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The revolution project: replacing coronary artery angiography with coronary computed tomography with functional evaluation

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In the last two decades, several studies and widespread clinical use demonstrated that coronary computed tomography angiography (CCTA) is 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. Moreover, 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 disease. Particularly, the SYNTAX II trial demonstrated the feasibility of planning interventional and surgical coronary procedures with CCTA thanks to its ability to combine, in a single method, precise stenosis quantification, accurate plaque characterization, functional assessment with fractional flow reserve derived from standard acquired CCTA datasets, and selection of the revascularization modality for any individual patient and of the vessels that need to be revascularized. More recently, the SYNTAX III Revolution trial showed, in patients with three-vessel CAD with or without left main involvement, that treatment decision-making between percutaneous coronary intervention and coronary artery bypass grafting based on CCTA only has an almost perfect agreement with the treatment decision derived from invasive coronary angiography (ICA). The high degree of correlation between CCTA and ICA suggests the potential feasibility of 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.

On 30 October 1958, the first selective coronary arteriogram was inadvertently obtained by Dr F. Mason Sones during an aortic root injection performed in the basement laboratory of an Ohio hospital in a 26-year-old patient with rheumatic heart disease, when the catheter unintentionally whiplashed into the ostium of the right coronary artery.[1] The serendipitous event opened the way to the clinical use of invasive coronary angiography (ICA). For the following six decades, ICA reigned over all other coronary imaging techniques for the management of coronary artery disease (CAD) and for guiding the treatment decision between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Moreover, it has played an integral role in the development of newer revascularization technologies.

In the last two decades, coronary computed tomography angiography (CCTA) has emerged as an alternative non-invasive imaging tool able to provide an accurate

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assessment of CAD.[2] With hardware and software having gone through tremendous developments, coronary CCTA is now considered a robust and accurate non-invasive imaging technique. Indeed, several studies demonstrated that CCTA might be appropriate for assessing patients with suspected CAD and low-to-intermediate pretest likelihood of the disease.[3] More recently, a growing body of literature showed that CCTA plays also a clinical role in patients with high pretest likelihood of CAD and known, and more complex and diffuse CAD. Moreover, multiple registries and randomized trials demonstrated that CCTA has the potential to guide clinical decision-making and even to predict hard cardiovascular events compared with current standards.[4-6] Furthermore, physiological assessment with fractional flow reserve derived from CCTA (FFR_{CT}) has been shown to be accurate in patients with multivessel disease.[7] For FFR_{CT} computation, a quantitative 3D anatomic model of the aortic root and epicardial coronary arteries is generated from CCTA images. Using advanced algorithms incorporating artificial intelligence, coronary blood flow and pressure are computed applying physiologic principles and computational fluid dynamics under conditions simulating maximal hyperaemia. The results provide FFR_{CT} values throughout the coronary arterial tree. The complete analysis is a colour-coded, digital 3D-model of the heart and coronary arteries, reflecting the impact that coronary stenosis has on blood flow (*Figure 1*).

The calculation of the CCTA-derived SYNTAX score has been shown to be accurate compared to the score resulting from ICA. Particularly, the SYNTAX II trial demonstrated the usefulness of CCTA in the field of non-invasive assessment of CAD patients.[8] The trial demonstrated the feasibility of planning interventional and surgical coronary procedures with CCTA thanks to its ability to combine, in a single method, precise stenosis quantification, accurate plaque characterization, functional assessment with FFR_{CT}, and selection of the revascularization modality for any individual patient and of the vessels that need to be revascularized. However, the diagnostic performance of the latest CT scanner generation and the agreement on treatment decisions in patients with multivessel CAD needed to be further investigated. Therefore, the SYNTAX III Revolution trial was designed to determine the agreement between separate and randomized heart teams on treatment recommendations based on either CCTA or ICA in patients with three-vessel CAD with or without the left main disease.[9] The trial, enrolling only patients with these anatomical features diagnosed by ICA, evaluated the agreement on treatment decision (CABG or PCI) of two heart teams of each centre who received—in order to make their verdict—either ICA or CCTA. Every week, during the conduct of the trial, a video conference review session of the cases was held involving the two heart teams formed by a surgeon, an interventional cardiologist, and a radiologist who were asked to sign off their treatment decision (*Figure 2*). The format of the presentation was always identical and extensively illustrated by CCTA maximum intensity projection and multiplanar reconstruction. The decision-making of 'CABG only', 'PCI only', or 'equipoise CABG/PCI' was concordant between the two heart teams in 86% with a Cohen's kappa of 0.82, qualifying the agreement as almost perfect according to the

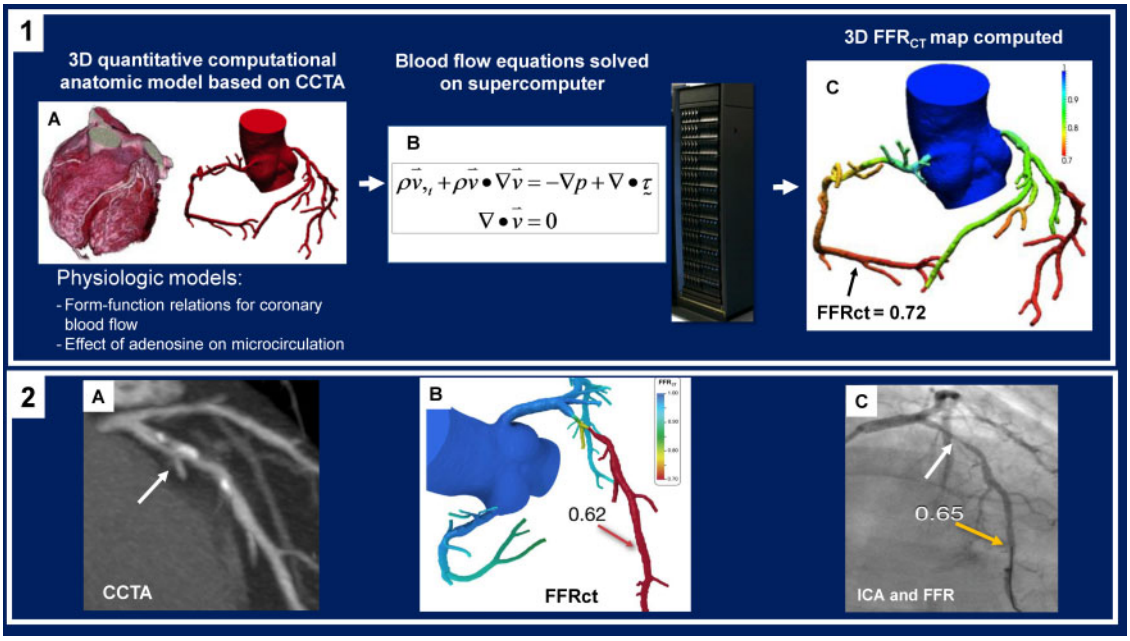

Figure 1 Panel 1: FFR_{CT} analysis provides noninvasively derived FFR information calculated from a standard CCTA (*A*) using machine-learning algorithms (*B*) to create a 3D model of the coronary arteries (*C*). Once this patient-specific model is completed, the process applies physiologic principles and computational fluid dynamics to compute the blood flow and FFR derived from CCTA (FFR_{CT}) values at every point in the model. The completed analysis is a color-coded, digital 3D model of the heart and coronary arteries reflecting the impact that a stenosis has on blood flow. Panel 2: CCTA showing a stenosis (arrow) of the proximal LAD (*A*). FFR_{CT} demonstrates ischemia in the LAD (computed value of 0.62) (*B*). Invasive coronary angiography (ICA) confirms the proximal stenosis (white arrow) while invasive FFR confirms ischemia (yellow arrow) in the LAD (0.65) (*C*). CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; LAD, left anterior descending

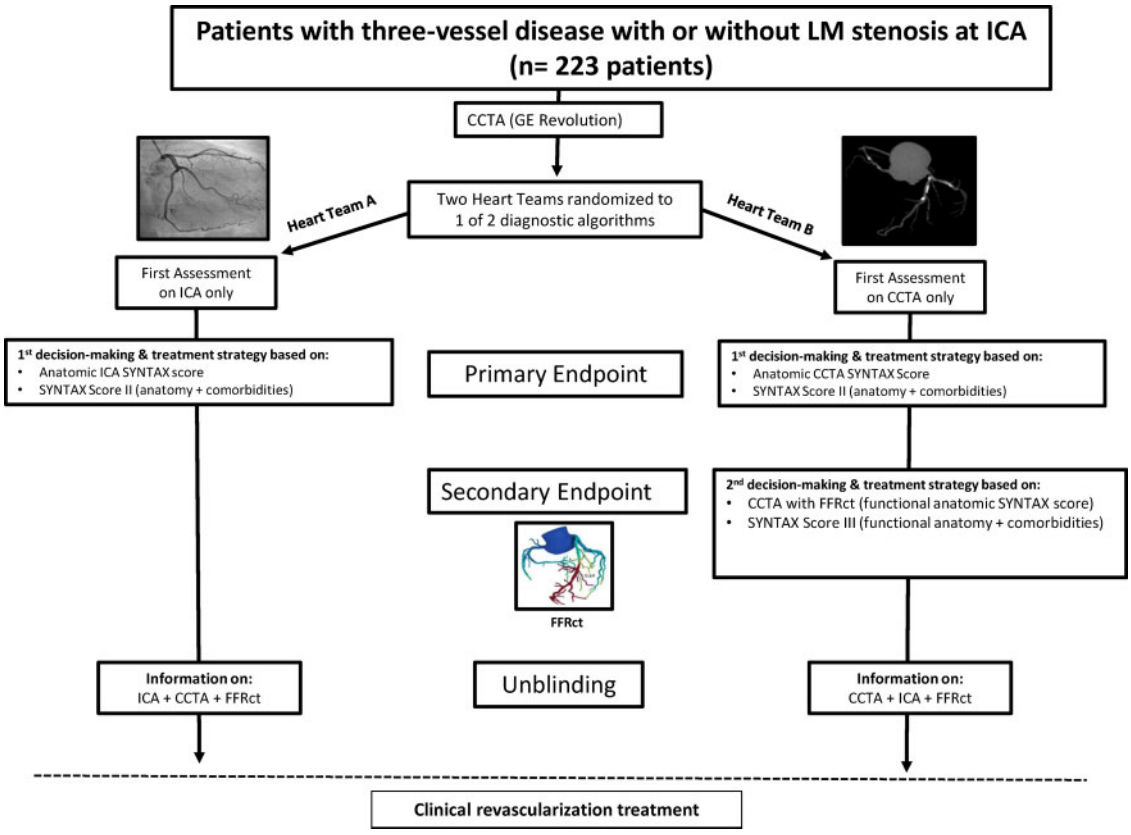

Figure 2 Flow diagram of the SYNTAX III Revolution trial. CCTA, coronary computed tomography angiography; FFRCT, fractional flow reserve derived from CCTA; ICA, invasive coronary angiography; LM, left main.

3VD patients with or without LM stenosis (n=223)	Heart Team treatment recommendation based on CCTA		
Heart Team treatment recommendation based on ICA	***CABG***	***PCI/Equipoise CABG and PCI***	
CABG	**23.4% (52/222)**	2.7% (6/222)	26.1% (58/222)
PCI/Equipoise CABG and PCI	4.5% (10/222)	**69.4%(154/222)**	73.9% (164/222)
	27.9% (62/222)	72.1 (160/222)	**92.8%(206/222)**
Agreement in 93% of the Heart Team's treatment recommendation **Cohen's kappa coefficient of 0.82 (95% CI 0.73 to 0.90)**			

Figure 3 Agreement on treatment recommendation between CCTA and ICA (primary trial endpoint). The heart teams agreed on treatment recommendation in 93% of the cases (Cohen's kappa coefficient 0.82, 95% confidence interval 0.73–0.90). CABG: coronary artery bypass grafting; CCTA, coronary computed tomography angiography; ICA, invasive coronary angiography; LM, left main; PCI, percutaneous coronary intervention; VD, vessel disease.

statistical Cohen's kappa categorization (*Figure 3*). FFR_{CT} led to a 2.9 (95% confidence interval 1.9–3.9) point reduction in the anatomical SINTAX score decreasing from 92.3% to 78.8% the proportion of patients with haemodynamically significant three-vessel CAD, changed treatment decision in 7% of patients, and modified the selection of vessels to be revascularized in 12% of patients. This was a virtual trial since, after signing off the decision-making, both heart teams were un-blinded so that they had all the information available prior to the real clinical treatment either in the catheterization laboratory or in the operating room (*Figure 2*).

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. The issue was addressed by a sub-analysis of the SYNTAX III Revolution trial. As expected, the sub-analysis showed that heavy coronary calcifications moderately affect CCTA capability to assess accurately the anatomical SYNTAX score, with a significantly higher difference between the CCTA-derived and ICA-derived anatomical SYNTAX score. 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 similar between the two groups of patients.

After the positive results of the SYNTAX III Revolution trial became available, the principal investigator of the study decided to evaluate whether the participating surgeons would be willing to perform surgery without prior ICA, using CCTA as the sole guidance of coronary grafting. Indeed, the revolutionary concept had to be tested first in a theoretical feasibility survey.[10] Therefore, the surgeons of the SYNTAX III Revolution trial were invited to participate in a review of the CCTA of 20 patients who had indeed been operated previously by them during the course of the trial. Each surgeon had to declare whether the planning and execution of CABG would be feasible and safe with the sole anatomic guidance of CCTA and the functional assessment of FFR_{CT}. It is noteworthy that the survey results showed that 85% of the cases would be eligible for surgery without preview assessment with ICA.

Based on these findings, a first in man, proof-of-concept feasibility and safety trial has been designed. The trial is due to start soon and will enrol 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 the correct anatomic location of the anastomoses. If the policy of surgical treatment without prior ICA guided solely by CCTA will demonstrate to be feasible and safe, then a major paradigm shift could be envisioned.[11]

In conclusion, recent studies open new perspectives on CCTA and FFR_{CT} use as a tool to provide interventional cardiologists and cardiac surgeons with an anatomy and functional non-invasive road-map for planning myocardial revascularization strategies.

Conflict of interest: none declared.

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