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

Antonio L. Bartorelli1,2*, Daniele Andreini1,3, Saima Mushtaq1, and Patrick W. Serruys4

1Centro Cardiologico Monzino, IRCCS, Milan, Italy; 2Department of Biomedical and Clinical Sciences “Luigi Sacco”, University of Milan, Milan, Italy; 3Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy; and 4Department of Cardiology, Royal Brompton and Harefield Hospitals, Imperial College London, London, UK

KEYWORDS
Coronary computed tomography angiography; Stable coronary artery disease; Fractional flow reserve

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. 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...
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. 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. Furthermore, physiological assessment with fractional flow reserve derived from CCTA (FFR\textsubscript{CT}) has been shown to be accurate in patients with multivessel disease. For FFR\textsubscript{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\textsubscript{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. 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\textsubscript{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. 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 assessment of CAD.
statistical Cohen’s kappa categorization (Figure 3). FFRCT 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. 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 CAGB would be feasible and safe with the sole anatomic guidance of CCTA and the functional assessment of FFRCT. It is noteworthy that the survey results indicated that 85% of the cases would be eligible for surgery without prior 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 CAGB without having access to ICA. Of note, CAGB 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.

Conflict of interest: none declared.

References

1. Ryan TJ. The coronary angiogram and its seminal contributions to cardiovascular medicine over five decades. Circulation 2002;106:752-756.
2. Menke J, Kowalski J. Diagnostic accuracy and utility of coronary CT angiography with consideration of unobservable results: a systematic review and multivariate Bayesian random-effects meta-analysis with intention to diagnose. Eur Radiol 2016;26:451–458.
3. Arbab-Zadeh A, Miller JM, Rochitte CE, Dewey M, Nilunna H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JAC. Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study. J Am Coll Cardiol 2012;59:379-387.
4. Pontone G, Bertella E, Muxtagh S, Loguerico M, Cortinovis S, Baggianio A, Conte E, Annani A, Formenti A, Beltrama V, Guaracci AI, Andreini D. Coronary artery disease: diagnostic accuracy of CT coronary angiography: a comparison of high and standard spatial resolution scanning. Radiology 2014;271:688-694.
5. Andreini D, Pontone G, Muxtagh S, Bertella E, Conte E, Segurini C, Giovannardi M, Baggianio A, Annani A, Formenti A, Petulà M, Beltrama V, Volpato V, Bartorelli AL, Trabattoni D, Florentini C, Pepi M. Diagnostic accuracy of rapid kilovolt peak-switching dual-energy CT coronary angiography in patients with a high calcium score. J Am Coll Cardiol 2015;64:746-748.
6. Andreini D, Pontone G, Muxtagh S, Granars H, Conte E, Bartorelli AL, Pepi M, Opolski MP, Ö Hartaig B, Berman DS, Budoff MJ, Achenbach S, Al-Mallah M, Cademartiri F, Callister TQ, Chang H-J, Chinnaiyan K, Chow BJW, Cury R, Delago A, Hadamitzky M, Hausleiter J, Feuchtner G, Kim Y-J, Kaufmann PM, Leipsic J, Lin FY, Maielli E, Rafi G, Shaw LJ, Villines TC, Dunning A, Marques H, Rubinstein R, Hindoyan N, Gomez M, Min JK. Long-term prognostic impact of CT-Leaman score in patients with non-obstructive CAD: results from the CORONARY CT Angiography Evaluation For Clinical Outcomes InteRnational Multicenter (CONFIRM) study. Int J Cardiol 2017;231:18-25.
7. Collet C, Miyazaki Y, Ryan N, Asano T, Tenekcioglu E, Sonck J, Andreini D, Sabate M, Brugalletta S, Stables RH, Bartorelli A, de Winter RJ, Katagiri Y, Chichareon P, De Maria GL, Suwannasom P, Cavalcante R, Jonker H, Morel M-A, Cosyns B, Kappetein AP, Taggart DT, Farooq V, Escaned J, Banning A, Onuma Y, Serruys PW. Fractional flow reserve derived from computed tomographic angiography in patients with multivessel CAD. J Am Coll Cardiol 2018;71:2756-2769.
8. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chleffo A, Kappetein AP, Colombo A, Holmes DR, Mack M, Feldman T, Morice M-C, Ståhle E, Onuma Y, Morel M-A, Garcia-Garcia HM, van ES GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639-650.
9. Collet C, Onuma Y, Andreini D, Sonck J, Pompliolo G, Muxtagh S, La Meir M, Miyazaki Y, de Mey J, Gaemperli O, Ouda A, Maureira JP, Mandy D, Camenzind E, Macron L, Doenst T, Teichgräber U, Sigosch H, Asano T, Katagiri Y, Morel M-A, Garcia-Garcia HM, van ES GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Eur Heart J 2013;34:3689-3698.
10. Sonck J, Miyazaki Y, Collet C, et al. Feasibility of planning coronary artery bypass grafting based only on coronary computed tomography angiography and CT-derived fractional flow reserve: a pilot survey of the surgeons involved in the randomized SYNTAX III Revolution trial. Interact Cardiovasc Thorac Surg 2019; doi: 10.1093/icvts/ivz046.
11. Andreini D, Onuma Y, Bartorelli AL, Serruys PW. The time has come to use coronary computed tomography angiography in patients with multivessel coronary artery disease. Eur Heart J 2019;40:1472-1472.