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Commentary: Fractional flow reserve for coronary artery bypass graft surgery—Not yet ready for prime time

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CENTRAL MESSAGE

Current evidence does not support the use of FFR in patients undergoing CABG.

In this edition of the *Journal*, Glineur and colleagues[1] discuss the role of fractional flow reserve (FFR) in patients undergoing coronary artery bypass graft (CABG).[1] The FFR technique is based on the ratio of maximal flow across a stenotic lesion achieved with a coronary vasodilator, such as adenosine, compared with normal flow.[2] The landmark FAME (Fractional Flow Reserve vs Angiography for Multivessel Evaluation) trials helped to establish the role of FFR in percutaneous coronary interventions (PCI).[3,4] The insertion of PCI stents based on FFR compared with angiography decreased the number of stents implanted, the amount of contrast used, procedural costs, and the incidence of myocardial infarction and mortality. An FFR <0.80 was observed to be predictive of a coronary artery stenosis responsible for ischemia. These trials demonstrated that PCI should be determined by physiology and not solely by anatomical stenoses. FFR is now a Class IA recommendation to guide revascularization in angiographic coronary stenoses in patients with stable angina.[5]

In view of the favorable outcomes of FFR in PCI, it was thought that FFR may also be beneficial in patients undergoing CABG by avoiding grafts to smaller vessels with stenoses of only 50% and to avoid grafts that result in competitive flow, especially arterial conduits in which the percent stenosis has been correlated with graft patency.[6] However, there are several issues with the FFR technique that has limited its use in clinical practice. FFR requires additional wire manipulations, which increases the risk for traumatic injury to coronary vessels. It requires the use of the coronary vasodilator adenosine, which can cause bradycardia, heart block, chest pain, and dyspnea and increases the cost of the procedure. FFR is not as accurate in patients with left ventricular hypertrophy and in smaller vessels with diffuse disease, as seen in patients with aortic stenosis and diabetes, patient populations that are more likely to be referred for CABG versus PCI. The accuracy of FFR in patients with bifurcation and tandem lesions frequently seen in patients undergoing CABG is unknown. In the FAME trials, the complexity of the coronary lesions was low and served areas of myocardium with normal wall motion. The FFR technique was based on models that assumed a normal distal microcirculation.[7] Its accuracy is less in vessels that supply areas of reduced wall motion. FFR values tend to be greater in infarcted myocardium, which reflects the decreased area of viable myocardium supplied by that vessel. But what about stunned myocardium seen at the time of CABG, which is potentially reversible and would benefit from a bypass graft? In patients with acute coronary syndromes (ACS), there are various degrees of transient microvascular dysfunction due to thrombus and embolization of plaque, and, therefore, FFR is not recommended to determine stenting of culprit vessels in the acute setting of an ST-elevation myocardial infarction.[8] Recently, instantaneous wave-free ratio (iFR) has emerged as an alternative technique to FFR.[9] iFr measures the resting pressure gradient across the lesion during diastole when microvascular resistance is lower and more stable. It avoids the need for adenosine and its side-effects and can reduce procedure time for each vessel by 5 minutes. Two recent studies

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in patients undergoing PCI demonstrated that iFR was noninferior to FFR in the need for repeat revascularization and major adverse cardiovascular events (MACE).[10,11] In the iFR technique, lesions deferred for stenting were >0.89 as opposed to >0.80 for FFR. In patients with ACS, those undergoing PCI who were deferred using FFR had significantly worse outcomes compared with patients with stable angina. However, lesion deferred using iFr had similar outcomes, regardless of stable versus ACS conditions. Data with iFR in patients undergoing CABG are, however, currently unavailable.

There have been a limited number of studies to determine the effects of FFR in patients undergoing CABG. Botman and colleagues,[12] in a trial of 164 patients undergoing CABG randomized to FFR-versus angiography-guided grafting, found that bypassing lesions with an FFR >0.075 resulted in a greater rate of graft occlusion for both vein and arterial conduits, but there was no significant difference in the incidence of recurrent angina or the need for repeat revascularization after 1 year.[12] Toth and colleagues,[13] in a retrospective study found that at 1-year follow-up, patients undergoing FFR-guided CABG had a lower incidence of Class II-IV angina, recurrent angina, and greater freedom from vein occlusion. In a 6-year follow-up study of this patient cohort, patients undergoing FFR-guided CABG had a lower incidence of death and myocardial infarction despite having fewer grafts.[14] In the GRAFFITI (Graft Patency After FFR-Guided vs Angiography-Guided CABG) trial involving FFR-versus angiography-guided CABG in patients with multivessel disease, there was no difference in overall graft patency or MACE after 1 year of follow-up.[15] This trial was underpowered to determine clinical outcomes, and graft patency and was ultimately terminated. In the FARGO trial, 100 patients undergoing CABG were randomized to receive FFR-versus angiography-guided grafting.[16] Follow-up angiograms at 6 months were not available in 25% of the patients. There was no difference in graft failure or MACE between the groups. However, in just 6 months, the FFR in the nongrafted lesions were significantly decreased from 0.89 ± 0.05 to 0.81 ± 0.11; $P < .002$. Thirty seven percent of "deferred" lesions now had a FFR <0.80. One area in which FFR may be beneficial is to determine which type of conduit should be used to bypass a specific vessel. Glineur and colleagues[17] found that FFR was a better predictor of arterial graft patency at 6 months. An anastomosis performed with an arterial graft to a vessel with an FFR <0.78 had a patency of 97%.

These trials illustrate the current knowledge gaps in determining the role of FFR in patients undergoing CABG. Most trials are retrospective, nonrandomized, from a single center, and are underpowered to determine the significance of important clinical end points. They lack routine angiographic follow-up to assess graft patency and most involve only 6 months to 1 year of follow-up, which is inadequate to determine graft patency and MACE following CABG. These studies fail to mention the quality and types of conduits that were used, the quality of the vessels bypassed—their size and the presence of distal disease. No mention is made of guideline-directed medical therapy, especially the use of statins and antiplatelet agents.

Glineur and colleagues concluded that the use of FFR to dictate which vessels should be bypassed "should be discouraged." This is in agreement with several other surgeons who have commented on this technique since its introduction into clinical practice.[18-20] Larger trials, prospectively randomized, and sufficiently powered, comparing FFR-versus angiography-directed CABG with long-term follow-up, are needed to determine the role of FFR in patients undergoing CABG. Until these data are available, FFR for CABG is not yet ready for prime time.

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