Special Report

Interventional Cardiology

Fractional flow reserve and appropriate use criteria

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Wide variations in clinical practice raise questions about the under- or over-use of expensive interventional coronary procedures. Appropriate Use Criteria (AUC) for percutaneous coronary intervention (PCI) were developed in 2009 and updated in 2012 to help guide clinicians regarding the decision to revascularize, based on a synthesis of available evidence. Despite these criteria, recent analyses have continued to show high rates of both inappropriate PCI and underutilization of PCI. Fractional flow reserve, which is a physiologic measurement of a coronary artery stenosis, provides objective evidence of the functional significance of a coronary lesion and has the potential to reduce variations in practice.

Keywords: Appropriate Use Criteria • cardiac catheterization • coronary artery disease • fractional flow reserve • percutaneous coronary intervention

Coronary artery disease (CAD) affects more than 16 million Americans [1]. For patients with acute coronary syndromes (ACS), percutaneous coronary intervention (PCI) unambiguously improves outcomes [2]. For patients with stable ischemic heart disease, the justification for revascularization is less clear especially when following the results of the COURAGE study [3], despite the perceived benefit of relieving obstructions to coronary flow. There are subsequently wide variations in the clinical practice of PCI, as reflected in regional differences in PCI rates, mostly driven by variations in nonurgent procedures [4]. In 2010, PCI rates were 461% higher in Arkansas (12 per 1000 Medicare enrollees), the US state with the highest PCI rates, than in Hawaii (2.6 per 1000 Medicare enrollees), the US state with the lowest PCI rates per 1000 Medicare enrollees [5].

The American College of Cardiology (ACC), along with the American Heart Association, Society for Cardiovascular Angiography and Interventions, and several other professional societies published Appropriate Use Criteria (AUC) for PCI in 2009 to help physicians consider when it is reasonable to revascularize coronary lesions and to decrease variation in clinical practice. These guidelines were recently updated in 2012. AUC provide physicians with a consensus opinion on common scenarios. Despite the AUC, substantial variability persists. In a review of the National Cardiovascular Data Registry (NCDR) evaluating nonacute indications for PCI, there was considerable variation in PCI appropriateness by facility. In the preferred terminology of the categories, 50% of nonacute PCI were found to be appropriate, 38% possibly appropriate and 12% were rarely appropriate [6]. Chan *et al.* found higher rates of inappropriate PCI to be more common in Caucasians, men and those with private insurance, which may partly be due to procedural overuse in these populations [7,8]. Overall, PCI may be underutilized. In a review of more than 1600 PCIs performed between 2006 and 2007, only 69% of patients with appropriate indications for PCI received coronary revascularization, and those patients who had intervention had significantly lower rates of death or recurrent ACS [9].

For individual patients and lesions, uncertainty regarding the need for revascularize-

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tion often remains due to the inherent limitations of angiography and noninvasive stress testing. It is within this framework that we discuss AUC and fractional flow reserve (FFR), a technique verified by clinical trials to be an important tool for hemodynamic coronary artery lesion assessment. FFR can be used to reduce PCI practice variation by providing objective evidence of the functional significance of a coronary lesion. The advent of FFR marks a fundamental transition from an anatomy-based intervention method to a combination of anatomy- plus functionality-based intervention.

Fractional flow reserve

FFR is a physiologic measure of the hemodynamic significance of a coronary artery stenosis. It is defined as the ratio of maximal myocardial flow through an artery in the presence of a lesion divided by myocardial flow in the theoretical absence of the lesion [10]. Physiologic lesion assessment prior to intervention is helpful to overcome the limitations and uncertainties of angiography alone, as an angiographic silhouette of a lesion may not reflect a lesion's true ischemic potential [11,12]. FFR provides concrete justification for proceeding with PCI by providing objective evidence of the physiologic significance of a coronary lesion. A prospective cost–utility analysis by Fearon *et al.* comparing costs and quality-adjusted life-years for 1 year of FAME 1 data showed the mean overall cost of FFR-guided PCI at 1 year was significantly less than angiography alone (US$14,315 vs 16,700; $p < 0.001$) [13].

FFR is one of several tehniques to evaluate the physiologic significance of a coronary lesion. Other techniques include instantaneous wave-free ratio functionality (iFR), which is based on the instantaneous ratio of trans-stenotic pressures during diastole, and coronary flow reserve. This review will focus on FFR.

FFR technique

In the cardiac catheterization laboratory, a 0.014-inch diameter pressure guidewire is passed through an angioplasty Y-connector attached to a guide catheter to measure intracoronary pressure. The pressure wire connects to an interface that displays the pressure signals and calculates FFR immediately. The pressures in the guide catheter and sensor wire are zeroed before introduction of the guidewire. The wire is advanced into the target artery, and the guide and guidewire pressures are equalized. The pressure wire is then advanced across the lesion. Coronary hyperemia is induced with intravenous or intracoronary agents to reveal the genuine effect of a stenosis on coronary blood flow. FFR is calculated by measuring the pressure distal to the stenosis divided by the aortic pressure during maximal hyperemia. The preferred agent to achieve maximal steady-state microvasculature vasodilation is intravenous adenosine. Intravenous infusion of adenosine through a central vein is considered the gold standard to induce steady-state hyperemia, but requires an additional procedure for femoral vein access and is difficult to use during transradial cardiac catheterization procedures. Peripheral administration is more convenient and as efficacious as achieving steady-state hyperemia as central adenonsine infusion [14].

FFR & ischemia

The diagnostic accuracy of FFR is well validated. It has an unequivocal normal value of 1 that holds true for all patients and all arteries. A FFR value <0.75 is associated with invariable myocardial ischemia and abnormal stress testing results with a diagnostic accuracy rate of 93%, a specificity of 100% and sensitivity rate of 88% [15,16]. A FFR <0.8 is like a positive ischemic stress test, and a flow-limiting stenosis has a FFR <0.8. A FFR >0.8 is associated with nonischemic lesions. For lesions with FFR between 0.75 and 0.8, the decision to intervene has been based on clinical judgment. The clearly defined cutoff value for ischemia provides guidance in the catheterization laboratory and justifies the decision to stent a lesion with a FFR <0.75 and to defer intervention in a lesion with FFR >0.8.

Clinical studies supporting FFR

The use of FFR in the evaluation of coronary lesions is supported by clinical evidence. The DEFER study showed PCI of a coronary lesion without functional significance can be safely deferred from stenting and treated medically [17]. A total of 325 patients with a single angiographically significant new stenosis in a native coronary artery without noninvasive evidence of ischemia underwent invasive functional assessment with FFR. If the FFR was ≥0.75, then patients were randomized into either a PCI performance group (n = 90) or a deferral group (n = 91). After 5 years, there was no difference in event-free survival between the deferral group and the PCI performance group (79 vs 73%; $p = 0.52$), and the rate of cardiac death and acute myocardial infarction (MI) was approximately 4% lower in the deferral group as compared with the performance group (3.3 vs 7.9%; $p = 0.21$) [17]. DEFER laid the groundwork for two important trials that provided further evidence for FFR-guided revascularization.

In the FAME 1 trial, Tonino *et al.* showed that, for patients with multivessel CAD, FFR-guided PCI compared with angiography alone resulted in a significant reduction in major adverse events (including death, MI and repeat revascularization) at 1 year, while simultaneously reducing the length of hospital stay, and the number of stents and contrast used [18].

The lower rate of mortality or MI continued to be seen after 2 years [19].

Recently, FAME 2 studied patients with stable multivessel CAD suitable for PCI. Those randomized to FFR-guided PCI with optimal medical therapy (OMT) had superior outcomes compared with those treated with OMT alone. The primary end points were death, MI and unplanned rehospitalization leading to urgent revascularization during the first 2 years. Secondary end points included cardiac death, nonurgent revascularization and angina class. Enrollment was prematurely terminated because the patients randomized into the FFR-guided PCI group were significantly less likely to need urgent revascularization compared with patients receiving OMT [20]. A total of 4.3% in the PCI group versus 12.7% in the medical therapy group (hazard ratio with PCI: 0.32; 95% CI: 0.19–0.53; $p < 0.001$) had a primary end point. The FFR-guided PCI group had lower rates of urgent revascularization (1.6 vs 11.1%; $p < 0.001$), particularly urgent revascularizations triggered by an MI or unstable angina with evidence of ischemia on EKG (0.9 vs 5.2%; $p < 0.001$), and nonurgent revascularizations. In the medical therapy group, 50% had urgent revascularization for ACS with positive troponins. The results of these trials provide clinical outcome evidence for the use of FFR to guide PCI with improved outcomes.

Limitations of FFR

There are several limitations of FFR. For occluded vessels with retrograde collaterals, coronary steal induces a pressure drop that results in a falsely low FFR despite the lack of significant stenosis. For tandem lesions, the hemodynamic significance of each stenosis cannot be calculated by the simple classical equation, and more complex approaches must be used [21]. For left main stenoses, FFR has been shown to be useful, but assessment is complicated as the accuracy of FFR is affected by the presence of downstream lesions in the left main or left circumflex. Pressure signal drift can be confused for a true pressure gradient, which can be corrected by pulling the sensor back to the tip of the guiding catheter to equalize pressures.

Appropriate use criteria

The 2009 AUC consisted of 180 commonly encountered clinical scenarios written and reviewed by a 17-member panel composed of eight general cardiologists, four interventional cardiologists, four cardiovascular surgeons, internists and specialists in health outcomes research. It was created in an effort to provide evidence-based recommendations and consensus opinion in an area where variability in practice raised questions of over- and under-use of invasive coronary inter-

Low-risk findings on noninvasive study							
Symptoms Med. Rx	**Appropriate use rating**						
Class III or IV Max. Rx	U	A	A	A	A	A	
Class I or II Max. Rx	U	U	A	A	A	A	
Asymptomatic Max. Rx	I	I	U	U	U	U	
Class III or IV No/Min. Rx	I	U	A	A	A	A	
Class I or II No/Min. Rx	I	I	U	U	U	U	
Asymptomatic No/Min. Rx	I	I	U	U	U	U	
Coronary anatomy	CTO of 1 v; no other disease	1–2-vz disease; no prox. LAD	1-vz disease of prox. LAD	2-vs disease with prox. LAD	3-vz disease, no left main		

Asymptomatic						
Stress test Med. Rx.	**Appropriate use rating**					
High risk Max. Rx	U	A	A	A	A	
High risk No/Min. Rx	U	U	A	A	A	
Int. risk Max. Rx	U	U	U	U	A	
Int. Risk No/Min. Rx	I	I	U	U	A	
Low risk Max. Rx	I	I	U	U	U	
Low risk No/Min. Rx	I	I	U	U	U	
Coronary anatomy	CTO of 1 v; no other disease	1–2-vz disease; no prox. LAD	1-vz disease of prox. LAD	2-vs disease with prox. LAD	3-vz disease, no left main	

Figure 1. Appropriate use ratings by low-risk findings on noninvasive imaging and asymptomatic (patients without prior bypass surgery).
A: Appropriate; CTO: Chronic total occlusion; I: Inappropriate; Int.: Intermediate; Max.: Maximum; Med.: Medical; min: Minimal; prox. LAD: Proximal left anterior descending artery; Rx: Treatment; U: Uncertain; vz: Vessel.
Reproduced with permission from the *Journal of the American College of Cardiology* [22].

Intermediate-risk findings on noninvasive study						
Symptoms Med. Rx	**Appropriate use rating**					
Class III or IV Max. Rx	A	A	A	A	A	A
Class I or II Max. Rx	U	A	A	A	A	A
Asymptomatic Max. Rx	U	U	U	U	A	A
Class III or IV No/Min. Rx	U	U	A	A	A	A
Class I or II No/Min. Rx	U	U	U	A	A	A
Asymptomatic No/Min. Rx	I	I	U	U	A	A
Coronary anatomy	CTO of 1 v; no other disease	1–2-vz disease; no prox. LAD	1-vz disease of prox. LAD	2-vs disease with prox. LAD	3-vz disease, no left main	

CCS class I or II angina						
Stress test Med. Rx.	**Appropriate use rating**					
High risk Max. Rx	A	A	A	A	A	A
High risk No/Min. Rx	U	A	A	A	A	A
Int. risk Max. Rx	U	A	A	A	A	A
Int. Risk No/Min. Rx	U	U	U	A	A	A
Low risk Max. Rx	U	U	A	A	A	A
Low risk No/Min. Rx	I	I	U	U	U	U
Coronary anatomy	CTO of 1 v; no other disease	1–2-vz disease; no prox. LAD	1-vz disease of prox. LAD	2-vs disease with prox. LAD	3-vz disease, no left main	

Figure 2. Appropriate use ratings by intermediate-risk findings on noninvasive imaging and Canadian Cardiovascular Society (CCS) class I or II angina (patients without prior bypass surgery).

A: Appropriate; CTO: Chronic total occlusion; I: Inappropriate; Int.: Intermediate; Max.: Maximum; Med.: Medical; min: Minimal; prox. LAD: Proximal left anterior descending artery; Rx: Treatment; U: Uncertain; vz: Vessel.

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ventions. Coronary revascularization was defined appropriate when "the expected benefits, in terms of survival or health outcomes … exceed the expected negative consequences of the procedure" [22] depending on clinical presentation, severity of angina, extent of ischemia on noninvasive testing, extent of medical therapy and extent of anatomy. The appropriateness of an intervention was rated on a scale of 1–9 by the panel. Scores of 7–9 indicated revascularization was appropriate and likely to improve health outcomes or survival, scores of 4–6 indicated uncertain improvement of outcomes and scores of 1–3 indicated revascularization was inappropriate and unlikely to improve health outcomes or survival. The ACC has subsequently preferred the less judgmental terms 'appropriate', 'possibly appropriate' and 'rarely appropriate' to reflect the uncertainly involved in the care of specific patients. The change in terminology aims to lessen the confusion the previous terms created for the press, population and profession, and to refocus the definitions to reflect physician clinical judgment. A focused update was released in 2012 to address changes in the medical literature and gaps from prior criteria [23].

In the 2009 AUC, FFR <0.75 is used as the cutoff value to rate appropriateness of intervention in patients with one- or two-vessel CAD with borderline stenosis and equivocal noninvasive stress test results. The FFR cutoff point was changed from 0.75 to 0.80 in the 2012 update.

AUC documents differ from clinical practice guidelines in that the latter tend to be restricted to the narrow clinical situations tested in randomized trials and limit their recommendations to those areas where the trial data or clinical consensus is clear. The AUC recommendations focus more generally on common clinical situations or strategies that may or may not have been tested in trials, and tend to have a lower threshold of evidence. The AUC have been a controversial topic and have inspired vigorous debate among interventional cardiologists. After Chan and colleagues published in *The Journal of the American Medical Association* that only half of nonacute PCIs are 'appropriate', Marso and colleagues quickly issued a critique of AUC [24] commenting on inherent methodological problems.

AUC guidelines attempted to simplify decision-making regarding revascularization, but instead have arguably made the process more complex. According to AUC guidelines, patients must fulfil an intricate set of criteria to be considered 'appropriate' for revascularization (Figures 1 & 2). In real-world practice, the majority of patients do not neatly fall into prespecified criteria of appropriateness and their complexity sometimes puts clinicians at odds with AUC

benchmarks. For example, to fulfil appropriate criteria, patients need to have Canadian Cardiovascular Society (CCS) class III or above angina, intermediate-risk findings on noninvasive testing and failure of two antiischemic medications.

The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) have given FFR a class I recommendation for detection of ischemia-producing lesions when objective evidence of vessel ischemia is not available.

FFR & the most 'appropriate' use of PCI

The results of the clinical trials discussed above can be used to support changes in future versions of AUC to allow PCI in the setting of positive FFR. Positive FFR indicates ischemia, favoring appropriate versus uncertain versus inappropriate. The results of FAME 1 and 2 are particularly poised to affect AUC criteria because they specifically addressed those with stable CAD, the population of patients in which the decision to revascularize has the most variability. Based on the results of FAME 2, PCI in patients with stable CAD and FFR <0.8 could be justifiable despite the AUC requirement of a trial of medical therapy because patients receiving PCI had lower rates of urgent revascularization. The effectiveness or cost–effectiveness of requiring the failure of two antianginal drugs prior to PCI compared with immediate PCI has not been tested. In FAME 2, more than 75% of the patients who received FFR-guided PCI did not fulfill 'appropriate' criteria because they had less than CCS class III angina, yet FFR-guided PCI was associated with better outcomes. A significant proportion of patients with class II angina have severely limited quality of life and desire intervention, a presentation that may justify PCI despite having less than class III angina. The improved outcomes in those undergoing FFR-guided PCI as seen in FAME 1 and 2 support modifying AUC criteria to justify PCI if FFR is positive.

Clinical evidence supports an expanded role of FFR in the AUC and the AUC scenarios. It can be the decision-maker in cases where angiographic findings are intermediate, do not correspond with symptoms or do not correlate with the results of noninvasive testing. It may curb the underutilization of PCI by providing real-time functional assessment of a coronary lesion, allowing all physiologically important lesions to be accurately identified and intervened upon. By providing objective evidence of a coronary lesion's functional significance, FFR can help physicians adhere to the principles, if not the letter of the AUC guidelines.

Conclusion

In the current era of cost constraints and increasing focus on best practices, FFR is an invaluable tool to help reduce practice variation and meet the principles behind appropriate use criteria for coronary intervention.

Future perspective

FFR is the gold standard of invasive assessment of ischemic coronary lesions, but there is room for expansion of this critical technology. It is currently used in less than 10% of PCI cases in the USA [25]. The application of FFR to determine the outcome of surgical revascularization with CABG is an area of active study. Botman found that saphenous vein grafts applied to vessels that did not have a physiologic stenosis by FFR led to

Executive summary

FFR

- Fractional flow reserve (FFR) is a physiologic measure of the hemodynamic significance of a coronary artery stenosis.

FFR technique

- A pressure guidewire is advanced through a coronary lesion and the pressures distal to the stenosis and proximal to the stenosis are measured to calculate the FFR.

FFR & ischemia

- A normal FFR value is 1. A FFR <0.75 is associated with myocardial ischemia. A FFR >0.8 is associated with nonischemic lesions.

Clinical studies supporting FFR

- The DEFER, FAME 1 and FAME 2 clinical trials demonstrated the clinical benefits and improved outcomes associated with the use of FFR-guided percutaneous coronary intervention.

Appropriate use criteria

- The Appropriate Use Criteria (AUC) were created in 2009 and updated in 2012 to provide evidence-based recommendations and consensus opinion in an area where variability in practice raised questions of over- and under-use of invasive coronary interventions.

FFR & the most 'appropriate' use of PCI

- Changes to future versions of the AUC to allow percutaneous coronary intervention in the setting of positive FFR are supported by the DEFER, FAME 1 and FAME 2 trials.

a higher rate of graft occlusion [26]. Ferguson demonstrated with an intraoperative myocardial perfusion technique that perfusion was not improved in all patients despite patent grafts [27]. Finally, the FAME 3 trial is in development, and will compare FFR-guided PCI with surgical revascularization. The broader application of FFR will support the effective and efficient use of PCI to provide maximum benefit to the patient and the healthcare system.

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