

# Ischemia-guided percutaneous revascularization

**Abbreviations:** SCAD, stable coronary artery disease; PCIs, percutaneous coronary interventions; CABG, coronary artery bypass graft; MACCE, major adverse cardiac and cerebrovascular events; FFR, fractional flow reserve

## Opinion

Revascularization therapy for stable coronary artery disease (SCAD) guided by induction test of ischaemia is one of the principal hot topics in the actual guidelines. The presence and extension of inducible ischemia is one of the most important factors related to bad outcome.<sup>1</sup> In patients with SCAD, a number of studies have analysed the role of ischemia-guided percutaneous revascularization, either by non-invasive or invasive methods. Non-invasive imaging studies with exercise echocardiography suggest that treatment of non ischemic coronary lesions may be safely deferred with an annual estimated incidence of death or MI of 0.6%, as reported in the meta-analysis of Meltz et al.<sup>2</sup> The study of Hachamovitch et al.<sup>3</sup> emphasized the relationship between inducible ischemia on SPECT and the presence of short-term survival benefits with early revascularization vs. medical therapy. Revascularization was associated with a reduction in mortality for patients having moderate to severe ischemia. The cut-off level of ischemic myocardium, assessed by summed stress scores, to predict lower mortality using revascularization was approximately 10-12.5%.<sup>3</sup> Kim et al.<sup>4</sup> supported the benefit of ischemia-guided revascularization with myocardial perfusion imaging for patients with multivessel coronary artery disease. The outcomes of ischemia-guided revascularization were retrospectively compared with those of non ischemia-guided revascularization in a registry of 5,340 patients with multivessel coronary disease comprising 2,587 percutaneous coronary interventions (PCIs) with drug-eluting stents and 2,753 coronary artery bypass graft (CABG) surgeries. The incidence of major adverse cardiac and cerebrovascular events (MACCE) was significantly lower in the ischemia-guided than in the non ischemia-guided group, primarily driven by the lower repeat revascularization rate. Subgroup analysis showed that ischemia-guided reduced the risk of MACCE in PCI but not in CABG patients.<sup>4</sup> Several diagnostic modalities are available for use as tools to establish the initial diagnosis, assess disease severity, and select the appropriate treatment strategy in symptomatic patients suspected of having SCAD. In relation to this point, a multicenter study performed in Japan hypothesise that the choice of the initial diagnostic test might influence the treatment strategy. They showed that patients receiving initial SPECT had a lower rate of revascularization than those receiving coronary angiography.<sup>5</sup>

In relation to invasive methods assessing ischemia, fractional flow reserve (FFR) is considered nowadays the elective way for invasive assessment of physiological stenosis significance and a decisive tool for decision making in coronary revascularization. The recently published ESC guidelines on the management of stable coronary artery disease endorse the use of FFR for risk stratification. FFR is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperaemia. A normal value for FFR is 1.0. Stenoses with a FFR >0.80 are hardly ever associated with exercise-induced ischaemia.<sup>6</sup> The principal utility of FFR is in certain situations when it is not clear whether an intermediate angiographic lesion causes ischemia. The use of FFR in the catheterization laboratory accurately identifies which lesions should be revascularized and improves the

Volume 4 Issue 2 - 2015

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**Received:** November 30, 2015 | **Published:** December 01, 2015

outcome in most elective clinical and angiographic conditions, as compared with the situation where revascularization decisions are simply made on the basis of angiographic appearance of the lesion.<sup>7</sup> The DEFER study evaluated the 5-year outcomes in 325 patients assigned to 3 groups: deferred group (FFR  $\geq 0.75$  without PCI), PCI group (FFR  $\geq 0.75$  with PCI), and a control group (FFR <0.75 with PCI). 5-year event-free survival rates were similar in the deferred and PCI groups, with a risk of cardiac death or MI in patients with normal FFR inferior to 1% per year.<sup>8</sup> FAME study evaluated angiography-guided versus FFR-guided percutaneous revascularization in patients with multivessel disease. Routine measurement of FFR in patients with multivessel coronary artery disease who were undergoing PCI with drug-eluting stents significantly reduced the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularization at one year of follow up.<sup>9</sup> The 2-year outcome report of the FAME study supported the safety of deferring PCI for non ischemic lesions.<sup>10</sup> Of interest, a sub analysis of the FAME study also showed that angiography is inaccurate in assessing the functional significance of a coronary stenosis when compared with the FFR in the 50% to 70% category but also in the 70% to 90% angiographic severity category.<sup>11</sup> The FAME-2 trial tested the benefits, for SCAD, of FFR-guided PCI plus optimal medical therapy with optimal medical treatment alone. PCI group had significant lower rate of primary endpoint event: death, MI, or urgent revascularization. Also there was a lower rate of urgent revascularization in the PCI group than in the medical therapy group.<sup>12</sup>

Some nonrandomized observational studies have also shown the benefits of ischemia-guided revascularization. In the post acute coronary syndrome setting, once the culprit lesion has been treated, the severity of different stable lesions can also be assessed by FFR. Non-invasive stress testing immediately after the acute phase may be not possible, and furthermore, non-conclusive or contraindicated. In stabilized patients with recent acute coronary syndrome, FFR of non-culprit lesions can be safely evaluated, either during the index procedure or in a staged procedure.<sup>13</sup>

The usefulness of FFR-guided revascularization strategy have been consistently demonstrated in different angiographic scenarios like left main, isolated left anterior descending coronary artery, small vessels or bifurcation lesions. Hamilos et al.<sup>14</sup> reported that angiography alone did not allow appropriate individual decision making about the need for revascularization in patients with equivocal stenosis of

the left main coronary artery. Moreover, this study supported that angiography often underestimates the functional significance of the stenosis of the left main. The favourable outcome of an FFR-guided strategy suggests that FFR should be assessed in such patients before taking the decision about the need for revascularization.<sup>14</sup> Muller et al.<sup>15</sup> proposed the usefulness of FFR-guiding percutaneous revascularization of isolated proximal left anterior descending coronary artery. This study concluded that the medical treatment of patients with a hemodynamically non significant stenosis (FFR  $\geq$  0.80) in the proximal LAD was associated with an excellent long-term clinical outcome with survival at 5 years similar to an age- and sex-matched control population.<sup>15</sup> In a study reported by Puymirat et al.<sup>16</sup> FFR-guided percutaneous revascularization of small coronary arteries was safe and resulted in better clinical outcome when compared with an angio-guided PCI.<sup>16</sup> The utility of FFR in percutaneous intervention for bifurcation lesions has been evaluated by Kumsars et al.<sup>17</sup> The usefulness of FFR in this situation was to identify the functional grade of stenosis of the side branch.<sup>17</sup>

All these studies indicate that ischemia guided PCI may reduce the cost, radiation exposure and procedural complications by avoiding unnecessary, complex procedures and consequently improving long-term prognosis. In addition, several studies have suggested that patients with more extensive ischaemia benefit from revascularization therapy, and this benefit could achieve long-term survival benefit if the ischaemia is severe and if significant reduction of ischaemia is achieved. The future directions of this field are focus on the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial. This is a clinical trial that randomizes SIHD patients at a uniformly higher risk prior to cardiac catheterization to determine optimal management for patients with SIHD. This trial will better clarify the benefits of ischemia-guided revascularization for stable CAD patients.

We would like to remark that all patients with SIHD benefit from optimal medical therapy in addition to a healthy lifestyle. Revascularization exerts favourable effects on symptoms, quality of life, exercise capacity, and survival in some cases. The decision to revascularize a patient should be based on the presence of significant obstructive coronary artery stenosis, the amount of related ischaemia and the expected benefit to prognosis. Revascularization can offer survival benefits in high-risk, stable-angina patients, who are formally defined as those with multivessel coronary artery involvement or left main CAD, LVEF dysfunction and extensive ischemia. Stable-angina patients who are low risk on the basis of these criteria should not undergo revascularization procedures unless they experience significant angina, in which case revascularization can improve quality of life.

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