion not affecting the calculation of CCTA-derived (A) and ICA-derived (B) SYNTAX scores. CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography; LAD: left anterior descending; LCX: left circumflex.
obstructive and obstructive CAD and to provide a long-term warranty in clinically high-risk patients, including diabetics, in whom coronary arteries have been shown to be free from atherosclerotic disease [11, 12].

To further support the use of CCTA as a tool to provide interventionalists and cardiac surgeons with a non-invasive roadmap for myocardial revascularization, further innovative technologies, including new softwares addressing residual motion artefacts and beam-hardening artefacts [13], should be assessed and clinically validated. However, innovative image acquisition technologies, particularly when dual-energy instead of single-energy scanners are used, seem to be a more promising approach than new image reconstruction modalities. Dual-energy computed tomography (DECT) using calcium removal by material decomposition imaging has been proposed for improving the diagnostic performance of CCTA, particularly for the reduction of beam-hardening artefacts in patients with severe calcification [2]. This technique may be promising when used for the same purpose of the present study, i.e. treatment decision and procedural planning in patients with multivessel CAD. Indeed, in a recent study, Rodriguez-Granillo et al. [14] showed that, compared to ICA, monochromatic imaging from DECT was able to identify a

| Table 3: Agreement between 2 heart teams on the treatment planning, defined as the coronary vessels to be revascularized |
|-------------------------------------------------------------|
| Patients without heavy calcification                        |
| LAD (concordance 94.9%)                                     |
| Not intended to be treated                                  | 0.8% (1/118) | 4.2% (5/118) |
| Intended to be treated                                      | 0.8% (1/118) | 94.1% (111/118) |
| LCx (concordance 64.4%)                                     |
| Not intended to be treated                                  | 41.5% (49/118) | 12.7% (15/118) |
| Intended to be treated                                      | 22.9% (27/118) | 22.9% (27/118) |
| Diagonals (concordance 90.7%)                               |
| Not intended to be treated                                  | 66.9% (79/118) | 8.5% (10/118) |
| Intended to be treated                                      | 14.4% (17/118) | 10.2% (12/118) |
| RCA (concordance 90.7%)                                     |
| Not intended to be treated                                  | 14.4% (17/118) | 6.8% (8/118) |
| Intended to be treated                                      | 2.5% (3/118) | 76.3% (90/118) |

| LM (concordance 77.1%)                                      |
| Not intended to be treated                                  | 17.8% (21/118) | 16.1% (19/118) |
| Intended to be treated                                      | 6.8% (8/118) | 59.3% (70/118) |
| Ramus (concordance 92.4%)                                   |
| Not intended to be treated                                  | 83.9% (99/118) | 5.1% (6/118) |
| Intended to be treated                                      | 2.5% (3/118) | 8.5% (10/118) |

Angio first team: first decision based on ICA (columns) versus CCTA first team: first decision based on CCTA only (rows). All vessels concordance 82.8% (586/708 vessels).

CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography; LAD: left anterior descending; LCx: left circumflex; LM: left main; Ramus: intermediate ramus; RCA: right coronary artery.

| Table 4: Agreement between 2 heart teams on the treatment planning, defined as the coronary vessels to be revascularized |
|-------------------------------------------------------------|
| Patients with heavy calcification                           |
| LAD (concordance 94.2%)                                     |
| Not intended to be treated                                  | 1.0% (1/104) | 4.8% (5/104) |
| Intended to be treated                                      | 1.0% (1/104) | 93.3% (97/104) |
| LCx (concordance 66.3%)                                     |
| Not intended to be treated                                  | 53.8% (56/104) | 11.5% (12/104) |
| Intended to be treated                                      | 22.1% (23/104) | 12.5% (13/104) |
| Diagonals (concordance 66.3%)                               |
| Not intended to be treated                                  | 50.0% (52/104) | 21.2% (22/104) |
| Intended to be treated                                      | 12.5% (13/104) | 16.3% (17/104) |
| RCA (concordance 87.5%)                                     |
| Not intended to be treated                                  | 4.8% (5/104) | 11.5% (12/104) |
| Intended to be treated                                      | 1.0% (1/104) | 82.7% (86/104) |
| LM (concordance 79.8%)                                      |
| Not intended to be treated                                  | 50.0% (52/104) | 21.2% (22/104) |
| Intended to be treated                                      | 1.9% (2/104) | 16.3% (17/104) |
| Ramus (concordance 87.5%)                                   |
| Not intended to be treated                                  | 3.8% (4/104) | 77.9% (81/104) |
| Intended to be treated                                      | 78.8% (82/104) | 4.8% (5/104) |
| Intended to be treated                                      | 7.7% (8/104) | 8.7% (9/104) |

Angio first team: first decision based on ICA (columns) versus CCTA first team: first decision based on CCTA only (rows). All vessels concordance 80.3% (501/624 vessels).

CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography; LAD: left anterior descending; LCx: left circumflex; LM: left main; Ramus: intermediate ramus; RCA: right coronary artery.
though predefined in the protocol, the present study is a post hoc analysis of the SYNTAX III study. Second, the Agatston score was not calculated in the present study, which limits the comparability with previous CCTA studies regarding coronary calcium burden. Indeed a non-contrast scan of the chest was not acquired, to limit the radiation exposure. Moreover, in the present study, 53.2% of patients with three-vessel CAD did not present heavy calcifications. This rate may appear low in a setting of complex CAD. However, in 533 patients with three-vessel CAD undergoing CABG in the ACUITY trial, none-to-mild calcification based on angiography was observed in 289 patients (54.2%) [19]. Therefore, heavy calcifications could be observed in ~50% for patients with three-vessel CAD, although the rates should be further evaluated. Third, the use of a cut-off value of 180\(\mu\)calcification to define the heavy calcific lesions, although proposed in a prospective multicentre trial on CCTA [1], remains subjective in separating patients in a calcified versus non-calcified group. Finally, because the evaluation of clinical outcome was not included in SYNTAX III trial, the clinical relevance of our findings needs to be confirmed by further prospective and randomized studies.

### CONCLUSIONS

In patients with three-vessel CAD with or without left main disease, despite heavy coronary calcifications affected in part the correlation between CCTA and ICA with regard to the anatomical SYNTAX score, the agreement on treatment decision was high and modestly influenced by the presence of heavily calcified lesions.

### SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online.

### Funding

The European Cardiovascular Research Institute sponsored this study with unrestricted research grants from General Electric Health Care and Heart Flow Inc.

### Table 5: SYNTAX score II and heart team’s treatment recommendation based on CTA-Syntax score and ICA-Syntax score

| CTA-Syntax score, mean ± SD | Patients with heavy calcification | Patients without heavy calcification | P-value |
|-----------------------------|----------------------------------|-------------------------------------|---------|
| Syntax score II (PCI), mean ± SD | 39.4 ± 11.0 | 34.6 ± 10.5 | 0.001 |
| Syntax score II (CABG), mean ± SD | 34.4 ± 11.4 | 30.4 ± 11.6 | 0.010 |
| Heart team’s treatment recommendation, % (n) | | | |
| CABG | 65.4 (68/104) | 42.4 (50/118) | <0.001 |
| Equipoise: final decision CABG | 24.0 (25/104) | 22.0 (26/118) | |
| Equipoise: final decision PCI | 6.7 (7/104) | 17.0 (20/118) | |
| PCI | 3.9 (4/104) | 18.6 (22/118) | |
| ICA-Syntax score, mean ± SD | 32.7 ± 12.9 | 28.2 ± 11.3 | 0.005 |
| Syntax score II (PCI), mean ± SD | 37.8 ± 10.9 | 34.3 ± 10.5 | 0.015 |
| Syntax score II (CABG), mean ± SD | 34.4 ± 11.5 | 30.1 ± 11.5 | 0.006 |
| Heart team’s treatment recommendation, % (n) | | | 0.004 |
| CABG | 56.7 (59/104) | 38.1 (45/118) | |
| Equipoise: final decision CABG | 21.2 (22/104) | 18.6 (22/118) | |
| Equipoise: final decision PCI | 5.8 (6/104) | 18.6 (22/118) | |
| PCI | 16.4 (17/104) | 24.6 (29/118) | |

CABG: coronary artery bypass graft; CTA: computed tomography angiography; ICA: invasive coronary angiography; PCI: percutaneous coronary intervention.
Conflict of interest: Patrick W. Serruys reports consultancy fees from Abbott, Biosensors, Medtronic, Micell, Qualimed, Sinomedical Sciences, St. Jude Medical, Stentys, Svelte Medical Systems, Philips/Volcano, Xeltis, Stenttt and HeartFlow. All other authors declared no conflict of interest.

Author contributions

Daniele Andreini: Conceptualization; Data curation; Investigation; Supervision; Visualization; Writing—original draft; Writing—review & editing. Kuniaki Takahashi: Data curation; Formal analysis. Saima Mushtaq: Data curation; Methodology; Writing—review & editing. Eduardo Conte: Formal analysis; Investigation. Rodrigo Modolo: Data curation; Formal analysis. Jeroen Sonck: Data curation; Formal analysis; Validation; Writing—review & editing. Johan De Mey: Investigation; Methodology; Writing—review & editing. Paolo Ravagnani: Data curation; Investigation; Writing—review & editing. Danny Schoors: Data curation; Investigation. Francesco Maisano: Data curation; Formal analysis; Investigation. Philipp Kaufmann: Conceptualization; Data curation; Investigation. Wietze Lindeboom: Data curation; Formal analysis; Investigation. Marie-ange Morel: Conceptualization; Data curation; Methodology; Project administration; Resources. Torsten Doenst: Data curation; Formal analysis. Ulf Teichgraber: Data curation; Formal analysis; Validation. Gianluca Pontone: Formal analysis; Investigation; Methodology; Writing—review & editing. Giulio Pompilio: Formal analysis; Methodology. Antonio Bartorelli: Data curation; Writing—original draft; Writing—review & editing. Yoshihiko Onuma: Data curation; Formal analysis; Investigation; Methodology; Writing—review & editing. Patrick W. Serruys: Conceptualization; Data curation; Formal analysis; Funding acquisition; Supervision; Writing—review & editing.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Daniyar Gilmanov, Ardawan J. Rastan and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Vavere A, Arbab-Zadeh A, Rochitte CE, Dewey M, Ninuma H, Gottlieb I et al. Coronary artery stenosis: accuracy of 64-detector row CT angiography in segments with mild, moderate, or severe calcification—a subanalysis of the CORE-64 trial. Radiology 2011;261:100–8.

[2] Andreini D, Pontone G, Mushtaq S, Bertella E, Conte E, Segurini C et al. Diagnostic accuracy of rapid kilovolt peak-switching dual-energy CT coronary angiography in patients with a high calcium score. JACC Cardiovasc Imaging 2015;8:746–8.

[3] Pontone G, Bertella E, Mushtaq S, Loguerico M, Cortinovis S, Baggioni A et al. Coronary artery disease: diagnostic accuracy of CT coronary angiography—a comparison of high and standard spatial resolution scanning. Radiology 2014;271:688–94.

[4] Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. Eur Heart J 2018;39:3689–98.

[5] Cavalcante R, Onuma Y, Sotomi Y, Collet C, Thomsen B, Rogers C et al. Non-invasive Heart Team assessment of multivessel coronary disease with coronary computed tomography angiography based on SYNTAX score II treatment recommendations: design and rationale of the randomized SYNTAX III Revolution trial. EuroIntervention 2017;12:2001–8.

[6] Andreini D, Pontone G, Mushtaq S, Conte E, Perchinunno M, Guglielmo M et al. Atrial fibrillation: diagnostic accuracy of coronary CT angiography performed with a whole-heart 230-μm spatial resolution CT scanner. Radiology 2017;284:676–84.

[7] Bland JM, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. Lancet 1995;346:1085–7.

[8] Bablok W, Passing H, Bender R, Schneider B. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, part III. J Clinic Chem Clin Biochem 1998;36:783–90.

[9] Andreini D, Pontone G, Bartorelli AL, Agostoni P, Mushtaq S, Antonioli L et al. Comparison of the diagnostic performance of 64-slice computed tomography coronary angiography in diabetic and non-diabetic patients with suspected coronary artery disease. Cardiovasc Diabetol 2010;9:80.

[10] Monizzi G, Sonck J, Nagumo S, Buytaert D, Van Hoe L, Grancini L et al. Quantification of calcium burden by coronary CT angiography compared to optical coherence tomography. Int J Cardiovasc Imaging 2020;36:2393–402.

[11] Blanke P, Naoum C, Ahmadi A, Cheruvi C, Soon J, Arepalli C et al. Long-term prognostic utility of coronary CT angiography in stable patients with diabetes mellitus. JACC Cardiovasc Imaging 2016;9:1280–8.

[12] Andreini D, Pontone G, Mushtaq S, Bertella E, Conte E, Baggioni A et al. Prognostic value of multidetector computed tomography coronary angiography in diabetes: excellent long-term prognosis in patients with normal coronary arteries. Diabetes Care 2013;36:1834–41.

[13] Li P, Xu L, Yang L, Wang R, Hsieh J, Sun Z et al. Blooming artifact reduction in coronary artery calcification by a new de-blooming algorithm: initial study. Sci Rep 2018;8:6945.

[14] Rodriguez-Granillo GA, Carrascosa P, Deviggianno A, Capunay C, de Zan MC, Goldsmith A. Extensión y distribución espacial de la carga aterosclerótica mediante imágenes monocrómicas virtuales derivadas de tomografía computarizada de doble energía. Rev Esp Cardiol 2016;69:915–22.

[15] Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.

[16] Collet C, Miyazaki Y, Ryan N, Asano T, Tenekcioglu E, Sonck J et al. Fractional flow reserve derived from computed tomographic angiography in patients with multivessel CAD. J Am Coll Cardiol 2018;71:2756–69.

[17] Collet Bortone CA. Expanding the Indications of Coronary Computed Tomography Angiography. Radiology 2017;284:676–84.

[18] Collet C, Sonck J, Leipsic J, Monizzi G, Buytaert D, Kitalaar P, Andreini D, De Bruyne B. Implementing Coronary Computed Tomography Angiography in the Catheterization Laboratory. JACC Cardiovasc Imaging 2020;13:1936–878X(20)30911-6.

[19] Ertelt K, Genereux P, Mintz G, Reiss G, Kirtane A, Madhavan M et al. Impact of the severity of coronary artery calcification on clinical events in patients undergoing coronary artery bypass grafting (from the Acute Catheterization and Urgent Intervention Triage Strategy Trial). Am J Cardiol 2013;112:1730–7.