Fractional flow reserve as the standard of reference: *All that glistens is not gold*

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The burden of disease is directly linked to the prognosis of the patient—in cardiology as well as in any other field in medicine. The challenge, however, is whether and how the markers of clinical risk can guide patient management.[1] While therapeutically targeting *risk factors* like LDL-cholesterol or blood pressure has substantially reduced major adverse cardiovascular events,[2,3] this association has not yet been demonstrated for a *risk marker* like HDL-cholesterol.[4] In contrast to statins or ACE-inhibitors that treat patients at risk holistically, the management of symptomatic patients with stable coronary artery disease (CAD) often demands vessel- or even lesion-specific therapies by coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCI).[5] The value of anatomical and functional markers of disease burden in this setting, however, has been controversially debated over the last decades. Although the extent of CAD as defined by coronary artery calcium score or coronary CT angiography is a strong predictor of cardiovascular risk,[6] the role of extensive or high-risk CAD in assigning patients to either myocardial revascularization or optimal medical treatment has so far been limited to observational data.[7] Yet, comparing PCI to optimal medical treatment, one of the largest randomized trials to date demonstrated that anatomical disease burden—although a marker of cardiovascular risk in the study—did not identify patients benefiting from PCI.[8] As a result, the focus has shifted back to functional assessment of CAD as a marker of cardiovascular risk to potentially guide treatment strategy.[9–11] Indeed, there is an indication from observational data that the burden of vessel-specific ischemia affects the response to revascularization.[12] Whether the risk associated with higher ischemic burden can be reduced by revascularization is currently being prospectively investigated in the ISCHEMIA trial.[13]

Meanwhile, fractional flow reserve (FFR) in invasive coronary angiography has been validated against quantitative myocardial perfusion positron emission tomography (PET) imaging and non-invasive imaging [14,15] and emerged as a tool to assess lesion-specific ischemia. The severity of FFR has not only been linked to subsequent cardiovascular outcome[16] but more importantly, an FFR-guided PCI strategy resulted in a significant reduction in urgent revascularizations.[17] While FFR has since then been considered the gold standard for diagnostic accuracy studies as well as in clinical decision making,[5] the technique appears to be underutilized in clinical routine [18]—due to a lack of experience, time, or reimbursement. Another reason might originate from the challenges in the interpretation of the FFR measurement: since the pathophysiological mechanisms leading to an abnormal FFR are still insufficiently understood, physicians might at times be confronted with striking discrepancies to findings from angiography or myocardial perfusion imaging. Consequently, reasonable doubts emerge.

In the current issue of the *Journal of Nuclear Cardiology*, Yokota et al. have addressed this issue of great clinical relevance in a prospective cohort study.[19] In a sample of 133 patients with normal myocardial perfusion SPECT imaging, invasive coronary angiography with FFR measurement was performed due to

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persistent symptoms within 6 months after the SPECT scan. From the 85 FFR measurements that were performed in the LAD, 35% were abnormal (FFR $\leq$ 0.8). In contrast, only 10% of the 82 FFR measurements in non-LAD vessels were abnormal. Since only 30% of LAD measurements with abnormal FFR had angiographically obstructive CAD (compared to 75% of non-LAD measurements), the authors suggested that—in view of the normal SPECT findings—FFR might overestimate the severity of LAD lesions.

The authors should be commended for their effort to investigate this scientifically and clinically unsolved issue of discrepant FFR measurement. Although the authors' study design limits an analysis of the underlying mechanisms, their findings not only reflect the high prevalence but also elegantly highlight the clinical dilemma. Indeed, the reluctancy of revascularizing an angiographically non-obstructive lesion with a normal SPECT scan but an abnormal FFR is comprehensible to any physician—randomized data, nevertheless, would suggest an outcome benefit. Although the inaccuracy of angiography in assessing the functional relevance of obstructive CAD[20] and the poor concordance of FFR with myocardial perfusion SPECT imaging is well established,[21] the limitations of the axiomatic FFR are rarely called into question. While technical reasons might play a role in some cases, the discrepancies unfold hidden physiological interrelations too.

It has not been until recently that—beyond stenosis severity—atherosclerotic plaque characteristics such as positive remodeling or low attenuation plaque have been linked to abnormal FFR.[22,23] Furthermore, the presence of abundant intracoronary and intercoronary collaterals impedes a direct comparison between lesion-specific ischemia from FFR and vessel-specific ischemia from myocardial perfusion SPECT imaging.[24] Last but not least, applying Ohm's law to fluid flow, the pressure-drop (as measured by FFR) is directly related to (blood) flow. In patients with diffuse CAD or microvascular dysfunction where flow reserve is limited, there is less pressure-drop at a comparable lesion's resistance (or severity of stenosis). Conversely, non-obstructive CAD with low resistance could lead to an abnormal FFR if the flow is higher in healthier patients. Therefore, the results of the FAME 2 trial are not necessarily generalizable to all CAD patients. In view of the severity-benefit continuum for any risk factor, healthier patients might, therefore, only benefit from revascularization at a much lower threshold than the one suggested (e.g., 0.67 vs 0.80).[16] Thanks to significant reduction in radiation exposure from coronary CT angiography,[25–27] coronary lesions of younger and healthier patients are now being tested by CT-FFR or other CT-derived measurements.[28–30] As a consequence, the interaction between lesion-specific ischemia and myocardial blood flow warrants further investigation to prevent overestimation of coronary lesions.

Since treating the risk factor *FFR* by revascularization has improved cardiovascular outcomes in randomized trial, it is the most glittering tool that there is to guide treatment strategy. However, to correctly identify those patients that accrue prognostic benefit from revascularization, FFR should be assessed in the context of other risk markers like myocardial perfusion. Individualizing the threshold for an abnormal FFR by myocardial perfusion imaging or even quantification of myocardial blood flow could, therefore, result in an optimized—and potentially golden not only glittering—patient management.

Disclosure

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