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The role of functional assessment in the management of ischaemic heart disease

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Over the past three decades, ischaemia research has been the cornerstone of the management and treatment of patients with atherosclerotic CAD. A robust body of evidence, including non-randomized and randomized trials, has supported the use of invasive and non-invasive coronary function tests to guide coronary revascularization. However, more recent data have questioned the clinical benefits of adopting this approach, especially in patients admitted with acute myocardial infarction. The increasing use of intracoronary imaging has identified the morphological features of plaques at higher risk of causing subsequent acute coronary events, despite the fact that they were not obstructive at the time of the index investigation. However, although functional assessment does not appear to have the same potential for identifying high-risk plaques as imaging modalities, it offers the simplicity and reproducibility of plaque assessment as a unique advantage. Furthermore, the ideal approach for the treatment of the so-called vulnerable plaques is still far from being identified, while a robust body of evidence supports the role of functionally guided revascularization, especially in stable patients. Overall, ischaemia research still provides non-negligible information that contributes to a personalized approach to improve patient outcomes.

Among patients with atherosclerotic CAD, a rich literature has supported the search of ischaemia causing lesions by means of intracoronary functional assessment with fractional flow reserve (FFR) or non-hyperaemic indexes. Several registries and non-randomized studies have been performed to address the role of an FFR-guided vs. isolated angiography revascularization strategy, highlighting the superiority of the former approach. The DEFER study was the first to demonstrate that deferral of coronary interventions in functionally negative lesions (non-ischaemic FFR values) is safe and not associated with impaired outcomes at a long-term follow-up.[1] However, recent evidence challenged these results as we will discuss later. Piròth *et al.*[2] studied the association between FFR-positive non-culprit lesions and occurrence of myocardial infarction (MI) at 24 months. A higher risk of MI was found in patients with infarct-related FFR-positive lesions that were not treated with PCI. Omran *et al.*[3] showed in a retrospective study on 304 548 patients with acute coronary syndrome (ACS) that FFR-guided PCI was accompanied by a reduced rates of in-hospital mortality, peri-procedural bleeding, acute kidney injury, and total length of stay.

Randomized trials

After these initial encouraging results, several randomized trials studied the clinical effectiveness of physiology-guided

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percutaneous coronary intervention. Results were not consistent in showing a benefit from a functional guided approach. The FAME I trial[4] recruited 1005 patients with multivessel disease who underwent an FFR-guided or angiography-guided PCI. At a 1-year follow-up, the FFR-guided strategy led to reduced rates of the composite endpoint of death, MI, and repeat revascularization (18.3% vs. 13.1%, $P = 0.02$). Notably, the difference between the two strategies was not statistically significant when follow-up was prolonged to 5 years (31% vs. 28%, $P = 0.31$).[5]

More recently, the FFR vs. Angiography for Multivessel Evaluation 2 (FAME II) trial[6] studied patients with functionally significant stenoses, to compare clinical results obtained with PCI vs. optimal medical treatment. Recruitment was halted prematurely because of a significant between-group difference in the percentage of patients with primary endpoint events [4.3% in the PCI group vs. 12.7% in the medical-therapy group; HR 0.32 (95% CI: 0.19–0.53), $P < 0.001$]. Although the FAME I and FAME II trials were synergistic in showing, in a stable setting, the superiority of an interventional approach based on FFR guidance of coronary stenoses, different conclusions were reached in recent large randomized studies.

The Functional Testing Underlying Coronary Revascularization (FUTURE) trial[7] assigned patients with multivessel disease to two different treatment strategies [physiology-guided or angio-guided angioplasty of all stenotic (≥50%) coronary arteries]. The primary endpoint [a composite of major adverse cardiac or cerebrovascular events at 1 year] did not differ between groups [14.6% in the FFR group vs. 14.4% in the control group; HR: 0.97 (95% CI: 0.69–1.36); $P = 0.85$].

Use of functional assessment in patients with acute coronary syndrome

The prognosis of patients with ACS still suffers from a non-negligible rate of adverse events.[8] As prognosis appears to be highly affected by complete revascularization of the coronary artery bed, many studies focused on the comparison between the clinical effectiveness of functional vs. angiography guided interventions. Both the DANAMI PRIMULTI trial[9] and the study by Smits *et al.*[10] addressed the impact of physiology-guided complete revascularization vs. treatment of the culprit lesion only in patients with ST segment elevation MI (STEMI). In both studies, the addition of FFR-guided complete revascularization of non-infarct-related arteries resulted in a reduced risk of a composite cardiovascular outcome compared with that of those who were treated for the infarct-related artery only. The recent Functional Assessment in Elderly MI Patients With Multivessel Disease trial[11] evaluated the effectiveness of physiology-guided PCI in 1445 patients aged ≥75 years, with multivessel disease and either STEMI or non ST segment elevation MI. Consistently with other studies, the physiology-guided complete approach proved to be superior to revascularization of culprit-only PCI with a 27% relative risk reduction in a composite of mortality, stroke, MI, or ischaemia-driven revascularization.[9,10] Opposite conclusions were reached by the 'FLOW Evaluation to Guide Revascularization in Multi-vessel ST-elevation MI' trial.[12] The trial compared the two different strategies (FFR vs. angio-guided PCI) in 1163 STEMI patients applying a different study design. Instead of comparing physiology-guided complete revascularization of non-culprit lesions vs. a less aggressive approach of no further revascularization, the trial required a multivessel complete revascularization guided by either FFR or angiography. FFR failed in improving the clinical outcome (composite of death from any cause, nonfatal MI, or unplanned hospitalization leading to urgent revascularization at 1 year) respect to angiography (5.5% vs. 4.2%, $P = 0.31$). In conclusion, there is overall evidence that functional assessment is clinically effective in improving the clinical outcome, mainly by reducing the incidence of new revascularisations in both stable and unstable settings. However, not all studies are concordant in showing the superiority of this approach.

Use of functional assessment for predicting hard cardiac events

There exists a rationale for the use of functional assessment of coronary lesions for identifying patients at risk of MI or cardiac death. Narrowing severity is an established feature of plaque vulnerability together with superficial lipid content and local inflammation.[13–15] Furthermore, coronary plaques causing hard cardiac events are more commonly in an advantage stage of disease. FFR-positive lesions are therefore more likely to portend features of vulnerability compared with lesions that do not cause ischemia. Despite that, among studies on percutaneous coronary revascularization with FFR guidance, only the FAME I[4] study showed a reduction in the combined rate of death and MI (11.1% in the FFR arm vs. 7.3% in the angiography arm, HR 0.66, $P = 0.04$) with the vast majority of other reports tackling this preliminary finding. The FAME II study[6] showed a similar incidence of death or MI in the functionally guided and angio-guided arms (3.4% vs. 3.9%, respectively, HR 0.61, $P = 0.22$). Same conclusions were reached in the ACS setting with all published trials excluding any causal relation between treatment of functionally significant lesions and hard cardiac endpoints. In the DANAMI PRIMULTI trial,[9] the 1-year incidence of cardiac death and or non-fatal MI were similar between patients undergoing complete revascularisation with FFR or culprit lesion PCI alone (6% vs. 8%, respectively, HR = 0.8, $P = 0.47$). Similarly, Smits *et al.*[10] showed that complete revascularization accomplished with FFR guidance vs. culprit lesion PCI treatment alone did not reduce the 1-year incidence of MI (2.4% vs. 4.7%, HR = 0.5, $P = 0.1$) and/or cardiac death (1.4% vs. 1.7%, HR = 0.7, $P = 0.8$) among patients admitted with STEMI. The FUTURE trial[7] did not show significant difference in the incidence of MI (6.0% vs. 6.1%, HR = 1.0, $P = 0.9$) and in all-cause mortality (3.7% in the FFR group vs. 1.5% in the control group; HR = 2.34; 95% CI: 0.97–5.18; $P = 0.06$).

Thus, all published functional studies are consistent in showing that there is a residual risk for death or MI in physiologically non-severe lesions. This conclusion is further supported by studies that addressed plaque morphology in coronary segments that did not cause ischemia at the time of functional assessment. The COMBINE study[16] addressed the role of intracoronary imaging, by means of intracoronary optical coherence

tomography (OCT), for predicting clinical outcome in patients with diabetes mellitus and FFR negative lesions. Vulnerable lesions with OCT-detected thin-cap fibroatheroma were identified in 25% of patients despite the absence of ischaemia and were associated with a 5-fold higher rate of the primary endpoint defined as the target lesion-related composite major adverse clinical event including cardiac mortality and target vessel MI (13.3% vs. 3.1%, HR = 4.65, $P < 0.001$).

What is the ideal approach for targeting and treating vulnerable plaques?

Functional assessment does not seem to have the same potential for identifying high risk plaques as imaging modalities do, although it offers as a unique advantage the simplicity and reproducibility of plaque assessment. There is overall evidence that functional assessment reduces the incidence of new revascularization, although it does not seem the ideal solution for identifying and treating vulnerable plaques in the attempt of reducing hard cardiac events. On the other hand, intracoronary imaging modalities represent valid solutions with great potential for depicting such lesions.[17] Plaques with a high lipid content and/or thin fibrous cap can be targeted and treated if judged at high risk. Intracoronary imaging can also study other mechanism of plaque instability, including disrupted calcified nodules.[18] While functional assessment represents a one fits all approach, imaging modalities can potentially offer different treatment solutions according to the composition of the plaque, with both local or systemic treatment potentially useful. Recent large, randomized trials employing serial intravascular imaging have highlighted the vascular benefits of potent lipid-lowering therapy.[19] On the other hand, the PREVENT multicentre study[20] showed for the first time the effectiveness of a vulnerable plaque sealing approach with angioplasty, despite most plaques were imaged by intra vascular ultra sound (IVUS) and OCT and near-infrared spectroscopy-IVUS modalities were less frequently employed to detect vulnerable plaques. Non-flow-limiting vulnerable plaques were studied in 1606 patients with non-flow-limiting (FFR >0.80) vulnerable coronary plaques. at 2 years, the primary outcome (composite of death from cardiac causes, target-vessel MI, ischaemia-driven target-vessel revascularization, or hospitalization for unstable or progressive angina) occurred in 0.4% patients in the PCI group and in 3.4% in the medical therapy group (95% CI: −4.4 to −1.8; $P < 0.001$). Differences were not any more statistically significant at a 4-year follow-up. The study should be waived as the first preliminary evidence of the usefulness of a strategy based on the search and treatment of plaques at risk of cardiac events. The fact that the interventional arm lost efficacy at a longer 4-year follow-up may be due to the applied methodology; particularly, the use of multiple imaging modalities and criteria to address vulnerability and the extensive use of biovascular scaffolds. Interestingly, patients who showed a stronger benefit from local plaque pre-emptive treatment were those with stenosis >55%. This finding appears in line with the recent publication of the PACMAN-AMI lesion-level analysis, where potent lipid-lowering therapy was effective in inducing a plaque stabilization of thin-cap fibroatheroma and lipid-rich plaques in angiographically maximum 50–55% stenosis.[21]

Ongoing randomized studies will further explore this issue, in the effort of identifying the most effective modality for searching and treating intermediate coronary narrowings. The COMBINE INTERVENE trial (ClinicalTrials.gov: NCT05333068) will study the additional value of vulnerable plaque local treatment in intermediate lesions that were judged non-ischaemic at functional assessment. The INTERCLIMA study (ClinicalTrials.gov: NCT050227984) will compare directly a functional vs. an OCT-guided stenting strategy for treatment of non-culprit intermediate coronary narrowings in 1460 patients with ACS. These studies will clarify whether identification and treatment of vulnerable plaques can be pursued and will provide evidence on the most suitable solution for studying plaques at risk of hard events.

In conclusion, functional assessment is still a valuable tool in the management of ischaemic heart disease, but more and more evidence point to the usefulness of direct imaging of coronary atherosclerosis. Ultimately, all data move in the same—desirable—direction of a personalized approach to improve patient outcomes.

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Data availability

No new data were generated or analysed in support of this research.

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