

## Are coronary CT angiography and CT-Based FFR set to become a game-changer in the diagnosis and treatment decisions in coronary artery disease?

Ever since publication last year, the results of the SYNTAX III Revolution trial [1] have been making waves and stimulating intense debate between radiologists, interventional cardiologists and cardiac surgeons involved in the treatment of patients with coronary artery disease.

The trial results showed that there was almost perfect agreement between heart teams who used either conventional invasive coronary angiography (ICA) or Coronary CT angiography (CCTA) to decide which revascularization approach should be used for the treatment of patients with severe, multi-vessel coronary artery disease.

We wanted to find out more about the trial and the implications of the results, so we spoke to Prof. Patrick Serruys, Principal Investigator of the trial.



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**Q** So, what is the significance of the findings of the SYNTAX III Revolution trial, Do the results mean that invasive coronary angiography will be replaced by coronary CT angiography?

Well that is a big question, but to cut to the chase, yes many of us in the field do believe that conventional ciné angiography that is used as a diagnostic tool will progressively be replaced by multi-slice CT scans. More work and further trials will be needed, but the results of our SYNTAX III trial do suggest a promising, real change in future practice, with a central place for CCTA in guiding decisions for the treatment of patients with coronary artery disease. There are many reasons and data to support this belief, but one key underlying factor is



Figure 1. The CT scanner used in the Syntax III trial was the GE Revolution, a state-of-art system which delivers high image quality through the convergence of coverage, spatial resolution and temporal resolution

that the technology — both hardware and software — behind CT scans has made dramatic and continuing advances over the years. In the SYNTAX III Revolution trial, the multislice CT scanner used to carry out the CCTA examinations was the Revolution scanner from GE Healthcare [Figure 1]. With a 160 mm coverage in the z-axis and 0.28 second rotation speed, the system allows the acquisition of the whole heart within a single beat; any motion artefacts can be handled by post-processing; all-in -all a performance that was unimaginable several years ago. In addition CCTA exams carried out on the Revolution multislice scanner involve relatively low levels of ionizing radiation of approximately 5mSv versus a typical 10mSV for conventional angiography.

The technological progress of multislice CT scanners and their suitability for cardiac imaging is beginning to be recognized by the advisory authorities. Recently, the UK's **National Institute for Health and Care Excellence (NICE)** issued guidelines (CG95) for the management of stable chest pain which recommended coronary CTA as a preference over functional testing for the first-line test for evaluation of chest pain in patients without known coronary artery disease (CAD). Importantly, the NICE guidelines suggest first-line coronary CTA testing

at all levels of pre-test risk probability of CAD. This is a radical departure from existing U.S. and European societal guidelines, which currently recommend limiting the use of coronary CTA to patients with low to intermediate pre-test risk.

In practice, NICE proposed that in the UK the number of tests carried out in the future by other cardiac imaging modalities, such as stress echocardiography, myocardial perfusion imaging, stress MRI, CT calcium scoring and invasive coronary angiography should be reduced by 100%; 50%; 50%; 50%; 100% and 60% respectively. However, NICE proposed a 400% increase in the number of CT angiography tests to be carried out. The contrast with NICE's proposed usage of invasive coronary angiography (60% decrease) is striking. In addition, a financial analysis of the impact of these proposed NICE guidelines showed a cost saving of nearly 20 million pounds.

The manufacturers of CT scanners are also aware of the increasing potential of CT technology in cardiac imaging. To meet this potential GE Healthcare have for example recently introduced a new CT system, the CardioGraphe specifically designed for cardiology. The CardioGraphe is a small multi-slice CT scanner which only takes up 15 sq metres floor



Figure 2. Specifically designed for cardiology, GE's CardioGrappe addresses the growing need for a CT scanner that is optimized for cardiac applications.

space. The small size of the system means that the rotation speed can be high, so giving a temporal resolution of 120 msec. The spatial resolution is about 285 micron, so not so far from the resolution of coronary angiography which is typically 200 – 220 micron. Image quality is high and the system gives whole heart, one beat cardiac image acquisition.

## Q Now let's turn to the Syntax III Revolution trial in more detail

Yes but let's first recap a bit on the various SYNTAX Scores,

Approximately 10 years ago I created the original SYNTAX scoring system with my team in the Thorax Center in Rotterdam when we were conducting a large trial comparing the two different cardiac revascularization approaches, namely surgery (Coronary Artery Bypass Grafting, CABG) versus Percutaneous Coronary Intervention (PCI) in patients with multi-vessel three vessel and main stem disease. The SYNTAX score we developed is an angiographic grading tool to determine the complexity of coronary artery disease. One advantage of the scoring system was that it forced the surgeons and the interventional cardiologists to closely examine the angiography images before taking any decision about the revascularization approach to be adopted. Although in the beginning, the surgeons and interventional cardiologists did not fully understand the significance of the actual numerical value the detailed attention they paid to the angiography images was very useful. In addition, soon after its introduction, we realized that the score correlated with the patient outcomes and so had an important prognostic value. However we also noted that the prognostic value of the score could be affected by

the patients' clinical characteristics and co-morbidities, e.g. Chronic Obstructive Pulmonary Disease (COPD), Peripheral Vascular Disease, creatinine clearance, etc., etc.

So we took the anatomic SYNTAX score and combined these with the clinical co-morbidities to create the SYNTAX II score, which was very reliable in predicting all-cause mortality at four years. This robust score allows for meaningful discussions between surgeons and patients in terms understandable to the patient. The score in fact became a decision maker so that although the patient is unaware of the underlying algorithms that generate the score, it enables the patient to better appreciate, in conjunction with the interventionalist or cardiologist, the relative chance of mortality associated with the choice of therapeutic route. For example it is now possible to say to a patient "if you opt for CABG surgery you have a 15 % chance that you will be dead in four years whereas if you opt for PCI the risk is 42%, or vice versa".

Powerful as the SYNTAX II score is, it soon became clear that this was not the whole story. Even precise anatomical measurements of the coronary vasculature such as measures of stenoses did not correlate with the actual physiological characteristics of the hemodynamic flow as measured by Fractional Flow Reserve (FFR). Traditionally FFR is measured in the cath lab by the invasive procedure based on the use of a pressure sensitive wire. In recent years the development of advanced CT systems has enabled the production of high quality images of the coronary tree to which sophisticated flow dynamic algorithms and software (for example from the Heart Flow company) can be applied to generate an FFR value derived from the CTA dataset (FFR<sub>CT</sub>). The correlation between the FFR and FFR<sub>CT</sub> has been carefully studied and has been shown to be quite good, with FFR<sub>CT</sub> having the clear advantage of not being as invasive as the conventional wire-based system [Figure 3, 4] The UK's NICE guidelines mentioned above predicted an additional cost saving if the HeartFlow FFR<sub>CT</sub> was used rather than invasive investigation and treatment.

So, to recap, after the SYNTAX score based on anatomy, we can add the physiological consequences of the anatomy via FFR and build in the effect of any co-morbidities to yield the SYNTAX III score

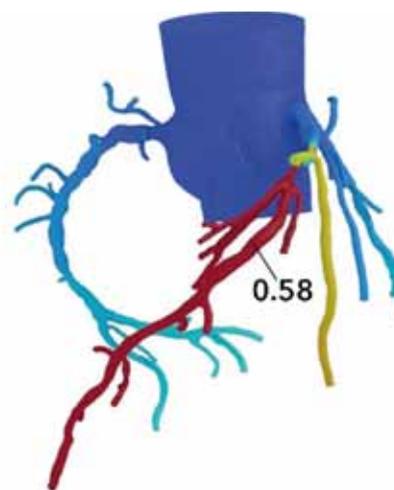


Figure 3. Using data from a standard CT dataset, the non-invasive HeartFlow Analysis from the HeartFlow company creates a personalized 3D model of the coronary arteries and analyzes the impact that blockages have on blood flow. The color-coding makes it easier for surgeons to identify the areas of the coronary tree needing attention.

## Q So what was the design of the SYNTAX III Revolution trial?

The aim of the trial was to determine, the level of agreement between heart teams on treatment decision-making using either CCTA or conventional angiography. The patients all had severe coronary artery disease (so at the tip of the CAD pyramid, Figure 5) and the treatment options were either CABG or PCI. The design of the trial is shown in Figure 6. Separate heart teams, composed of an interventional cardiologist, a cardiac surgeon, and a radiologist (the inclusion of a radiologist in the heart team is an innovation) were randomized to assess the coronary artery disease with either coronary CTA or conventional angiography. Each

## UK adoption of FFR<sub>CT</sub>

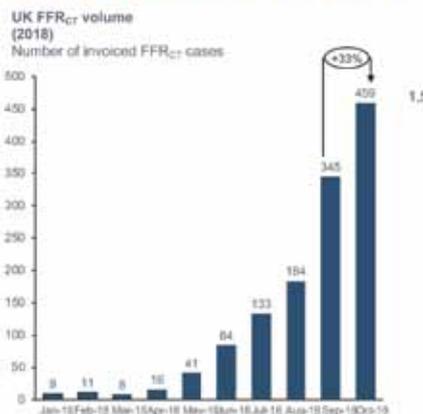


Figure 4. In the UK, there has been a rapid rise in the number of FFR<sub>CT</sub> analyses being carried out. Data from 2018.

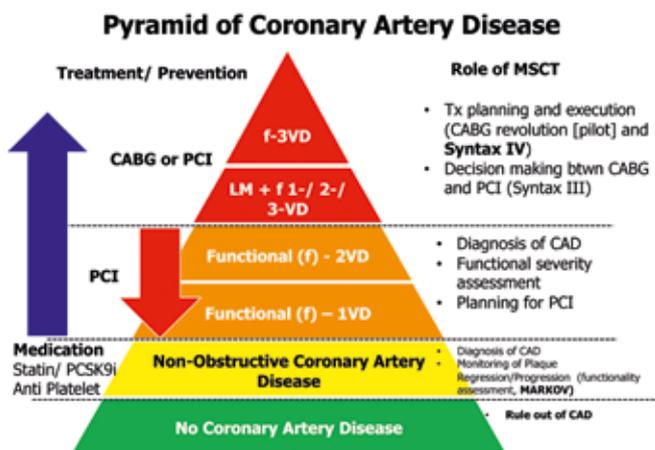


Figure 5. Levels of severity of coronary artery disease. The patients in the SYNTAX III trial all had three vessel disease so were at the tip of the pyramid.

heart team, blinded for the other imaging modality, quantified the anatomical complexity using the SYNTAX score and integrated clinical information using the SYNTAX Score II to provide a treatment recommendation based on mortality prediction at 4 years

Thus, for the first time in a clinical trial the clinicians, namely the two heart teams were randomized to the patients as opposed to the patients being randomized to one methodology or another. The primary endpoint was the level of agreement between heart teams on the revascularization strategy, with a secondary end-point being the impact of FFR<sub>CT</sub> alone on treatment decision and planning.

*“... the role of gate-keeper to cardiac surgery will increasingly be fulfilled by the radiologist...”*

**Q** So what were the results of the trial?

The results were outstanding. We found that there was an almost perfect statistical agreement on the decisions regarding the

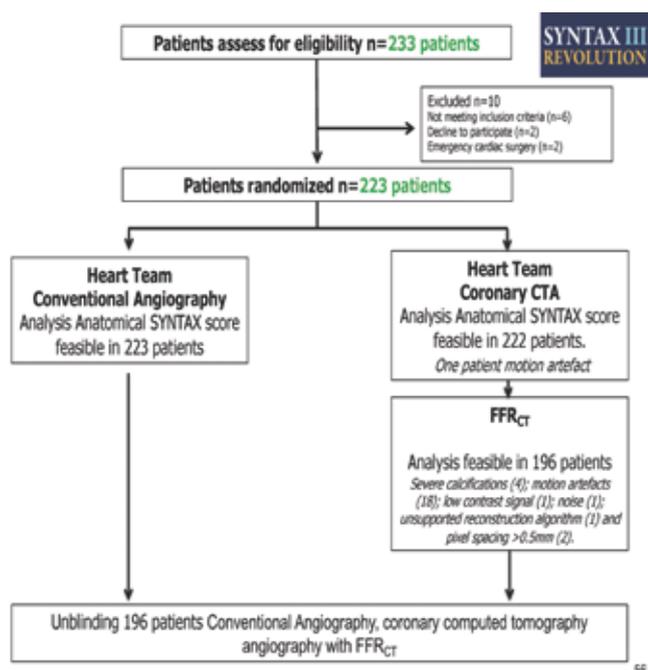


Figure 6. Flow chart of the Syntax III Revolution trial.

optimal revascularization strategy that the heart teams came to, no matter whether they used conventional angiography or CCTA-derived information. As regards the secondary end-point, namely the impact of CCTA and FFR<sub>CT</sub>, (i.e. without using any conventional angiography data) on the surgeon’s willingness to carry out CABG or not, it was found that 84% of the surgeons who were presented with only the CCTA and FFR<sub>CT</sub> data indicated that they would be happy to base their CABG surgery decision on these data alone.

**Q** And what are the implications of these findings?

Well as regards the agreement on treatment options between CCTA or conventional angiography, this clearly suggests the feasibility of treatment decision-making based solely on non-invasive imaging modality and dramatically extends the use of CCTA to patients with severe CAD. Some observers have described this as a “paradigm shift to a situation where CAD is diagnosed and thoroughly characterized non-invasively, with revascularization planning made in a collaborative fashion integrating the heart team”. The implications could be far-reaching, particularly as regards the future roles of the members of the heart team. Up till now the role of “gate-keeper” of access to the cardiac surgeon lay with the interventionalist.

Now, given the potential of CCTA and FFR<sub>CT</sub>, the role of gate-keeper to cardiac surgery will increasingly be fulfilled by the radiologist. In such a scenario, a third party, such as an internal medicine clinician can could request a multi-slice CT exam for the patient. As a function of the results, the radiologist would then propose the case to the surgeon or the interventionalist. Of course, the people in the diagnostic cath labs are uneasy with these scenarios, particularly since diagnostic conventional angiography is a significant revenue source for the cath lab.

**Q** What are the next steps?

There are many next steps and one has already begun, namely a trial to confirm that surgeons are really confident to base their surgical decisions on CCTA and FFR<sub>CT</sub> alone. Of course, the study of the cohort of the SYNTAX III Revolution trial suggested that they would be, but this was a retrospective analysis, and we have to recognize that surgeons are not (yet) really familiar with analyzing multi-slice CCTA or FFR<sub>CT</sub> data. So making a decision purely on CCTA and FFR<sub>CT</sub> data alone and without any access to conventional ciné angiography could be tough for a surgeon and at least require a learning curve. The CABG Revolution trial that we are currently undertaking is designed to answer these questions.

In the longer term, who knows, we could imagine applying CCTA and FFR<sub>CT</sub> to all categories of patients with CAD, not just the severe cases at the tip of CAD pyramid who participated in the SYNTAX III Revolution trial.

**REFERENCES**

1. Collet et al. Coronary Computed Tomography Angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J.* 2018; 39(41): 3689 doi: 10.1093/eurheartj/ehy58