

# openheart CT coronary angiography: a paradigm shift for functional imaging tests

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## ABSTRACT

The UK National Institute for Health and Care Excellence (NICE) have just updated their guideline on new-onset stable chest pain, recommending that all patients should be investigated with a CT coronary angiography (CTCA). In a separate guideline, NICE recommended CT fractional flow reserve (CT-FFR), to assess coronary stenoses, found on CTCA, stating that this would reduce the need for invasive coronary angiography and hence reduce cost. We discuss the evidence base for CT-FFR and emphasise that we already have established functional imaging tests, with extensive evidence base for efficacy and prognosis and that CT-FFR should be compared with this standard of care and not with the much more expensive and invasive fractional flow reserve undertaken during invasive coronary angiography.

The introduction of CT coronary angiography (CTCA) into clinical practice over a decade ago was described as a paradigm shift in the diagnosis of coronary artery disease (CAD), from functional testing, to investigate for the presence of ischaemia, to anatomical testing to investigate for the presence of atherosclerotic CAD. A large number of studies demonstrated that CTCA has an excellent negative predictive value (NPV),<sup>1,2</sup> and hence CTCA was incorporated into international guidelines as an alternative to functional imaging tests in patients with low-intermediate pretest probability of CAD.<sup>3</sup> The UK National Institute for Health and Care Excellence (NICE) in 2010 recommended cardiac CT for patients with chest pain and low pretest probability of CAD, functional imaging tests for patients with intermediate probability of CAD and invasive coronary angiography (ICA) for patients with high probability of CAD. However, in their 2016 guideline, NICE expanded the role of CTCA to be the first-line investigation for all patients with new-onset typical or atypical chest pain. They stated that functional imaging tests should be reserved for the assessment of patients with chest pain and known CAD and for patients where the CTCA is non-diagnostic or has shown CAD of uncertain significance.<sup>4</sup> The NICE health economic evaluation and the guideline were

influenced by the low cost of CTCA and the excellent NPV, based on studies in populations with relative low prevalence of CAD.<sup>2</sup>

Large clinical trials such as Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) (n=10 000), which compared CTCA versus functional imaging tests for the initial assessment of patients with suspected CAD, found no difference in outcome. The average pretest probability risk score (RS) in the trial was 53.3%. However, the actual prevalence of CAD was low with 6.2% of the CTCA cohort and 3.2% of the functional imaging test cohort going on to have revascularisation.<sup>5</sup> The higher rate of revascularisation in the CTCA arm should be considered carefully, as we expand the role of CTCA into populations of higher prevalence of CAD, as it would increase the overall cost to healthcare services, without any evidence of change in outcome, based on PROMISE. This is particularly important as CTCA is known to have a low positive predictive value (PPV).<sup>1,2</sup> Hence, a case can be made that patients found to have anatomically significant CAD on CTCA should undergo a test for ischaemia before ICA and revascularisation are considered. CT fractional flow reserve (CT-FFR) has been proposed as this gatekeeper and has now been recommended by NICE, in a separate guideline, for patients with stable chest pain who had a CTCA. The guideline states that CT-FFR may avoid the need for ICA and save the National Health Service a £214 per patient and £9.1 million by 2022 by reducing the need for ICA.<sup>6</sup>

Several studies have been undertaken comparing CT-FFR with invasive FFR to establish the accuracy of the technique. Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) (n=252) compared CT-FFR with invasive FFR in patients scheduled to have ICA and found the accuracy to be 73% with sensitivity of 90%, specificity of 54%, PPV of 67% and NPV of 84%.<sup>7</sup> The



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NXT trial (n=365) also compared CT-FFR with invasive FFR in patients scheduled to have ICA. In NXT, only 251 patients, with excellent image quality, were included in the final analysis and the diagnostic accuracy improved to 81% with sensitivity of 86%, specificity of 79%, PPV of 65% and NPV of 93%.<sup>8</sup>

The largest CT-FFR trial to date is the Platform study (n=585) which compared CTCA plus CT-FFR versus the standard of care. The end point of the study was reduction of ICA that showed no obstructive CAD. The standard of care was unusually skewed towards direct invasive management and in the analysis the patients were divided into two substudies, an invasive study (n=380) and a non-invasive study (n=204). In the invasive study, CTCA plus CT-FFR reduced the rate of ICA significantly as only patients found to have significant coronary stenosis and positive CT-FFR went on to have ICA, while in the invasive arm of the invasive study all patients, by definition, underwent ICA±invasive FFR. In the non-invasive study, there was no difference in the rate of ICA and revascularisations between functional imaging tests and CTCA plus CT-FFR. The Platform concluded that CTCA plus CT-FFR was associated with a significantly lower rate of ICA showing no obstructive CAD.<sup>9</sup> Subsequent health economics study concluded that CTCA plus CT-FFR was a more cost-effective approach in the investigation of patients with stable chest pain.<sup>10</sup> NICE guideline on CT-FFR was based on the Platform health economics data.<sup>6</sup>

In NXT and Platform trials, CT-FFR was performed on all patients with a coronary stenosis on CTCA of ≥30%. CT-FFR is likely to perform well in patients with mild stenoses or very severe stenoses. This was demonstrated in a recent systematic review which showed that while the overall diagnostic accuracy of CT-FFR, compared with invasive FFR, was 81.9%, the highest accuracy for CT-FFR was below FFR of 0.60 at 86.4% and above FFR of 0.80 at 87.3%. The accuracy became very poor in patients with CT-FFR values in the range of 0.70–0.80 at 46.1%, which is where FFR is most important.<sup>11</sup> This questions the efficacy of routine use of CT-FFR as a gatekeeper to ICA and revascularisation.

Most recently, Dewey *et al*<sup>12</sup> undertook a clinical trial (n=340) randomising patients to CTCA versus direct invasive management with ICA and found that CTCA reduced the rate of ICA from 100% in the invasive arm to 14% in the CTCA arm. The pretest probability RS of the cohort was 34.6%, which is lower than the PROMISE trial. Demonstrating that CTCA reduces the need for ICA in patients who do not need to be investigated with an ICA is not very meaningful.

We already have well-established functional imaging tests with proven clinical efficacy and extensive prognostic data.<sup>13–18</sup> The PROMISE trial demonstrated that functional imaging tests lead to fewer revascularisations without a difference in outcome. Functional imaging tests in PROMISE did result, however, in more invasive angiograms that do not lead to revascularisations, compared with CTCA (4.3% vs 3.4%). At least some of these patients, with false positive functional imaging tests, do in fact have

ischaemia, but with microvascular CAD, and they do have an adverse outcome.<sup>19</sup> This is being investigated in the CIAO arm of the ischaemia trial which will report in 2019.<sup>20</sup> Functional imaging tests should be the default gatekeeper to ICA and revascularisations, in patients with significant anatomical CAD on CTCA. Studies comparing CTCA plus CT-FFR with ICA plus invasive FFR in these patients do not represent the clinical reality or international guidelines.<sup>3,4</sup> CT-FFR needs to be directly compared with functional imaging tests and the health economic evaluations of CT-FFR should be based on such studies. This is particularly important as the UK hospitals have recently had to expand their functional imaging test resources to be able to deliver the NICE 2010 guidelines. The British Society of Cardiovascular Imaging executive summary states that the switch to CTCA for all patients with stable chest pain will require a significant investment in CT scanners and workforce.<sup>21</sup> The tariff of CT-FFR is an additional £700 per patient, on top of the cost of the CTCA. This is significantly higher than the tariff for a functional imaging test such as stress echo at £270, which has the added advantage of an extensive evidence base.<sup>13–18</sup>

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