Coronary artery disease remains the leading cause of death around the world, even during the COVID-19 pandemic, and it is therefore essential that we continue our quest to improve the prevention, diagnosis, management and outcome of coronary artery disease. Fifty years ago, in 1971, the first CT scan was performed on a machine invented by Sir Godfrey Hounsfield who, even in those early days, realised the potential of CT to assess the heart and coronary arteries. 

Technological advances mean that it is now possible to obtain extensive information on the presence, severity and characteristics of atherosclerotic plaque from coronary CT angiography (CCTA). In addition, it is also possible to use computational modelling to obtain an estimate of fractional flow reserve from static CCTA images (FFRCT). CCTA now plays a central role in the assessment and management of patients with symptoms of suspected coronary artery disease in both national and international guidelines. However, the role of FFRCT in clinical practice is less certain.

Nørgaard et al. present a meta-analysis of the prognostic information provided by FFRCT from a single vendor (HeartFlow) in 5460 patients from 5 observational studies and registries. Coronary artery disease was prevalent in the population, with 72% having at least one stenosis >50% on CCTA and 61% having a positive FFRCT of ≤0.80. Overall event rates were low, with myocardial infarction or all-cause mortality occurring in 0.6% of FFRCT negative patients and 1.4% of FFRCT positive patients. Patients with FFRCT ≤0.80 were threefold more likely to experience myocardial infarction, unplanned coronary revascularisation and major adverse cardiac events, although there was no demonstrable difference in all-cause mortality. In addition, lower FFRCT values were associated with an increased risk of the primary endpoint of myocardial infarction and all-cause mortality, although only two studies were available for inclusion in the meta-analysis for FFRCT values ≤0.70.

This well-performed meta-analysis effectively summarises the available research from observational studies and registries regarding the prognostic information provided by FFRCT. It also provides the basis for more research into the prognostic utility of continuous FFRCT values and the change of FFRCT values across a lesion (delta FFRCT).

The results of this meta-analysis are not entirely surprising. FFRCT is one of many measures of disease severity that can be extracted from CCTA images (figure 1). These measures are all inherently related to the presence, severity and constituents of the atherosclerotic plaque and its surrounding environment. The prognostic implications of FFRCT are therefore intrinsically related to the presence and severity of plaque and stenoses. Previous studies have identified CCTA plaque characteristics that are related to FFR measurements. Yang et al. used machine learning to show that important predictors of invasive FFR ≤0.80 included minimum lumen area, per cent atheroma volume, fibrofatty and necrotic core volume, total plaque volume, proximal left anterior descending coronary artery location and remodelling index on CCTA. 

Driessen et al. showed that positive remodelling, non-calcified plaque volume, low-attenuation plaque, spotty calcification and stenosis severity on CCTA were independent predictors of invasive FFR. This begs the question of what is driving the association between FFRCT and clinical outcome. Is it the ischaemic burden measured by the fractional flow reserve or is it mediated through the association of fractional flow reserve with adverse plaque characteristics? In the Scottish Computed Tomography of the Heart (SCOT-HEART) trial, the presence of obstructive coronary artery disease did predict outcome but it was also correlated with quantitatively assessed plaque burdens, and in multivariable models, the low-attenuation plaque burden was the best predictor of outcome independent of stenosis severity. This meta-analysis does not determine which of these many CCTA-based measures, or combination of variables, are the most important to provide accurate prognostic information. This is an important point that needs to be established in population studies involving blinded CCTA, so that we can unravel what is the most important predictor of future outcome.

Fractional flow reserve is a key technique for the assessment of flow obstruction and ischaemia to select patients for coronary revascularisation during invasive angiography. While potentially valuable for symptom relief, the prognostic utility of coronary revascularisation is now debated. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial published in 2007 found that for patients with stable coronary artery disease, percutaneous coronary intervention did not alter the risk of death, myocardial infarction or major adverse cardiovascular events compared with a management strategy.
of optimal medical therapy alone.\(^7\) The recently published International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial recruited patients with stable coronary artery disease and moderate or severe ischaemia, and showed that patients treated with an initial invasive strategy had the same 3-year risk of cardiovascular events and death compared with patients treated with an initial conservative strategy.\(^8\) Thus, although fractional flow reserve will predict risk, treating and resolving the flow obstruction and normalising the fractional flow reserve will not change this risk. The impact of the COURAGE and ISCHEMIA trials will hopefully lead to more cautious use of coronary revascularisation worldwide, and thus information on the FFR\(_{CT}\) of an individual lesion is likely to become less important than knowledge of the patient’s symptoms after treatment with optimal medical therapy.

One of the key drivers behind the adoption of FFR\(_{CT}\) in the UK is the potential to reduce the necessity for invasive coronary angiography in patients who do not require revascularisation. CCTA alone will avoid the use of invasive coronary angiograms in patients with normal coronary arteries. However, FFR\(_{CT}\) has the potential to reduce the number of patients with non-obstructive disease who undergo unnecessary invasive coronary angiography. Invasive coronary angiography and pressure wire assessment are associated with a small risk of morbidity and mortality. With this in mind, the recently published Fractional Flow Reserve-Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain (FORECAST) multicentre randomised controlled trial aimed to assess whether management based on CCTA with selected FFR\(_{CT}\) would alter cardiac resource utilisation compared with standard National Institute of health and Care Excellence (NICE) guided management.\(^9\) In 1400 patients attending rapid access chest pain clinics, Curzen \textit{et al} found that the rate of invasive coronary angiography after 9 months was indeed lower in patients whose management involved FFR\(_{CT}\) (19\% vs 23\%, \(p=0.01\)), but there was no difference in the frequency of revascularisation (14\% vs 15\%, \(p=0.69\)). In addition, there were no demonstrable differences in mean total cardiac care costs, symptoms of angina, quality of life or major cardiac or cerebrovascular events. Thus, the role of FFR\(_{CT}\) within the National Health Service is uncertain and perhaps should be reserved for patients in whom revascularisation is actively being considered after CCTA-guided optimal medical therapy provides insufficient symptomatic relief.

Our understanding of how best to diagnose and to manage coronary artery disease continues to evolve. CCTA has opened a window into the anatomy and physiology of coronary atherosclerosis that can help improve our understanding of coronary artery disease. Nørgaard \textit{et al} present a well-written meta-analysis which confirms the prognostic importance of FFR\(_{CT}\) for important outcomes, including myocardial infarction. However, FFR\(_{CT}\) is only one of the many measures that CCTA can provide and other variables, such as quantitative plaque assessment, are emerging as important prognostic indicators. We now need to identify which are the best to use for diagnosis, risk stratification and treatment decisions to enable the optimal management and outcomes for our patients.

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