Invited Commentary on FAME 3 Trial for Cardiovascular Research

“FAME3: good science, bad reception?”

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When the Fractional Flow Reserve–Guided PCI as Compared with Coronary Bypass Surgery (FAME3) trial was presented and published in November 2021 [1], it stimulated considerable debate. This was partly because the result did not fit with the expectations of some clinicians. However, the FAME3 trial is just like any other scientific experiment, which asks a valid question and designs the methodology to address a hypothesis as objectively as possible. The reaction to FAME3 included many theoretical explanations for the “failure” of the experiment. Such activity can be valuable in sponsoring further hypotheses, even if the experiment had not actually failed in any way.

FAME3 is a meticulously designed, well conducted multicentre, randomised trial whose aim was to compare (a) multivessel percutaneous coronary intervention (PCI), using contemporary drug-eluting stents and guided by fractional flow reserve (FFR) measured using an intracoronary pressure wire, with (b) coronary artery bypass graft (CABG) surgery. It randomised patients with >50% stenoses in all 3 main coronary arteries, but not the left main, to either FFR-directed PCI (n=757) or to CABG (n=743). It is important to appreciate that patients had to be deemed suitable for both modes of revascularisation. The primary endpoint was a composite of death, myocardial infarction, stroke and repeat revascularisation at 1 year and occurred in 10.6% of PCI patients versus 6.9% in the CABG group (hazard ratio 1.5, 95% CI 1.1-2.2, p=0.35 for non inferiority).

Thus, the headline result is that FFR-guided PCI did not meet criteria for non inferiority in patients with 3 vessel disease when compared with CABG surgery. In common with all clinical trials, there are a variety of criticisms/mitigating features that may help to explain this result, which we will explore later. Nevertheless, the most plausible explanation for this finding is that CABG surgery is indeed a more clinically effective treatment than multivessel PCI, *in patients who are suitable for both types of revascularisation*. Although unpopular with some, this explanation is the most logical and is consistent with previous evidence. In particular, the Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three vessel or left main coronary artery disease: 10 year follow up of the multicentre randomised controlled SYNTAX trial (SYNTAXES) study assessed the 10 year survival status of patients in the original SYNTAX cohort of 1800 patients [2]. Vital status information at 10 years was available for 93% & 95% of the PCI and CABG patients respectively, and, overall, there was no difference between the groups (248 (28%) of PCI and 212 (24%) of CABG patients had died; p=0.066). However, in the subgroup with 3 vessel disease 151 of 546 (28%) had died in the PCI group compared with 113 of 549 (21%) in the CABG group; HR 1.41 (95% CI 1.10-1.80).

The result of FAME3 is also consistent, in some ways, with the findings of several other randomised trials. RIPCORD2 is an 1100 patient multicentre randomised trial that assessed the benefit of routine systematic FFR assessment of all epicardial coronary arteries of stentable or graftable diameter at the stage of diagnostic angiography [3]. Patients, who had either stable coronary disease or non-ST elevation MI, were randomised to either (a) angiographic assessment alone or to (b) angiography plus FFR measurement of all epicardial vessels (median vessels = 4). The co-primary endpoints were resource utilisation and quality of life at 1 year, and there was no significant difference between the groups. Prespecified secondary endpoints included major adverse cardiac events (all-cause mortality, myocardial revascularisation, stroke and unplanned revascularisation), and, again, there was no significant difference. The conclusion was that routine systematic FFR assessment of all significant coronary arteries did not yield any advantage over angiography alone. These results are consistent with those of the FUTURE trial, which had a similar design but was terminated early [4]. Finally, the FLOWER MI trial [5] also holds some relevance to the FAME3 discussion. In FLOWER MI, 1171 patients with ST elevation MI, in whom the infarct-related artery had been treated with primary PCI, and who had bystander disease in non-infarct arteries, were randomised to have angiogram-only guided PCI or angiogram- and FFR-guided PCI. At one year, there was no significant difference in the composite primary endpoint (all cause death, non fatal MI and unplanned hospitalisation leading to urgent revascularisation).

In all these trials, routine physiological assessment of the coronary circulation failed to show any overall clinical advantage compared to angiographic assessment alone. It is this that makes their findings relevant to an analysis of FAME3… the very novelty of the FAME3 test arm (as a comparator with CABG) was that the multivessel PCI was FFR-guided, as it had been in the original FAME and FAME2 trials, in distinction to SYNTAX in which multivessel PCI was angiogram-guided. FAME3 therefore also raises important questions about the role of routine physiological assessment of coronary disease. The outcome for all these trials is, to some extent, counterintuitive. Many of us have been brought up on the evidence that patient- and vessel-specific ischaemia is the most important determinant of clinical outcome in patients with coronary atheroma. Whilst there is no doubt that ischaemia is indeed associated with future clinical events, increasingly the evidence suggests that the burden of atheroma is a better predictor of events. Thus, for example, *post hoc* analyses of both the PROMISE [6] and ISCHEMIA [7] trials have demonstrated that the burden of atheroma is superior at predicting events in these populations than the burden of ischaemia. These observations may go some way to explain the results of FAME3, RIPCORD2, FUTURE and FLOWER MI?

There has been detailed discussion about whether some features of the design and methodology of FAME3 could explain the negative overall result. Firstly, that FFR could only be performed in 82% of vessels, mainly because of the inclusion of chronic total or subtotal occlusions. It is unclear to what extent the latter lesions were successfully revascularized in the PCI group. Secondly, that the use of intracoronary imaging was only 11.7% in the PCI group. Given the extensive data from both randomised trials and observational studies showing outcome benefit in image-guided, compared to angiogram alone-guided, PCI it is plausible that routine use of intracoronary imaging could have improved the outcome in this group… although that would, of course, be a different randomised trial entirely! Finally, there is the concept, as yet unproven, that the outcome in the PCI group would have been significantly better had operators routinely checked the FFR result at the angiographic end of the procedure. There has been circumstantial evidence for many years that there is an inverserelationship betweenthe post PCI FFR in a vessel and the subsequent rate of major adverse cardiac events [8]. Most recently, the DEFINE PCI study demonstrated that 24% of angiographically completed PCI vessels were still in the ischaemia range (using iFR<0.89) [9]. Importantly, a substantial proportion of these vessels could be moved into the non-ischaemic range by further imaging-directed intervention. The ongoing international randomised trial, DEFINE GPS, is formally assessing the concept that post PCI iFR assessment and directed therapy can improve patient outcomes, which, if positive, would have profound implications for routine PCI practice.

Whilst disappointing to some clinicians, FAME3 was a meticulously conducted clinical experiment that yielded a clear result. However, based upon the results of DEFER, FAME and FAME2, which had demonstrated the profound benefit of FFR-guided PCI versus angiogram guidance alone, it seems plausible to speculate that the PCI group in FAME3 would have had significantly worse outcomes than they did if they had not had FFR measurement. Furthermore, the result of FAME3 does not mean that there is no benefit for routine physiological assessment of coronary vessels in the management of patients with chest pain: after all, 24% of lesions were deferred after FFR measurement in the trial! In fact, the potential value of knowing about the physiological significance of coronary disease in a specific patient is being suggested by a number of studies. For example, the use of FFRCT at multidisciplinary meetings to choose patients for CABG surgery, who may never undergo invasive angiography [10], and the clear cut efficiency of FFR-directed multivessel PCI compared to angiographic guidance alone.

The result of FAME3 is probably explained by clinical outcome superiority of CABG surgery in patients with multivessel disease, at least of a more complex variety (all but low SYNTAX tertile patients). This is not a “defeat” or “win” for one modality versus another: rather it helps us inform the shared decision-making process that we lead with our patients and their relatives.

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