



# TCT Connect 2020 Trial Update: FORECAST, COMBINE OCT-FFR and DEFINE-PCI

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## Abstract

Recent studies reported at TCT Connect 2020 have investigated a number of open clinical questions regarding the role of coronary physiology and the assessment of plaque morphology for diagnosis (FORECAST), risk stratification (COMBINE OCT-FFR) and treatment evaluation (DEFINE-PCI) of patients with coronary artery disease. In this article, the authors provide a critical appraisal of these studies and evaluate how they add to the current evidence base for management of patients with epicardial coronary artery disease. Furthermore, they discuss their potential impact on clinical practice, limitations of these studies and unanswered clinical questions that are areas for future research.

## Keywords

Trials, coronary physiology, coronary artery disease

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Recent studies reported at TCT Connect 2020 have investigated a number of open clinical questions regarding the role of coronary physiology and the assessment of plaque morphology for diagnosis (FORECAST), risk stratification (COMBINE OCT-FFR) and treatment evaluation (DEFINE-PCI) of patients with coronary artery disease (CAD). We provide a critical appraisal of these studies and their potential impact on clinical practice.

## FORECAST Trial

The UK's National Institute for Health and Care Excellence (NICE) has recommended CT coronary angiography (CTCA) as the first-line investigation for patients with suspected cardiac chest pain.<sup>1,2</sup> Recent developments now enable physiological lesion assessment in epicardial coronary arteries to be performed using computational fluid dynamic simulations based on 3D coronary arterial geometries derived from CT coronary angiograms.<sup>3,4</sup> Adoption of this technology into the routine clinical algorithm for investigation of patients with suspected cardiac chest pain has been advocated primarily on the basis of cost-effectiveness modelling.<sup>5</sup> The FFR-CT RIPCORD study of 200 consecutive patients with stable chest pain in whom CTCA was performed as a first-line non-invasive investigation for CAD evaluated the impact of the addition of FFR-CT on top of conventional CTCA analysis.<sup>6</sup> The primary endpoint was the difference between a consensus management plan derived from CTCA information versus CTCA combined with FFR-CT. The investigators showed that disclosure of FFR-CT data substantially affected the categorisation of CAD severity and changed management in 36% of patients, driven mainly by re-classifying patients from treatment with PCI to medical therapy. Analyses from this study also suggested that FFR-CT might lead to a cost saving of £214 per patient and reduce the need for invasive coronary angiography, its associated costs and potential complications.<sup>5</sup>

The preliminary data from FFR-CT RIPCORD were used to inform the design of the prospective FORECAST trial, which randomised 1,400

patients presenting to 11 UK rapid-access chest pain clinics.<sup>7,8</sup> It compared resource utilisation using an algorithm incorporating FFR-CT if a >40% stenosis was identified on CTCA (31.5%) against a conventional chest pain assessment pathway involving CTCA (60.1%), stress echocardiography (14.7%) and treadmill exercise ECG (10.0%).<sup>7,8</sup> At 9 months, the number of invasive angiograms in the FFR-CT arm was reduced by 14% compared to the reference group ( $p=0.02$ ) with 22% fewer patients undergoing invasive investigation ( $p=0.01$ ). The utilisation of non-invasive tests was also higher in the conventional arm. However, these differences did not translate to a reduction in the FFR-CT arm of per-patient resource utilisation (£1,491.46 with conventional versus £1,605.50 with FFR-CT;  $p=0.962$ ), major adverse cardiovascular events, revascularisation or improved angina class or quality of life.

While these neutral results may appear on the surface somewhat disappointing and discrepant with previous cost-effectiveness modelling, there are reasons for optimism. The reduction in referral for invasive angiography using the FFR-CT strategy, without any compromise of clinical outcomes, symptom status and quality of life, will be welcome to patients. Further analyses should help to refine the CTCA criteria which trigger referral for FFR-CT analysis and the price point at which FFR-CT can achieve cost-effectiveness. This technology is likely to form an important addition to an algorithm of initial non-invasive CTCA-driven diagnosis, risk stratification and medical therapy as demonstrated in the ISCHEMIA trial.<sup>9</sup> In other clinical scenarios, potential advantages of FFR-CT when coupled with improved CT scanning platforms are being investigated and have the potential to change practice. These include its utility in revascularisation decision-making by the heart team, as well as procedure planning of PCI.<sup>10</sup>

## COMBINE OCT-FFR Trial

Identification of patients and plaques at risk of future cardiovascular death, MI or worsening angina remains an important unmet clinical need.<sup>11</sup>

Studies using intracoronary imaging by intravascular ultrasound (IVUS),<sup>12</sup> optical coherence tomography (OCT)<sup>13</sup> and near-infrared spectroscopy-IVUS (NIRS-IVUS)<sup>14</sup> have been reported to identify lesion characteristics associated with increased future adverse clinical events. Previous studies have demonstrated that mild to moderate non-flow-limiting lesions are often responsible for subsequent MI.<sup>15</sup> Coronary lesions with FFR >0.8 and iFR >0.92 are safe to defer and lesions with FFR <0.8 have not been associated with an increased risk of death or MI.<sup>16–20</sup> Furthermore, patients with diabetes remain a high-risk group at increased risk of future MACE.<sup>21</sup>

Against this backdrop, the COMBINE OCT-FFR study was an international multicentre observational prospective study in 547 patients with diabetes presenting with either acute or chronic coronary syndromes, which evaluated whether further stratification of coronary lesions (40–80% angiographic diameter stenosis) with FFR >0.8 (n=423) according to the presence (n=98) or absence (n=292) of thin-cap fibroatheroma defined by OCT (OCT-TCFA) was associated with differences in risk of future adverse clinical events. Only two patients were lost to follow-up and evaluable OCT was acquired in 92% of cases. At 18 months, the primary composite endpoint of target lesion MACE (cardiac death, target vessel MI, clinically-driven target lesion revascularisation, or hospitalisation due to unstable or progressive angina) was significantly higher among patients with OCT-TCFA compared with those without OCT-TCFA: 13.3% versus 3.1% (HR 4.7; 95% CI [2.0–10.9], p=0.0004). The major drivers for increased MACE were clinically driven target lesion revascularisation and hospitalisation in patients with OCT-TCFA rather than the hard endpoints of death or MI.

People with diabetes are a known high-risk group. While the results of this study are certainly of interest, they do not demonstrate that additional OCT evaluation is either necessary or significantly alters their risk assessment or approach to management. Patients with diabetes require intensive guideline-directed medical therapy for blood pressure, lipid, and glycaemic control combined with antiplatelet therapy and these should be the primary goals when managing non-flow limiting coronary lesions. For instance, previous studies have shown the disease-modifying effects of intensive lipid lowering which can promote the development of increased fibrous cap thickness which can be considered a more favourable plaque morphology.<sup>22</sup> At the current time, despite the results of early studies, such as PROSPECT-ABSORB (TCTMD2020), there is no indication to consider pre-emptive percutaneous intervention of high-risk lesions defined by intracoronary imaging to reduce future clinical risk, though results from studies, such as PREVENT (NCT02316886), will provide further insights.

### DEFINE-PCI at 1 Year

In contemporary interventional practice, clinical guidelines recommend invasive wire-based coronary physiology lesion assessment using fractional flow reserve (FFR) or instant wave free ratio (iFR), to stratify revascularisation decisions for relief of symptomatic angina in patients with chronic coronary syndromes.<sup>18,19,16,20,23</sup> However, angina persists in up to 30% of patients after ‘successful’ PCI, adjudicated by angiographic criteria. Persistence of angina may be caused by stent failure, inaccurate identification of the segment of epicardial coronary disease requiring treatment resulting in residual ischaemia, incomplete revascularisation, e.g. residual chronic total occlusion, diffuse small vessel epicardial disease or coronary microvascular dysfunction.

DEFINE-PCI was a prospective study of 467 patients who had successful PCI and documented post-procedure iFR data. Twenty-four per cent of patients had residual haemodynamically significant lesions, defined as

iFR <0.90, mostly due to a focal treatable stenosis. In a post-hoc analysis, investigators identified a post-PCI iFR value of  $\geq 0.95$  being associated with fewer clinical events. The investigators now present the 1-year outcomes data for this group using an iFR  $\geq 0.95$  cutoff. At 1 year, patients with post-PCI iFR <0.95 had a rate of cardiac death, spontaneous MI, or clinically-driven target vessel revascularisation of 5.7% compared with 1.8% in those with an iFR  $\geq 0.95$  (HR 3.38; 95% CI [0.99–11.6]; log-rank p=0.04). The secondary endpoint of death or spontaneous MI occurred in 3.2% in patients with an iFR <0.95 compared to 0% in those with higher iFR values. This was a small study with a small number of events and the difference in outcomes between the two groups can only be considered hypothesis generating. The unanswered question remains as to why adverse events occur in patients with iFR values that are above the ischaemic threshold. Furthermore, the additional intervention that may be required to provide an optimised PCI by iFR may incur a risk of added procedural complication and additional cost due to increased procedure time and the need to employ additional adjunctive technologies, such as IVUS or OCT.

Previous studies have suggested the importance of intracoronary imaging guidance to optimise PCI.<sup>24,25</sup> The ULTIMATE trial randomised all-comers undergoing PCI to either IVUS-guided or angiography-guided PCI and investigated a primary outcome of target vessel failure at 12 months.<sup>25</sup> IVUS-guided PCI was superior (2.9% MACE rate) compared to angiography-guided PCI (5.4%; p=0.019). These improved outcomes with IVUS-guided PCI are durable, out to 3 years, mainly due to reduced clinically-driven target vessel revascularisation.<sup>26</sup> Similarly, the ILLUMIEN series of studies has demonstrated the benefit of OCT in PCI planning and stent optimisation.<sup>24,27–29</sup> Although ILLUMIEN I showed that OCT-driven PCI optimisation did not significantly improve post-PCI FFR ( $0.86 \pm 0.07$  to  $0.90 \pm 0.10$ ; p=0.1209), the study demonstrated that an optimal post-PCI FFR (>0.80) following OCT-guided PCI was achieved in a high proportion of patients.<sup>27</sup> Similarly, the DOCTORS study, a multicentre randomised study of 240 patients with NSTEMI undergoing PCI, also showed that OCT-guidance resulted in significantly greater FFR values compared to angiography ( $0.94 \pm 0.04$  versus  $0.92 \pm 0.05$ ; p=0.05) with a greater proportion of patients achieving a post-procedure FFR >0.90 with OCT guidance (p=0.0001).<sup>30</sup>

In our view, the current evidence base would support use of physiological lesion assessment for selection of location and length of ischaemia-causing lesions that may benefit from PCI for relief of symptomatic angina. Techniques such as iFR pullback combined with angiographic co-registration may well facilitate this strategy. The DEFINE GPS trial (NCT04451044) is an international multicentre 3,000 patient study, which will investigate whether iFR co-registration reduces target vessel failure or rehospitalisation for progressive or unstable ischaemia at 2 years. Pending the results of this study, PCI procedural optimisation may currently be guided better by an intracoronary imaging modality. New hybrid technologies that enable combined lesion morphology and haemodynamic assessment by OCT may play an important role in the future.<sup>31</sup>

### Future Directions

The studies presented at TCT Connect 2020 add to the current evidence base for management of patients with epicardial CAD. They affirm the complementary and clinically valuable information offered by coronary lesion morphology by intracoronary imaging and wire-based functional haemodynamic assessment for diagnosis, risk stratification, and treatment of symptomatic patients with atherosclerotic epicardial CAD.

These three studies highlight clinical questions that are being addressed further in ongoing randomised clinical outcomes studies. However, it should be noted that while these approaches focus on improving care for patients with epicardial coronary atherosclerosis, they largely ignore the needs of the increasingly recognised population of patients with

anginal chest discomfort of ischaemic origin caused by functional disorders of the epicardial and coronary microcirculation which can occur in both the presence and absence of epicardial coronary atherosclerosis, and who are also known to be at increased risk of future adverse events.<sup>32</sup> □

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