

## Optimal Prognostication of Patients with Coronary Stenoses in the Pre- and Post-PCI setting: Comments on TARGET FFR and DEFINE-FLOW Trials Presented at TCT Connect 2020

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### Abstract

The body of evidence for the use of coronary physiology assessments to guide percutaneous coronary intervention (PCI) has been growing continuously in recent decades. Two studies presented during TCT Connect 2020 added insights into the prognostic value of coronary physiology measurements in pre- and post-PCI settings. The first study, TARGET FFR, assessed whether a post-PCI fractional flow reserve (FFR)-guided incremental optimisation strategy (PIOS) was superior to angiography-guided PCI. The second study, DEFINE-FLOW, assessed the course of stenoses with fractional and coronary flow reserve (FFR+/CFR-) discordance when treated medically. This article summarises the main results from the TARGET FFR and the DEFINE-FLOW trials and puts them into the context of the existing literature.

### Keywords

Coronary flow reserve, coronary physiology, fractional flow reserve, intermediate stenosis, microvascular dysfunction, post-percutaneous coronary intervention, prognosis

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Controversy continues over how to evaluate the haemodynamic and prognostic relevance of intermediate coronary stenoses in the catheter laboratory. Many years before the advent of pressure-derived indices, the concept of coronary flow reserve (CFR) was introduced as a measure of the haemodynamic relevance of coronary stenoses.<sup>1</sup> However, since the DEFER and FAME trials, the field of stenosis severity evaluation has mostly been replaced by fractional flow reserve (FFR), a pressure-bound surrogate for CFR.<sup>2-4</sup> More recently, non-hyperaemic coronary pressure measurements have been introduced into clinical practice.<sup>5</sup>

Meanwhile, several large trials have proven that FFR allows prognostication of patients with angiographically intermediate stenoses and that FFR-guided percutaneous coronary intervention (PCI) is superior to PCI guided by angiography alone.<sup>6</sup> According to contemporary guidelines on chronic coronary syndromes, risk stratification using FFR is now a class 1A recommendation in patients without documented ischaemia and insufficient symptom control by medical treatment and/or a high-risk profile.<sup>7</sup>

However, despite these data and recommendations, it is still a matter of debate whether FFR should be considered the invasive gold standard for stenosis assessment, particularly considering the substantial number of patients with FFR/CFR-discordant stenoses.<sup>9-11</sup> Moreover, studies so far have failed to show a mortality benefit for FFR-guided PCI over angiography-guided PCI.<sup>12</sup> The growing body of evidence suggesting a prognostic relevance of FFR not only derived from pre-PCI measurements but also in the immediate post-PCI setting has recently been reviewed.<sup>13</sup>

In this article, we will set into perspective two studies presented during the 2020 virtual Transcatheter Cardiovascular Therapeutics congress (TCT Connect 2020, 14–18 October), which focused on post-PCI FFR (An Evaluation of a Physiology-guided PCI Optimisation Strategy [TARGET FFR]) and FFR/CFR discordance (Combined Pressure and Flow Measurements to Guide Treatment of Coronary Stenoses [DEFINE-FLOW]).

### TARGET FFR: Post-PCI FFR Ready for Clinical Use?

The first reports of a predictive value of post-PCI FFR in large patient cohorts were published almost 2 decades ago.<sup>14</sup> Since then, several retrospective and prospective studies have confirmed the association of post-PCI FFR with future cardiovascular events.<sup>15-22</sup> Different post-PCI FFR cut-off values have been proposed by these studies for optimal prognostication (most of them between 0.88 and 0.92) as well as the use of generally lower cut-off values for left anterior descending lesions.<sup>21</sup> Nonetheless, the relevance of post-PCI FFR in routine clinical practice has been debated.<sup>18</sup>

In the TARGET FFR trial presented at TCT Connect 2020, Damien Collison et al. investigated whether a physiology (post-PCI FFR)-guided incremental optimisation strategy (PIOS) was superior to angiography-guided PCI only. This study was a single-centre, investigator-initiated, randomised controlled and partly blinded trial, which enrolled patients undergoing PCI because of stable angina or non-ST-segment elevation MI between February 2018 and November 2019. The primary endpoint was the rate of

patients with an optimal post-PCI result, defined as a final FFR  $\geq 0.90$  at the end of the procedure. Secondary endpoints were the rate of patients with suboptimal final FFR  $< 0.80$ , as well as symptom improvement after 3 months assessed by the Seattle Angina Questionnaire 7 (SAQ-7) and target vessel failure during follow-up.

Initially, 721 patients consented to take part in the study. Almost 50% of participants dropped out because they were referred to the multidisciplinary team meeting (13.9%); were found to have unobstructed coronary arteries (9.8%) or FFR-negative lesions (7.6%); or a decision for either medical (12.5%) or surgical treatment (2.9%) had been made.

Of the 371 patients who proceeded to PCI, 111 were excluded for reasons such as incomplete data, meeting the exclusion criteria or technical/operational reasons. The remaining 260 patients underwent blinded post-PCI coronary physiology assessment using FFR and CFR followed by randomisation to either the angiography-guided control group or the PIOS intervention group. In patients randomised to the PIOS group, further PCI optimisation was intended if post-PCI FFR was  $< 0.90$ . This included either post-dilatation of the employed stent if a trans-stent gradient  $\geq 0.05$  was present or additional PCI if a focal FFR step  $\geq 0.05$  was detected proximally or distally of the initially treated lesion.

Patients in this study were on average 59 years old and predominantly male (87%). Patient and lesion characteristics were similar in both the control and the intervention group. In line with previous studies, Collison et al. observed suboptimal post-PCI FFR ( $< 0.90$ ) in the majority of patients. FFR pullback most frequently revealed diffuse atherosclerotic disease proximally or distally to the treated target lesion in 66% and 85%, respectively, followed by a trans-stent gradient  $\geq 0.05$  in 39% and focal lesions (proximal 7%; distal 15%). Among the 131 patients randomised to the PIOS group, 93 (71%) had a post-PCI FFR  $< 0.90$  and were thus eligible for further post-PCI FFR-guided optimisation. Eventually, PIOS was applied in only 40 patients (31%). The remaining patients were either felt to have rather diffuse disease or the operator or patient declined further optimisation. In the patients who finally underwent PIOS, FFR improved by  $0.06 \pm 0.07$  (from  $0.76 \pm 0.08$  to  $0.82 \pm 0.06$ ;  $p < 0.001$ ) and CFR improved by  $1.0 \pm 2.2$  (from  $3.0 \pm 1.6$  to  $4.0 \pm 2.1$ ;  $p = 0.02$ ).

The primary outcome (proportion of patients with final FFR  $\geq 0.90$ ) was reached in 38.1% of patients in the PIOS group compared to 28.1% in the control group. This 10% difference was statistically not significant ( $p = 0.099$ ), so the study failed to demonstrate superiority of the PIOS intervention. Regarding the secondary endpoint (proportion of patients with final FFR  $\leq 0.80$ ), a significant result in favour of the PIOS intervention was observed (18.6% versus 29.8%;  $p = 0.045$ ). No difference was found regarding the change in symptom severity 3 months after PCI. During a mean follow-up of  $1.7 \pm 0.9$  years, only a single event of target vessel failure was observed (PIOS group). In the as-treated analysis, Collison et al. observed a significant increase in FFR and CFR in patients in whom PIOS was actually performed.

These results have several implications.

First, they demonstrate how challenging it is to conduct randomised coronary physiology/interventional studies, as the intervention could be performed in only 31% of patients randomised to the PIOS group because of the above-mentioned reasons (diffuse atherosclerotic disease and physician/patient preference). In the sample size calculation, a substantial difference between intention-to-treat and as-treated because of the

absence of a target for additional optimisation measures was already expected in 60% of patients, which was even surpassed in the actual trial (69%).<sup>23</sup> In addition, the investigators aimed to detect a 20% difference between groups regarding the primary endpoint.<sup>23</sup> With regards to the p-value of 0.099 of the primary analysis, one can conclude that: the initially assumed effect of the intervention (PIOS) on final FFR was overestimated; and the study was underpowered considering the low rate of actual PIOS interventions performed.

Second, the results of the secondary endpoint analyses are clinically much more relevant than the primary endpoint question regarding clinical value of post-PCI FFR measurements. The follow-up data demonstrate that this is a low-risk setting, given the an annual cardiovascular mortality in the overall study population was as low as 0.22%. Moreover, as described in the study design paper, the authors sought to eventually reduce the number of patients with persistent (or recurrent) symptoms after PCI by minimising suboptimal PCI results. With regards to the presented SAQ-7 results at 3 months, which show no difference between the PIOS and the control groups, clinicians should bear in mind that other mechanisms of post-PCI angina might be more relevant than suboptimal PCI results, such as disorders of vasomotor function including microvascular and vasospastic disease or structural alterations of the microvasculature accompanying diffuse epicardial disease.<sup>24,25</sup> Finally, we need to acknowledge the additional procedural details – i.e. the longer procedure duration and fluoroscopy time, as well as higher contrast and adenosine doses with side-effects in the PIOS group.

Nonetheless, additional data in the field of post-PCI FFR are most welcome and will be provided e.g. by the ongoing FFR REACT trial that evaluates a potential benefit of high-definition intravascular ultrasound-guided PCI optimisation in patients with a post-PCI FFR  $< 0.90$ .<sup>26</sup>

### DEFINE-FLOW: Renaissance of Coronary Flow Reserve in Guiding PCI?

As mentioned at the beginning, there is an ongoing controversy over whether the pressure-derived FFR or the original flow-derived CFR should be considered the gold standard for invasive assessment of epicardial coronary stenosis severity.<sup>10,25</sup>

The DEFINE-FLOW trial, which was presented at TCT 2020 by Nils Johnson, was a sponsor-initiated multicentre trial that was designed to investigate the natural course of patients with angiographically intermediate coronary stenoses and discordant FFR/CFR results. The hypothesis of this non-inferiority study was that patients with an epicardial stenosis with FFR  $< 0.80$  and CFR  $> 2.0$  (FFR+/CFR-) have a similar favourable prognosis as patients with concordant normal results of FFR  $> 0.80$  and CFR  $> 2.0$  (FFR-/CFR-) when treated medically.

The rationale behind this hypothesis is that patients with a pathologic FFR  $< 0.80$  yet a normal CFR  $> 2.0$  have an intact coronary microvasculature. When challenged with adenosine, this healthy microvasculature dilates maximally, leading to an adequate increase in coronary blood flow. The physiological hyperaemic coronary blood flow response results in a high pressure drop across the stenosis, resulting in a pathologic FFR value despite preserved CFR. Hence, FFR may overestimate the haemodynamic relevance of the stenosis in this group of patients.

The primary endpoint of the study was a combined major adverse cardiovascular event endpoint, including all-cause death, MI and PCI or

coronary artery bypass graft (CABG), and the follow-up period was 2 years. The secondary endpoint was target vessel failure, which included MI and repeat PCI or CABG of the target vessel.

Of the 455 enrolled patients with angiographically intermediate ( $\geq 50\%$  diameter) coronary stenosis, 430 were treated according to the study protocol. Patients were on average 67 years old, predominantly men (74%) and every other patient was already taking two or more anti-anginal drugs at enrolment. Patients were allocated to four groups according to the results of the coronary physiology assessment (FFR-/CFR-: n=207 patients with 236 lesions [44%]; FFR-/CFR+: n=108 patients with 123 lesions [23%]; FFR+/CFR-: n=74 patients with 74 lesions [14%]; FFR+/CFR+: n=94 patients with 100 lesions [19%]). FFR+/CFR+ patients underwent revascularisation while all other patient groups did not undergo revascularisation and were treated medically.

The lowest rate of the primary endpoint was observed in patients with concordant normal FFR/CFR results (FFR-/CFR-), while the highest rate was observed in patients who had concordant pathological results (FFR+/CFR+) despite undergoing revascularisation. Interestingly and contrary to the hypothesis of the investigators, the 'natural course' of medically treated patients with pathological FFR but normal CFR (FFR+/CFR-) was not non-inferior to the FFR-/CFR- group, with a difference in event rates of 5%, i.e. event rates of 10.8% versus 5.8%, respectively ( $p=0.065$  for non-inferiority). Instead, the Kaplan-Meier curve for FFR+/CFR- rather parallels the curve for FFR-/CFR+, both ranging between the two FFR/CFR concordant groups.

Regarding the secondary endpoint of 'target vessel failure', the FFR+/CFR- group even had the numerically highest rate of events during the 2-year follow-up period, although it must be taken into account that all FFR+/CFR+ patients did undergo PCI as per protocol. Using a time-to-failure Cox mixed effects model, the authors found that FFR was a highly significant continuous predictor for events (HR  $<0.01$ ;  $p=0.0067$ ), while CFR was no significant predictor (HR 0.74;  $p=0.44$ ).

These results can be interpreted as a throwback for CFR in the battle against FFR for the gold standard of epicardial stenosis assessment. However, we need to keep in mind that there was no comparator arm of patients with FFR+/CFR- patients who underwent PCI, which must be considered the current standard of care, and we do not know what the prognosis of this group would have been. Conversely, it would have been interesting to see how PCI would have impacted on the prognosis in patients with FFR-/CFR+; however, this was also not part of the study design.<sup>27</sup>

Generally, in the current post-ISCHEMIA era, we need to acknowledge that the indication for PCI in chronic coronary syndromes with proof of ischaemia (excluding left main stenosis and a left ventricular ejection fraction  $<35\%$ ) is symptom control rather than the prevention of hard clinical endpoints.<sup>28</sup> Therefore, it is reasonable to question whether

future studies on chronic coronary syndromes should not be designed based on soft primary endpoints such as symptoms. In addition, the distribution of primary endpoint events (death, MI, any PCI/CABG) and whether they can be attributed to the untreated lesions or were driven by *de novo* lesions have not yet been reported by the investigators. The detailed results that will follow with the publication of the study will also hopefully give more insights into 'softer' endpoints of patients depending on their FFR/CFR status.

Moreover, the following aspects should be taken into account when interpreting the results of the DEFINE-FLOW study:

- Compared to patients with FFR-/CFR+, the event rate in patients with FFR+/CFR- was numerically lower. This could point towards the fact that the FFR in the FFR-/CFR+ group was at least in part false negative. Especially in patients with concomitant microvascular disease, disturbed autoregulation may prevent maximal vasodilatation in response to adenosine. Studies have shown that this may lead to higher and thus in some cases negative FFR values.<sup>29</sup>
- When analysing the differences between patients with FFR-/CFR- and those with FFR+/CFR- more detailed information regarding resting flow and flow under maximal hyperaemia is needed. Although CFR was  $>2.0$  in both groups, the absolute flow values may still be statistically different. This could at least in part explain the different results between the two groups.
- The observed difference in outcome between the patients with FFR-/CFR- and FFR+/CFR- may also be explained by differences in coronary microvascular resistance. Although hyperaemic microvascular resistance was most likely assessed during the invasive procedures in the DEFINE-FLOW study, these values have not yet been reported. However, increased microvascular resistance – despite a CFR of  $>2.0$  – may be a marker for adverse outcome.

Taking the findings together, the study should be seen as hypothesis generating. Despite the non-significant results, the good news is that the trial proves the feasibility of a multicentre study focusing on intracoronary Doppler flow measurements, which is the base for future coronary physiology studies that will probably focus more on coronary microvascular disease than on obstructive epicardial disease.

### Conclusion

The field of invasive coronary physiology assessments is continuously moving forward. The data from TARGET FFR show that post-PCI FFR is not yet ready for use in daily clinical practice. The DEFINE-FLOW study has shown excellent feasibility of a multicentre study using a combination of intracoronary Doppler flow and pressure measurements. It has opened avenues for new coronary physiology research aiming at comprehensive assessments of the epicardial coronary arteries as well as the coronary microcirculation. However, its results also indicate that PCI of lesions with pathological FFR values is currently still the way to go. □

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