The usefulness of cardiac CT integrated with FFRCT for planning myocardial revascularization in complex coronary artery disease: a lesson from SYNTAX studies

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Abstract: After two decades of clinical use, during which coronary CT angiography (CCTA) was considered an appropriate method for the non-invasive assessment of patients with suspected stable coronary artery disease (CAD) and low-to-intermediate pretest likelihood of CAD, a growing body of literature is showing that CCTA may have also a clinical role in patients with high pretest likelihood of CAD, known CAD and complex and diffuse CAD. Particularly, the SYNTAX studies demonstrated the usefulness of CCTA in the field of non-invasive assessment of these patients and planning of interventional and surgical coronary procedures, thanks to its ability to combine, in a single method, precise stenosis quantification, accurate plaque characterization, functional assessment and selection of the revascularization modality for any individual patient and of the vessels that need to be revascularized. Of note, the SYNTAX III Revolution trial showed, in patients with three-vessel CAD, that treatment decision-making between PCI and CABG based on CCTA only has an almost perfect agreement with the treatment decision derived from invasive coronary angiography (ICA). Moreover, the SYNTAX Score II demonstrated a high degree of correlation between the two diagnostic strategies, suggesting the potential feasibility of a treatment decision-making based solely on non-invasive imaging and clinical information. New research prospects have opened up for the future to demonstrate the true feasibility and safety of this innovative approach in the clinical arena.

Keywords: Cardiac CT; revascularization; syntax score

Introduction

Nearly fifteen years ago, some studies performed with old scanner generations such as 4- or 16-slice CT have shown that coronary CT angiography (CCTA) was a promising non-invasive tool for the detection of significant coronary stenoses. Particularly, the method has shown high sensitivity and excellent negative predictive value for ruling out obstructive coronary artery disease (CAD) (1). With the introduction in the clinical field of 64-slice CT between 2004 and 2006, CCTA started to be considered as

an appropriate tool for the evaluation of coronary arteries in some specific clinical subsets. As reported by the European Society of Cardiology (2), the main clinical application of CCTA includes assessment of patients with stable chest pain and intermediate pretest likelihood of CAD (3).

During the last decade, an extensive literature confirmed the very high sensitivity, specificity and diagnostic accuracy of CCTA for the detection of coronary stenoses when compared to invasive coronary angiography (ICA) (4). Seven prospective multicenter studies showed the diagnostic accuracy of CCTA in patients with suspected but unknown CAD (5-10). Apart from the absolute value in diagnostic accuracy (in these trials sensitivity and specificity ranged between 85% and 99% and 64% and 92%, respectively), the diagnostic performance of CCTA is influenced by the pre-test likelihood of disease. Indeed, this imaging modality is associated with higher diagnostic accuracy mainly in patients with low-to-intermediate CAD risk (9), while a moderate specificity and positive predictive value has been found in high-risk patients (11). In them, coronary artery calcification (CAC) has been found to be the major underlying reason for disagreement between CCTA and quantitative ICA for the assessment of coronary lumen obstruction, with CCTA limited by a higher rate of overestimation but also by some clinically more dangerous cases of underestimation (12). However, technology advancements have recently shown to improve CCTA diagnostic accuracy, mainly in positive predictive value terms, in patients with high CAC and/or high pre-test likelihood of CAD. Indeed, scanners equipped with improved spatial resolution along the X-Y planes partially improved the positive predictive value in patients with high prevalence of obstructive CAD (13), while a study performed with dual-energy CT and calcium removal by material decomposition imaging demonstrated a significant increase in specificity and positive predictive value in patients with high CAC (14). When compared with other non-invasive tests (exercise ECG, stress echocardiography, SPECT or PET myocardial perfusion imaging and cardiac magnetic resonance), commonly used as gatekeepers to ICA in stable symptomatic patients, CCTA has demonstrated higher sensitivity and specificity versus exercise ECG (15), nuclear imaging (8) and all other stress imaging modalities (8,10) in patients with intermediate pre-test probability and low prevalence of obstructive CAD (10). These results induced most of the people who drafted consensus documents, position papers and clinical guidelines to consider CCTA as a useful non-invasive tool in different clinical setting of patients with low-to-intermediate pre-

test likelihood of CAD and low-to-moderate prevalence of obstructive CAD. However, the information provided by CCTA was still regarded insufficient to have a clinical role for the assessment of patients with diffuse and complex CAD and for planning interventional and surgical procedures of myocardial revascularization (16-18).

In order to overcome these intrinsic limitation, the group of Patrick Serruys evaluated in 2013 the feasibility and reproducibility of adapting to CCTA the SYNTAX score, a well-recognized ICA-based tool for stratifying CAD severity and complexity and for helping in the treatment decision-making in multivessel disease patients (19-24). Both European and US revascularization guidelines have adopted the anatomical SYNTAX score as an important tool for establishing the best revascularization strategy in patients with complex CAD (with or without unprotected left main coronary artery involvement) (25,26). However, the absence of clinical variables in SYNTAX score calculation is a significant shortcoming of the method (27). Indeed, the guidelines state that clinical variables should also be taken into account during discussion of the multidisciplinary team consisting of a clinical cardiologist, a cardiac surgeon, and an interventional cardiologist (the so-called "heart team approach") when deciding for the best treatment modality. For this reason, a new score (SYNTAX score II) integrating six clinical variables (age, gender, creatinine clearance, peripheral vascular disease, COPD and left ventricular ejection fraction) has been developed. The addition of the patient clinical characteristics and comorbidities to the anatomical SYNTAX score giving rise to the SYNTAX Score II, provided a treatment recommendation based on the predicted 4-year mortality in patients undergoing coronary artery bypass grafting (CABG) surgery or percutaneous coronary intervention (PCI). Based on the SYNTAX Score II, in 2013 Serruys *et al.* created a dedicated nomogram that is able to provide a reliable and individualized prediction of 4-year mortality in patients undergoing CABG or PCI (27).

Technology advancements in the field of CCTA allowed expanding its use to patients with known CAD (28-32), thanks to a more accurate assessment of lumen narrowing and plaque burden (13,33). However, despite the calculation of the CCTA-derived SYNTAX score has been shown to be accurate compared to the score resulting from ICA (19), the diagnostic performance of the latest CT scanner generation and the agreement on treatment decision in patients with multivessel CAD remain to be investigated. Therefore, the SYNTAX III Revolution trial tried to determine the

agreement between separate heart teams on treatment recommendation based either on CCTA or ICA in patients with three-vessel CAD with or without left main disease (34).

Clinical evidence in favor of CCTA use for planning myocardial revascularization

The SYNTAX III Revolution trial was an international, multicenter study randomizing separate heart teams to make a treatment decision between CABG and PCI, using either CCTA or ICA, while blinded to the other imaging modality. Patients with three-vessel CAD with or without left main involvement but without prior revascularization who were diagnosed with either CCTA or ICA and were candidates for either CABG or PCI were assessed for eligibility (34). In addition to the initial imaging tool used for eligibility assessment, patients underwent evaluation with the alternative imaging modality. Separate heart teams constituted by an interventional cardiologist, a cardiac surgeon and a radiologist specialized in cardiac imaging were randomized to either assess the coronary anatomy with CCTA or ICA in addition to the patient clinical information. Each heart team calculated the anatomical SYNTAX score based solely on their allocated imaging modality and subsequently integrated the clinical information to compute the SYNTAX Score II risk prediction model providing a treatment recommendation, i.e., CABG, PCI, or equipoise between CABG and PCI. Patients underwent CCTA with one of the latest CT scanner generation, which has a nominal spatial resolution of 230 microns along the X-Y planes, a rotational speed of 0.28 s, and a Z-plane coverage of 16 cm enabling to image the heart in one heartbeat. Severity and extension of CAD were assessed using the anatomical SYNTAX score. Coronary segments showing narrowing with visual diameter stenosis >50% using CCTA or ICA and weighted according to their location in the coronary tree were included in the calculation. For the primary endpoint, the two local heart teams made their decision on the choice of revascularization mode based on their clinical and anatomical assessment. For the secondary endpoint, fractional flow reserve derived from CCTA (FFR_{CT}) was used to calculate the non-invasive functional SYNTAX score, which was computed subtracting non-flow limiting stenoses ($FFR_{CT} >0.80$) from the CCTA-derived anatomical SYNTAX score (35). Finally, the non-invasive functional SYNTAX score was used to calculate the SYNTAX Score III, which conceptually is a combination of coronary anatomy

complexity with its physiological repercussion and patient clinical characteristics and comorbidities. The diagnostic accuracy of FFR_{CT}, which is able to identify lesion-specific ischemia, has been validated in four prospective multicenter trials (36-38). In patients with multivessel disease, FFR_{CT} has shown good diagnostic performance with invasive pressure-wire assessment as reference in a sub-analysis of the SYNTAX II trail (35). Moreover, the extent, severity and functional component of CAD can be objectively quantified using the functional SYNTAX score, which has a higher discrimination for clinical events compared to the anatomic SYNTAX score, while reducing inter-observer variability (35). The main findings of the study (39) may be summarized as follows: (I) regarding the primary endpoint, the SYNTAX Score II provided a treatment recommendation of CABG in 28% of patients with CCTA and in 26% with ICA. The agreement concerning the recommendation on the type of revascularization between imaging modalities was high, as confirmed by the statistical nomenclature of Cohens' kappa showing a coefficient of 0.82 (95% CI: 0.73–0.90). The mean difference between CCTA-derived and ICA-derived SYNTAX Score II was –0.01 (limits of agreement –5.1 to 4.9) with a correlation coefficient of 0.98 (P<0.001) without systematic or proportional differences. Moreover, CABG was selected as the revascularization strategy in 164 patients using CCTA and in 155 patients with ICA and the heart teams agreed on the coronary segments to be revascularized in 81.1% of the cases; (II) as regards the secondary endpoint, the study demonstrated that (40): (i) by including the non-invasive functional evaluation with FFR_{CT}, the heart teams changed treatment recommendation in 7% of the cases and modified the selection of vessels to be revascularized in 12% as compared to a CCTA assessment alone. Moreover, inclusion of FFR_{CT} information on top of ICA changed treatment recommendation in 6.6% of the cases and modified revascularization planning in 18.3%; (ii) the non-invasive functional SYNTAX score reclassified 15.5% of the patients to a lower SYNTAX score tertile based on CCTA and 14% of the patients to a lower SYNTAX score tertile based on ICA; (iii) in patients assessed by CCTA, FFR_{CT} reduced from 92.3 to 78.8 the percentage of patients with hemodynamically significant three-vessel CAD; finally, use of the non-invasive functional SYNTAX score for the SYNTAX Score II calculation (SYNTAX Score III) corrected the overestimation of the predicted mortality for PCI at 4 years (40). Of note, the acceptance rate for FFR_{CT} analysis in the study was very high (88%),

particularly if compared with that reported in other prospective multicenter trials. For example, it was 33% in the PROMISE trial (41) and 69% in the SYNTAX II (35). The high rate of CCTA suitability for FFR$_{CT}$ appears not surprising if we consider the scanner used in the SYNTAX III trial that combines different technical features, including the intracycle motion-correction algorithm, able to reducing the impact of motion artefacts on image quality (42). Particularly, this novel scanner combines a 0.23 mm spatial resolution, that may be effective in the reduction of beam-hardening artefacts related to heavily calcific plaques, with a wide detector allowing 16-cm of Z-axis coverage and 0.28 seconds of gantry rotation time, allowing the acquisition in an axial scan mode of the whole cardiac volume in a single heart beat independently from the HR values, potentially avoiding motion artifacts due to high or irregular heart rate. Accordingly, recent phantom and human studies showed this scanner to be able to assess coronary arteries with excellent image quality and diagnostic accuracy up to HR of 100 bpm during scanning (43,44), including patients with rapid atrial fibrillation and HR-related small diastolic acquisition window (42,45). However, because the presence of atrial fibrillation was an exclusion criterion of the SYNTAX III study, this unfavorable heart rhythm remains a potential limitation for the use of CCTA in patients with complex CAD. In summary, by randomizing two heart teams, the SYNTAX III study showed that treatment decision-making based on CCTA is in almost perfect agreement with the treatment decision derived from ICA in patients with three-vessel CAD. Moreover, the SYNTAX Score II demonstrated a high degree of correlation between the two diagnostic tools, suggesting the potential feasibility of treatment decision-making based solely on this type of non-invasive imaging modality and clinical information. For patients with multivessel disease, a multidisciplinary heart team approach is currently advocated by the guidelines for treatment decision-making with a Class I recommendation, level of evidence 'C', in the absence of proof from randomized trial (46). The SYNTAX III REVOLUTION is the first trial to randomize the heart team and its almost perfect agreement upon treatment selection supports the usefulness of CCTA in patients with complex CAD. It should be also recognized that in the study the heart teams routinely included a radiologist in addition to an interventional cardiologist and a cardiac surgeon, which differs from the definition of a heart team given by the guidelines. Undoubtedly, the interaction with the radiologist enhanced image interpretation and the decision-making process.

Although these findings are encouraging, some concerns remain on CCTA capability to be used for decision-making in patients with a high calcific burden of the coronary arteries, 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 overestimation of lesion severity with a negative impact on specificity and accuracy of the method (1,47). This issue was addressed by a sub-analysis of the SYNTAX III trial showing, as expected, that heavy coronary calcifications moderately affect CCTA capability to accurately assess the anatomical SYNTAX score, with a significantly higher difference between the CCTA-derived and ICA-derived anatomical SYNTAX score (difference of 5.9 points in heavy calcification patients vs. 1.5 points in patients without heavy calcifications, respectively, P=0.004). However, despite the discrepancy in the anatomical SYNTAX score assessment, agreement on the heart team treatment decision did not differ in patients with (Cohen's Kappa 0.79) or without heavy calcifications (Cohen's Kappa 0.84). Similarly, agreement on treatment planning, defined as the coronary vessels to be revascularized, was high and did not differ between patients with (overall vessels concordance 80.3%) or without heavy calcifications (overall vessels concordance 82.8%) (48). Despite these findings it is important to note that use of CCTA in patients with complex CAD remains a promising new scenario for this non-invasive modality but lacks of widespread acceptance. Indeed, although the recent ESC Guidelines on chronic coronary syndrome promoted CCTA in Class I of recommendation in patients with suspected CAD, the method is still considered as the most appropriate in patients with low-to intermediate pretest likelihood of CAD, whereas imaging stress tests (echo, CMR, SPECT, PET) are preferable in patients at higher risk (49).

Clinical cases

We report two case examples (*Figures 1-5*) in which CCTA together with FFR$_{CT}$ was used successfully for planning PCI. The case shown in *Figures 1-3* illustrates the high diagnostic accuracy of FFR$_{CT}$ in a patient with multivessel CAD, confirming the findings of Collet *et al.* in a sub-analysis of the SYNTAX II trial (35). The case presented in *Figures 4,5* shows how the new dedicated CCTA software developed for plaque characterization and quantification is able to predict IVUS findings, as demonstrated by a recent
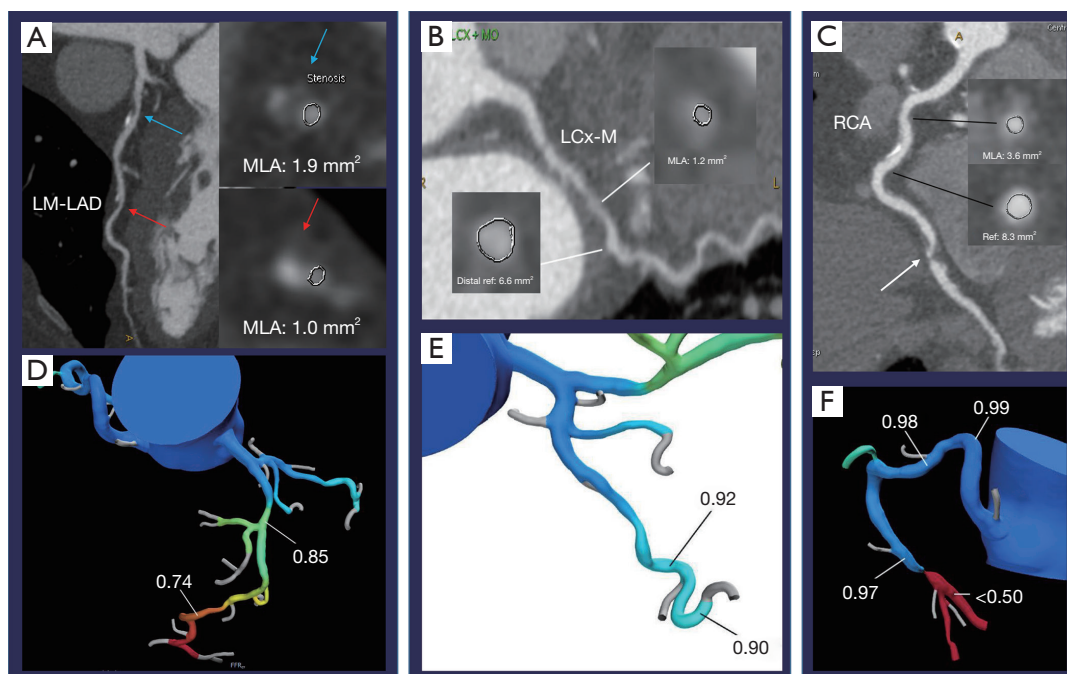
Figure 1 CCTA curved multiplanar reconstructions show the presence of two >50% stenoses of the proximal (arrow) and mid (arrow) LAD (A), a long stenosis of the proximal LCx (B) and two stenoses in the mid (>50%) and distal part (tight lesion, arrow) of the RCA (C). The FFR$_{CT}$ assessment confirmed the functional significance of the stenosis in mid LAD (D) and distal RCA (F), whereas the FFR$_{CT}$ value was >0.80 after the lesions in proximal LAD (D), LCx (E) and proximal RCA (F). CCTA, coronary CT angiography; LM, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; M, marginal branch; RCA, right coronary artery.

study of Conte *et al.* (33).

Future directions

The SYNTAX III Revolution study opens new perspectives on CCTA use as a tool to provide interventionalists and cardiac surgeons with an anatomy and functional non-invasive road-map for planning myocardial revascularization strategies. Moreover, future full automation of the SYNTAX III score calculation has the potential to further enhance and speed up the decision-making process in patients with multivessel disease. The interactive planner, which is a new application of FFR$_{CT}$, may improve treatment selection while tailoring procedural strategy based on assessment of functional outcome after virtual treatment (50). It is relevant to note that, although a prototype of the algorithm applied to coronary stents suggested a potential usefulness in this clinical field (51), the FFR$_{CT}$ calculation is still not validated and available for the routine clinical use in patients with stented coronary arteries. Although this limitation, a CCTA/FFR$_{CT}$ diagnostic work-

up has been demonstrated to be cost-effective in patients with suspected CAD and without history of previous coronary revascularization. In the PLATFORM study, at one-year follow-up of patients in the planned invasive test group, FFR$_{CT}$ guided strategy cost was $8,127 *vs.* $12,145 with a usual care strategy (P<0.0001), not accounting for the cost of the FFR$_{CT}$ test. The mean costs remained 26% lower among the FFR$_{CT}$ patients than among usual care patients ($9,036 *vs.* $12,145, P<0.0001) when factoring in the cost of the FFR$_{CT}$ analysis (52). At the present time, the major insurance companies in Europe and US recognize the reimbursement for FFR$_{CT}$ analysis. However, the FFR$_{CT}$ software is proprietary and still not widely available. In this novel and growing clinical field, stress myocardial CT perfusion (CTP) has been introduced as a new tool for evaluating the functional relevance of a coronary stenosis (53-57). In the field of complex CAD treated with PCI, the ADVANTAGE prospective study recently evaluated 150 patients with previous coronary stent implantation and demonstrated a CTP diagnostic accuracy significantly higher than that of CCTA in the territory-based and patient-

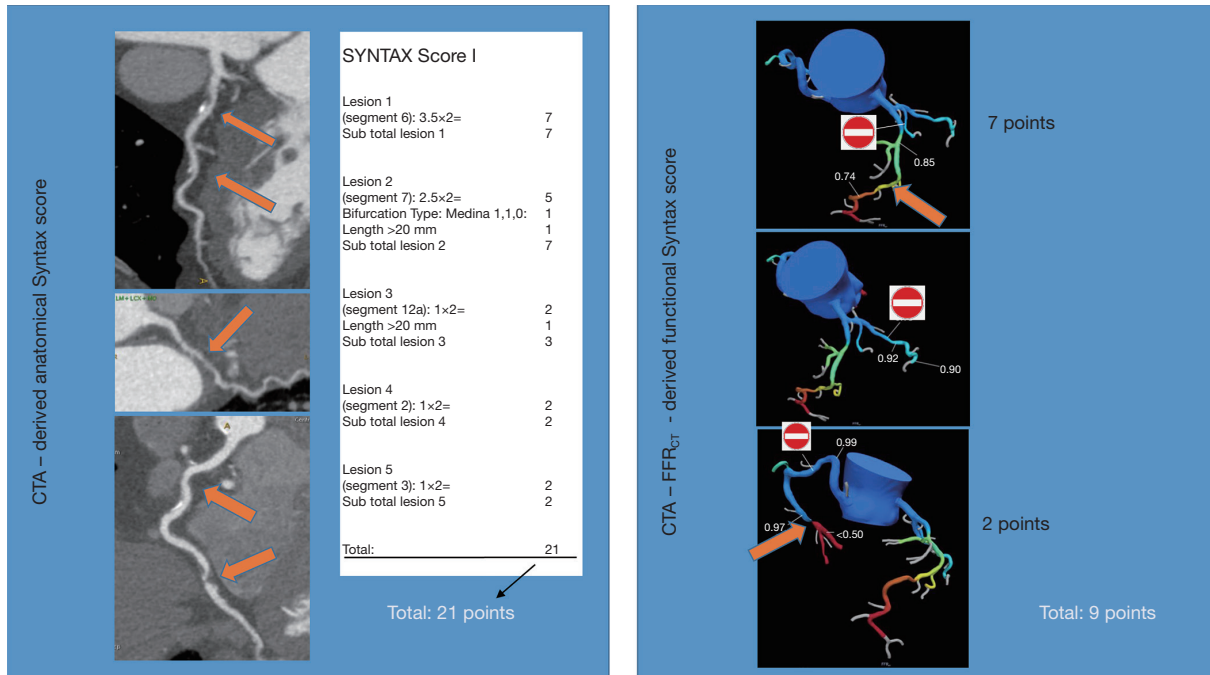Anatomical and Functional CCTA-derived SYNTAX Score

Figure 2 Anatomical (left panel) and functional (right panel) CCTA-derived SYNTAX Score calculations. The anatomical Syntax score of 21, derived by the scoring of five lesions (proximal-mid LAD, long lesion in LCx, mid-distal RCA, arrows) was downgraded to 9 points only after the incorporation of FFR$_{CT}$ into the functional Syntax score, by the exclusion of proximal LAD (arrow), LCx and proximal RCA (arrow) stenoses. The reduced value of the functional Syntax score suggested PCI instead of CABG. LM, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; M, marginal branch; RCA, right coronary artery.
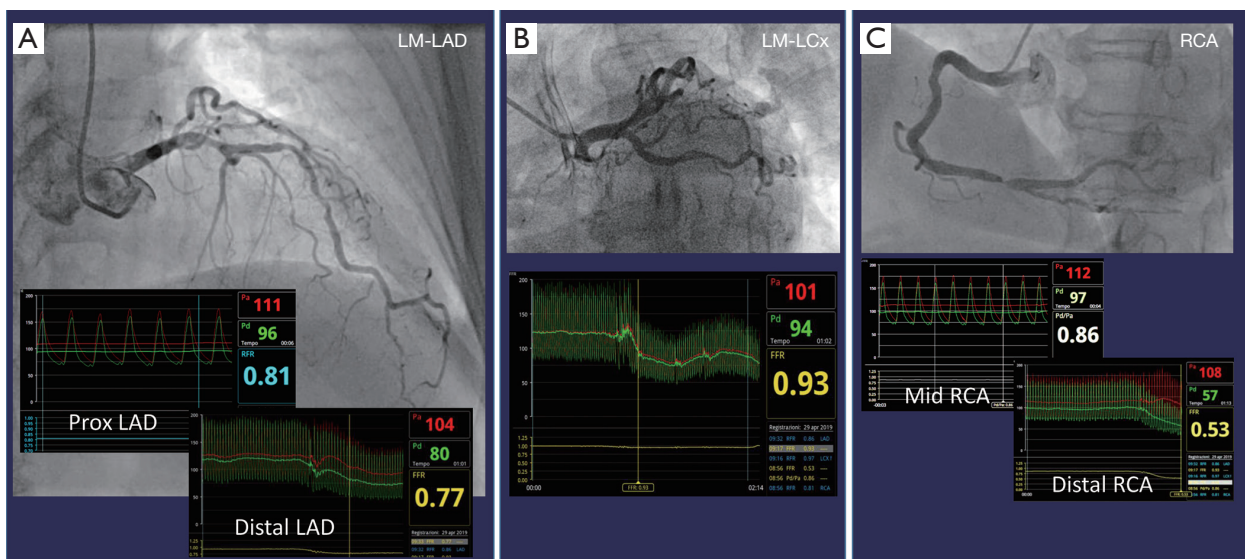

Figure 3 Invasive coronary angiography and invasive FFR assessment of LM-LAD (A), LCx-M branch (B) and RCA (C) show a very good agreement of both anatomical and functional invasive assessment with the correspondent non-invasive evaluation by CCTA- FFR$_{CT}$. LM, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; M, marginal branch; RCA, right coronary artery.
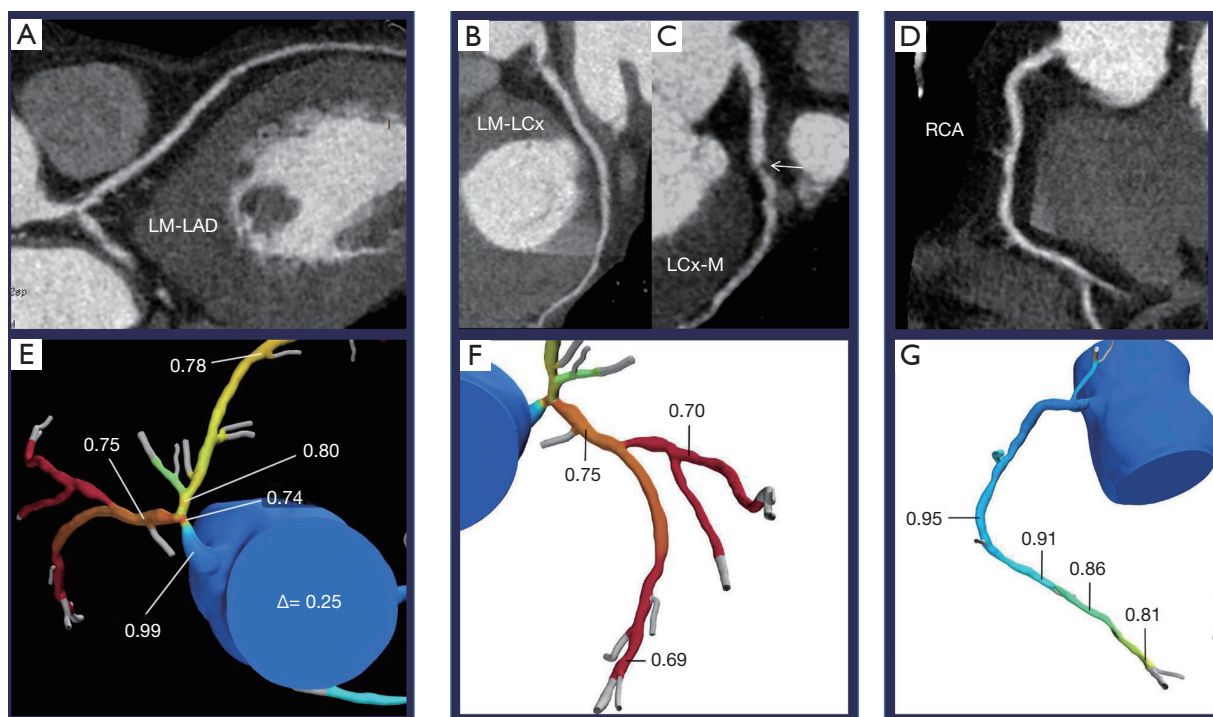
Figure 4 CCTA curved multiplanar reconstructions show a 70% stenosis of the distal left main coronary artery (A), involving the ostium of LCx (B) and a tight stenosis at the ostium of obtuse marginal branch (C, arrow), whereas the RCA was free from >50% stenosis (D). The FFR_{CT} assessment confirmed the functional significance of the stenosis in distal LM-ostial LCx (E) and obtuse marginal branch (F), whereas the FFR_{CT} values of the RCA were above the ischemia threshold of 0.80 (G). LM, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; M, marginal branch; RCA, right coronary artery.

based analyses (92.1% *vs.* 85.6% and 86.7% *vs.* 76.7%, respectively), using QCA as gold standard. Similarly, CTP specificity and diagnostic accuracy were significantly higher than those of CCTA when invasive FFR was employed as gold standard. Of note, the radiation exposure of cardiac CT (CCTA + CTP) was 4.15±1.5 mSv (32). To the best of our knowledge, only few studies addressed the prognostic role and the cost-effectiveness of CTP. In 2017, Meinel *et al.* enrolled 144 patients who underwent both CCTA and dynamic CTP. The study showed that CTP had incremental predictive value over clinical risk factors and detection of CAD with CCTA (58). More recently, CCTA, FFR_{CT} and dynamic CTP were evaluated in a multicenter trial that included 84 patients. The trial demonstrated that myocardial blood flow evaluated by dynamic CTP has the highest prognostic value, over CCTA and FFR_{CT}, in terms of future major cardiac events at 18-month follow-up (59).

The SYNTAX III study raises the question if a cardiac surgeon might be confident in using only the non-invasive coronary road-map provided by CCTA to plan CABG. The intriguing hypothesis was tested first in a theoretical feasibility survey study (60), in which six surgeons of the SYNTAX III Revolution trial were invited to review CCTA scans of 20 patients who previously underwent CABG during the course of the trial. Each surgeon had to declare whether planning and execution of surgery would be feasible and safe with the sole anatomical and functional assessment of CCTA as procedural guidance. The results of this "live survey" were quite impressive. The opinion of the surgeons was that 84% of the cases were eligible for surgery without ICA evaluation. Based on these findings, a "first-in-man", proof-of-concept feasibility and safety trial has been designed and will enroll 100 patients in whom surgeons will perform CABG without having access to ICA. Of note, CABG outcome will be assessed by CCTA 30 days after surgery in order to evaluate graft patency and correct anatomic location of the anastomoses (61).
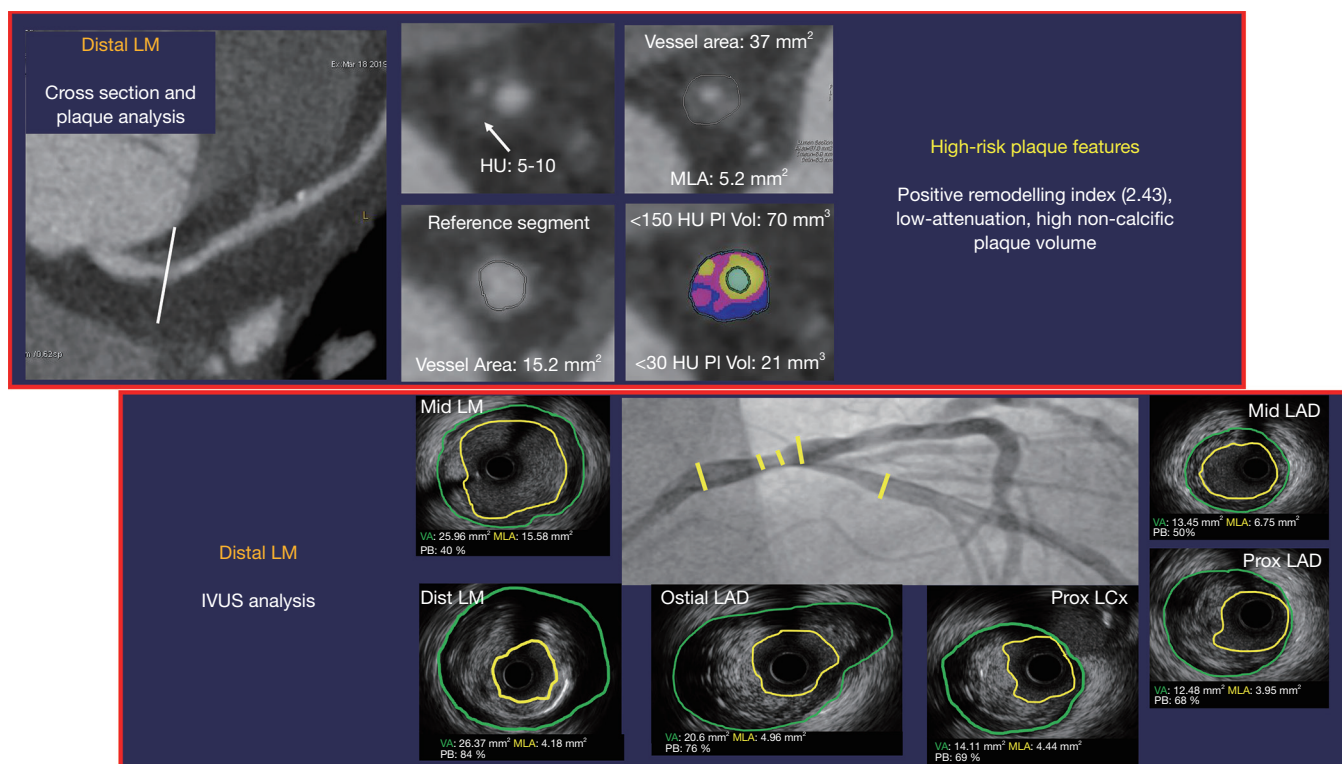
Figure 5 CCTA advanced plaque analysis by a dedicated software at the level of distal LM-ostial LAD (upper panel), showing the presence of qualitative (positive remodeling, low attenuation plaque) (arrow) and quantitative [high non-calcific (HU <150) plaque volume] high-risk parameters. IVUS assessment (lower panel) shows similar values of plaque volume and minimal lumen area (MLA) in comparison with those measured with CCTA (MLA at distal LM 5.2 *vs.* 4.96 mm², CCTA *vs.* IVUS, respectively). IVUS, intravascular ultrasound; MLA, minimal lumen area.

Conclusions

An emerging body of literature indicates that CCTA may have a clinical role also in patients with high pretest likelihood of CAD, known CAD and complex and diffuse disease. In particular, the SYNTAX studies demonstrated the usefulness of CCTA as a non-invasive tool for planning interventional and surgical coronary procedures, thanks to its ability to combine, in a single method, precise stenosis quantification, accurate plaque characterization, functional assessment and selection of the revascularization modality for any individual patient and of the vessels that need to be revascularized. It may be reasonable to state that the time has come to use CCTA for the assessment and decision making of patients with multivessel CAD (62).

Acknowledgments

Footnote

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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