Interventional Cardiology

Clinical outcome benefit associated with fractional flow reserve guided angioplasty, but is it 'one size fits all'?

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FAME 2: 2-year results

De Bruyne B, Fearon WF, Pijls NHJ *et al.* Fractional flow reserve-guided PCI for stable coronary artery disease. *N. Engl. J. Med.* 371, 1208–1217 (2014).

Trials comparing medical therapy with percutaneous coronary intervention (PCI) for stable coronary artery disease have not demonstrated a prognostic benefit [1,2]. However, previous trials have not confirmed the hemodynamic significance of treated stenoses. This may have led to the inappropriate stenting of nonflow-limiting lesions with the PCI-associated risks and negligible benefit. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation II trial, compared whether PCI plus medical therapy would be superior to medical therapy alone in patients with stable coronary artery disease and pressure wire confirmed functionally significant stenoses. The trial was stopped prematurely and reported early because of an excess of urgent revascularization in the medical therapy arm [3]. The current paper reported the prespecified primary outcome of major adverse cardiac events (MACE) at 2 years.

At least one stenosis in a major coronary artery with an fractional flow reserve (FFR) of ≤0.80 was identified in 888 patients who were randomized to undergo FFR-guided PCI plus medical therapy or to receive medical therapy alone. These patients had 1601 stenoses which were considered eligible for treatment with a mean FFR of 0.64 ± 0.13. The primary outcome, a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization within 2 years occurred in 8.1% of the PCI group versus 19.5% in the medical therapy group (HR: 0.39; 95% CI: 0.26–0.57; p < 0.001). This was largely driven by a difference in urgent revascularization: 4.0% in the PCI group and 16.3% in the medical therapy group. Critics of the study have noted that physicians were not blinded to the treatment allocation and that 9.8% of the medical therapy group underwent urgent revascularization without confirmatory objective evidence of ischemia, compared with only 0.7% in the PCI group.

There was no statistically significant difference in death, myocardial infarction or their composite identified between groups. However, a landmark analysis that blanked the first 7-day period after randomization (and therefore excluded the contribution of stent-induced MI 4a) showed that patients undergoing PCI had a 44% relative risk reduction for the composite of death or myocardial infarction (4.6 vs 8.0%; HR: 0.56; 95% CI: 0.32–0.97; p = 0.04).

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 trial has demonstrated superior outcomes for PCI and medical therapy over medical therapy alone, largely driven by a difference in urgent revascularization. However, a significant proportion of the medical therapy group had urgent revascularization arranged by unblinded physicians in the absence of objective evidence of ischemia. Nevertheless, the results of the current analysis support the concept that when the immediate risks of the procedure are offset, a reduction in ischemic burden afforded by PCI is associated with improved prognosis.

Incremental prognostic value of fractional flow reserve

Johnson NP, Tóth GG, Lai D *et al.* Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J. Am. Coll. Cardiol.* 64(16), 1643–1654 (2014).

Randomized trials of FFR guided revascularization have used a fixed treatment threshold of

Future Medicine part of fsg

either <0.75 or ≤0.80 [3–5]. However, FFR is a continuous variable that may also quantify the burden of ischemia. Revascularization by either PCI or coronary artery bypass graft surgery carries a small risk, which may be offset if there is concomitant relief of ischemia. The authors sought to investigate whether FFR provided an independent and continuous marker of future clinical outcomes by using a retrospective meta-regression approach. They assessed if FFR could stratify the prognostic significance of a coronary stenosis and if the post-PCI FFR was also predictive of subsequent events.

A systematic literature review identified 51 studies comprising 8418 patients in which FFR was measured and clinical outcomes were reported with a minimum follow-up duration of 180 days. The study level meta-analysis and meta-regression were undertaken in addition to a collaborative patient-level meta-analysis including 37 studies and 6061 patients. They found that there was a continuous inverse relationship between FFR and 12-month MACE rate in medically managed patients. The same regression analysis on the group receiving revascularization showed a weaker relationship with initial FFR. The regression lines diverged as FFR decreased suggesting that the net benefit of revascularization increased as FFR decreased. In theory, the point at which the two regression lines cross predicts the tipping point at which net benefit of revascularization becomes net harm and an appropriate FFR treatment threshold. This value was predicted as 0.75 for the study level meta-regression and 0.67 for the patient level Cox-regression. In 966 patients, in whom FFR was measured post-PCI, a significant inverse relationship between post-PCI FFR and MACE rate was also demonstrated.

This study supports the concept that ischemic burden quantified by FFR is continuously and inversely related to adverse clinical outcomes. This not only applies to patients who are managed medically; the same relationship was also seen with post-PCI FFR. Importantly, the study results support the principle that any net benefit of revascularization is dependent on the degree of ischemia reduction offset against the risk of revascularization. Caution should be employed in overinterpreting the FFR/normalized MACE regression coefficients that may have been confounded by skewed data. Although this was compensated for statistically, the authors rightly point out that the threshold values for the crossover point between net benefit and net harm of revascularization should not redefine the current FFR-treatment threshold.

Long-term clinical outcomes for patients with discordant fractional flow reserve and coronary flow velocity reserve

van de Hoef T, van Lavieren MA, Damman P *et al.* Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ. Cardiovasc. Interv.* 7, 301–311 (2014).

The use of FFR to establish the presence of inducible ischemia and guide revascularization using a treatment threshold of ≤0.80 has become established practice and is supported by the results of randomized trials [5–6]. The coronary flow velocity reserve (CFVR) is a Doppler-based means of assessment of inducible ischemia by measuring vasodilatory reserve and has a similar diagnostic accuracy to FFR [7]. However, FFR and CFVR correlate only modestly and their prediction of ischemia is frequently discordant [8]. This study aimed to establish the hemodynamic characteristics associated with discordance of FFR and CFVR. They also compared long-term clinical outcomes of patients with discordant FFR/CFVR results in whom PCI had been deferred, with normal controls.

A total of 157 patients with FFR and CFVR assessment of an intermediate lesion in whom PCI was deferred were identified retrospectively. Using the established FFR treatment threshold of ≤0.80, 36.9% of stenoses had discordant FFR/CFVR results: 30.6% had an FFR of ≤0.80 and CFVR >2.0, and 6.4% had an FFR >0.80 and CFVR of ≤2.0. The baseline microvascular resistance was low in the concordant abnormal group (FFR ≤0.80/CFVR ≤2.0) with vasodilatatory auto regulation compensating for a severe epicardial stenosis. However, in the discordant abnormal group (FFR ≤0.80/CFVR >2.0) baseline microvascular resistance was high, although a similar hyperemic microvascular resistance was achieved, elevating the CFVR.

Compared with the concordant normal group (FFR >0.80/CFVR >2.0), the (albeit small) discordant normal group (FFR >0.80/CFVR ≤2.0) with microvascular disease had a large excess of major adverse cardiac events (10-year MACE: 28 vs 80%, relative risk: 2.8 (1.8–4.6), p < .001). Perhaps surprisingly, no statistically significant difference in 10-year MACE was demonstrated between the concordant normal (FFR >0.80/CFVR >2.0) and the discordant abnormal (FFR ≤0.80/CFVR >2.0) groups (10-year MACE: 28 vs 40%; relative risk: 1.4 [0.9–2.4]; p = 0.13).

This study raises an interesting possibility that while the use of FFR to guide angioplasty with a threshold of ≤0.80 seems to work on a population level [5–6], there may be a subset of patients who are currently treated on the basis of an FFR ≤0.80 in whom angioplasty is best deferred. Long-term outcomes among this population will be further clarified by the DEFINE-FLOW study [9], a single arm prospective study where after assessment of an intermediate lesion with FFR and CFVR, only lesions with concordant abnormal results

(FFR ≤0.80/CFVR ≤2.0) will undergo PCI, the discordant groups will be managed medically and outcomes compared with the concordant normal group.

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