Fractional flow reserve measurements to identify justified targets for PCI in patients with stable angina: FAME 2 and beyond

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During the past decades, percutaneous coronary intervention (PCI) has become an important, widely applied therapeutic approach for the treatment of patients with symptomatic coronary artery disease and angiographically significant coronary obstructions. While the indication for PCI in the setting of acute coronary syndromes is established very well (1), there is an ongoing debate about the role of PCI in patients with ischemic heart disease and stable symptoms.

The doubt whether PCI in patients with stable coronary artery disease may be useful is based on studies such as the randomized COURAGE trial, which is the largest and most cited study in this field (2). In COURAGE, 2,287 patients with objective evidence of ischemia and significant coronary artery disease (defined by an angiographic stenosis >70% in at least one epicardial coronary artery) were randomly assigned to PCI plus optimal medical therapy (PCI-group) versus optimal medical therapy alone (medical-group). After 4.6 years of follow-up, there was no significant difference in the composite primary endpoint of death and non-fatal myocardial infarction (MI) between both groups. That result in conjunction with concerns about the rising costs of the health care system has fed a lively debate about the sense of widespread application of PCI in patients with stable angina. PCI as a treatment strategy for patients with stable symptoms was recently even declared to be an "expensive placebo for pain control" (3).

The recent publication of the FAME 2 trial has shed new light on the discussion of this issue (4). In contrast to previous studies, in which the evaluation of the extent of coronary artery disease was based on visual assessment of lesion severity, the FAME 2 investigators differentiated between significant, i.e. ischemia-inducing, and non-significant lesions by performing fractional flow measurements (FFR) with a pressure guide wire following coronary angiography. In fact, FAME 2 stands in the tradition of previous FFR-based PCI studies such as DEFER and FAME 1, which showed the benefit of deferring PCI in lesions with non-significant FFR and routinely using FFR in PCI patients with multi-vessel coronary disease to improve outcome (5,6). The primary hypothesis of FAME 2 was that PCI of significant lesions, based on FFR measurements, would reduce the incidence of death, MI, or urgent revascularization, as compared to the control group treated by optimal medical therapy alone. This randomized, multi-center trial in an all comer setting was initially designed to enroll a total of 1,632 patients with symptomatic ischemic heart disease and at least one significant coronary lesion based on FFR. An independent data safety and monitoring board stopped the trial prematurely after the enrollment of 888 patients because of a "highly significant difference in the incidence rates of the primary endpoint between the PCI and medical therapy groups". Although there were no differences in the "hard endpoints" death and MI, an 8-fold higher rate of urgent revascularization was noted in the medical therapy group as compared to the PCI group (11.1% *vs.* 1.6%; hazard ratio 0.13; 95% CI: 0.06-0.30). In addition, patients treated by FFR-justified PCI had significantly less severe angina pectoris and used less anti-anginal drugs than patients of the medical treatment group.

FAME 2 has provided evidence that PCI is a safe and effective therapeutic approach to obtain symptom relief and to decrease the rate of urgent revascularizations in patients with stable coronary artery disease (4). Nevertheless, it may be debatable whether the premature stop of patient enrolment, induced by the data safety and monitoring

board, was truly indispensable, as the difference between treatment groups was related to a relatively "soft" endpoint (rather than death or MI).

There are significant differences between FAME 2 and previous trials such as COURAGE. In the COURAGE trial (2), which enrolled patients between 1999 and 2004, 90% of the PCI patients were treated with bare metal stents, 3% with drug-eluting stents (DES), and 7% with balloon angioplasty only. This explains the high repeat revascularization rate of 21% in the PCI group, which certainly does not reflect current experience. During the last decade, PCI equipment, techniques, and co-medication have been improved, including the current use of contemporary DES in more than 90% of procedures. In FAME 2, all PCI patients were treated with second-generation DES. In addition, FAME 2 reflects the current practice of an increased use of FFR in most PCI centers. Earlier FFR studies such as DEFER and FAME 1 already indicated the important role of FFR measurements in the process of identifying justified targets for PCI procedures (i.e. lesions that can induce myocardial ischemia) (5,6). As a matter of fact, the era of purely visual assessment of lesion severity started to decline several years ago. Therefore, the COURAGE trial does not reflect the contemporary invasive assessment of coronary disease, as being performed by many interventional cardiologists, while FAME 2 does.

However, there are also some limitations of FAME 2 that warrant further discussion. For instance, FAME 2 has a non-blinded study design. Cardiologists who followed the study patients in the outward clinic were aware of the results of the FFR measurements and the consecutive treatment. We cannot exclude that this information might have influenced consecutive treatment decisions, as it is conceivable that patients from the medical therapy group when presenting with recurrent angina might more easily be referred for PCI rather than being treated by an increase in medical regimen. Nevertheless, in FAME 2 urgent revascularization was initiated in almost half of the patients by an acute coronary syndrome, defined by an increase in cardiac markers or evidence of ischemia on ECG (4 patients in the PCI group and 23 patients in the medical therapy group; P<0.001), and these are objective criteria that are independent of any potential bias of referring physicians.

The mean follow-up period of FAME 2 was only 7 months, as the trial was prematurely stopped after 20 months. One may argue that, in many patients, the short follow-up period did not permit the development of restenosis, which could otherwise have diminished the difference in rate of urgent revascularization between both treatment groups. However, the cumulative incidence curves of urgent revascularizations show that the difference in event rates between treatment groups was even more pronounced after a follow-up of one year compared to a shorter period of follow-up. In addition, recent randomized trials with drug-eluting stents in "real world" patient populations, as for instance the TWENTE trial (7), demonstrated very low rates of symptomatic restenosis and target lesion revascularization procedures. As a consequence, one may assume that even slight increases in the rates of restenosis and reintervention, which might be expected in the case of a longer follow-up of FAME 2, would have had little impact on the observed difference in urgent revascularization rate between the two treatment groups of FAME 2.

In coronary artery disease, the presence and extent of inducible ischemia is the most important factor related to outcome (8). Whereas non-invasive functional tests may be suitable in single-vessel disease, their application becomes limited in multi-vessel disease. However, more than half of the patients who present with an acute MI show multi-vessel disease on angiography. In patients who acutely underwent a (primary) PCI of the infarct-related artery but have residual lesions in other vessels, the ideal consecutive strategy is not well established, as in this particular field there is a lack of data from prospective randomized trials (9). Possible strategies range from a conservative approach, using medical therapy after primary PCI and performing the revascularization of residual lesions only in symptomatic patients and/or if ischemia has been proven, to a more aggressive approach with staged revascularization of all remaining lesions. FFR measurement in residual lesions may help the cardiologist (or heart team) to make a rational decision. Whether such FFR measurements are performed in the setting of primary PCI or in a secondary procedure will depend upon various factors such as the hemodynamic stability of the patient, the amount of contrast medium used, the duration of the procedure, and other local logistics. There is, however, good evidence that FFR measurements in non-culprit vessels, obtained at the end of a primary PCI, provide valuable, reliable insight in the ischemic potential of residual lesions (10), which will reduce the need for additional tests.

Recently, significant developments have been made in the field of FFR measurement. A novel non-invasive, multi-slice CT-based technique has yielded promising results, based on the adjunction of blood flow analysis to three-dimensional coronary arterial reconstructions (11). Direct comparison of conventional (invasive) FFR and CT-based FFR showed

a reasonable correlation (12). Nevertheless, the question of whether multi-slice CT-based FFR assessment may ever be able to equal the diagnostic accuracy of invasive FFR measurement can only be answered by future clinical trials. In addition, invasive FFR measurement may in the future be facilitated by other recent improvements, such as the use of wireless techniques, and novel FFR analysis techniques that do not require the use of hyperemia-inducing drugs (13).

In conclusion, FAME 2 has combined the highly reliable and discriminative FFR approach for ischemia testing with contemporary state-of-the-art PCI techniques. The study has demonstrated that invasive FFR measurement identifies justified targets for PCI which was shown to be safe and effective in relieving symptoms and decreasing the rate of urgent revascularizations in patients with stable coronary artery disease. Longer-term follow-up data of the FAME 2 patient population are awaited with much interest.

Acknowledgements

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