In recent years, fractional flow reserve (FFR) has become accepted as a clinically effective tool for guiding decisions about percutaneous coronary intervention (PCI). FFR poses a unique alternative to stress testing or angiography-guided PCI, in that it can interrogate the ischemic potential of an individual vessel on an impromptu basis once an angiogram is in progress, offering immediate data for decision making. With its recent greater adoption across the USA, its cost–effectiveness has become an important consideration. There have been a few key analyses over the last decade demonstrating the cost–effectiveness of FFR-guided PCI; we review the major cost–effectiveness analyses, showing the economic utility of FFR-guided PCI for the modern interventionalist.

Keywords: cost–effectiveness • fractional flow reserve • percutaneous coronary intervention

Although angiography is the established invasive approach for assessing coronary artery disease, its ability to evaluate the functional significance of stenoses is limited. Currently, the available options for assessing the hemodynamic significance of lesions include noninvasive functional testing, such as stress echocardiography or stress perfusion scintigraphy (SPS), or invasive testing, with fractional flow reserve (FFR). FFR is defined as the ratio of the distal coronary pressure to the proximal pressure during maximum hyperemia. It has been shown to be an effective method for guiding revascularization [1–6].

As such, it has received a class IA recommendation from the European Society of Cardiology and a class IIA recommendation from the American College of Cardiology [7,8].

Its clinical effectiveness was demonstrated in the FAME trial [2], which compared angiography guided PCI with FFR-guided PCI in patients with multivessel coronary disease. This prospective, multicenter, international trial randomly assigned 1005 patients with multivessel coronary disease to either PCI guided by FFR (PCI if FFR ≤ 0.8) or by angiography alone. Of note, this trial included patients presenting with acute coronary syndrome, with certain limitations (any ST elevation myocardial infarction had to occur more than 5 days prior to PCI, and in the case of non-ST elevation myocardial infarction, peak creatine kinase level had to be less than 1000 U/l). The trial met its primary endpoint of death, myocardial infarction, and repeat revascularization at 1 year, with an event rate of 18.3% in the angiography guided PCI group and 13.2% in the FFR-guided PCI group (p = 0.02). Subsequently, the FAME 2 clinical trial [9] was designed to test whether optimal medical therapy alone was superior to FFR-guided PCI plus optimal medical therapy in patients with stable coronary disease. Recruitment was halted early in this prospective, multi-center, international trial of 1220 patients (of whom 888 underwent randomization) due to an early finding of a significant difference between the groups in the primary endpoint event (death from any cause, myocardial infarction, or unplanned hospitalization leading to urgent revascularization). The PCI group had a primary event at a rate of 4.3% as compared with the medical therapy group.
that had an event rate of 12.7% (HR with PCI: 0.32; 95% CI: 0.19–0.53; p < 0.001). Of note, a lower rate of urgent revascularization in the PCI group drove this difference (1.6 vs 11.1%; HR: 0.13; 95% CI: 0.06–0.30; p < 0.001). Recently, the 2-year results of FAME 2 showed similar primary endpoint trajectories (8.1% event rate for the PCI group vs 19.5% event rate for the medical therapy group; HR: 0.39; 95% CI: 0.26–0.57; p < 0.001), driven by urgent revascularization (4.0% in the PCI group vs 16.3% in the medical therapy group; HR: 0.23; 95% CI: 0.14–0.38; p < 0.001). Additionally, though there were no significant differences between groups in myocardial infarction or death overall; notably, if the first week of outcomes was excluded to eliminate periprocedural events, there were significantly lower rates of myocardial infarction and death at two years for the PCI group (4.6 vs 8.0%; p = 0.04) [10].

FFR has not only shown clinical utility, but also economic utility, with robust evidence demonstrating its cost-effectiveness. Fearon et al. [11] first used computer modeling to compare three potential strategies for deciding whether or not to perform PCI on an intermediate lesion: 1) NUC strategy – deferring the decision for PCI to obtain nuclear stress imaging; 2) FFR strategy – using FFR to guide PCI at the time of; 3) STENT strategy – stenting all moderate lesions without further evidence of hemodynamic significance. They used marginal costs for both in-hospital and outpatient services to optimally estimate the cost of performing additional procedures. They measured the FFR cost as $761 (consisting of $550 for the wire, $36 for intracoronary adenosine and $175 for professional fees). Nuclear stress imaging was estimated to cost $1093. Based on prior published data, the medical cost of treating angina was $1775 per year. They assumed an estimated repeat PCI rate after stenting of 11% at 1 year and 2.5% per year for the next 4 years. Based on these calculations, the FFR strategy provided a savings of $1795 per patient as compared with the NUC strategy, and $3830 per patient as compared with the STENT strategy. Additionally, in terms of cost per quality-adjusted life-years (QALY) gained, though the NUC strategy was expensive (> $800,000/QALY), both FFR and NUC strategies were superior to the STENT strategy. Conclusions from this study are limited by the general limitations of modeling work, which require a number of assumptions to arrive at the conclusions.

Leesar et al. [12] provided the first clinical data by evaluating the impact of FFR compared with SPS in patients with unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI) (Figure 1). Specifically, 70 patients with UA/NSTEMI (312 patients originally screened) and single vessel disease with moderate stenoses based on coronary angiography were randomized to SPS (35 patients) or FFR (35 patients). In both groups, the patients were discharged and managed medically if ischemia was not present, otherwise PCI was performed on the lesion. They found that the FFR approach significantly decreased the cost ($1,329 ± $44 vs $2,113 ± $120; p < 0.05) and duration of hospitalization (11 ± 2 h vs 49 ± 5 h; p < 0.001). Arguably, a limitation of this comparison study is that it does not capture the potential value of using stress testing to guide PCI if performed prior to angiogram. The approach of taking a patient off the cardiac catheterization table after the angiogram to subsequently pursue stress imaging before returning to fix a lesion is the most expensive way to use stress imaging to guide coronary interventions. However, this study reinforced the safety and effectiveness of using FFR to defer PCI of hemodynamically insignificant lesions, even in the presence of an acute coronary syndrome.

In looking at the cost-effectiveness of FFR from a large randomized clinical trial perspective, the FAME investigators conducted an analysis prospectively in the FAME trial described above [13]. This study found that QALYs showed a nonsignificant trend to be higher in the FFR-guided arm compared with the angio-guided group (0.853 vs 0.838; p = 0.2) and the
mean overall costs at 1 year were significantly less in the FFR-guided arm ($14,315 vs 16,700; p < 0.001). Although the use of the pressure wire and adenosine adds cost, the reduction in unnecessary drug-eluting stenting and the decrease in adverse events lead to lower resource utilization in the FFR-guided PCI group compared with the angio-guided PCI group. Additionally, bootstrap simulation showed that the FFR-guided strategy was unique for a new technology. Many new techniques improve outcomes, but usually cost more money. FFR-guided PCI was found to be cost-saving (improve outcomes and cost less) in 91% and cost–effective at a threshold of US $50,000 per QALY in 99.96% (Figure 2). Additionally, sensitivity analyses showed robust results. Specifically, analyses were performed with ± 20% on prices and ± 10% on utilities, with the end results always favoring the FFR group. Note that one of this study’s limitations was that it applied US costs to the analysis, while the majority of patients were from outside the USA.

The FAME investigators also demonstrated the economic attractiveness of FFR-guided PCI in comparison to optimal medical therapy in the analysis of the FAME 2 clinical trial data [14]. Of note, the direct cost–effectiveness of FFR itself is difficult to assume from this analysis, as all patients underwent FFR for this trial. As expected, initial costs were significantly higher for the FFR-guided PCI group ($9927 vs 3900; p < 0.001) because of the cost of the drug-eluting

Figure 2. Bootstrap simulation of incremental costs and effects. Numbers on axes represent differences between FFR-guided and angiography-guided strategies. Positive incremental QALYs indicate higher effectiveness for FFR-guided treatment. Negative incremental costs indicate lower costs for FFR-guided treatment compared with angiography-guided strategy. Data are from 5000 bootstrap replications. Adapted with permission from Fearon et al. [13].

FFR: Fractional flow reserve; QALY: Quality-adjusted life-years.
FFR is a cost-effective tool to determine the hemodynamic significance of coronary lesions, and can be used to guide appropriate PCI in the cost-conscious setting. However, its adoption is still relatively low in the USA and remains to be fully evaluated in different medical systems and among diverse patient groups.

**Future perspective**

Current use of FFR is still limited; a nationwide survey of 1089 interventionalists reported that they use FFR measurement in less than one third of cases and 15%...
never use it [19]. However, in the coming decade, further developments in the pharmacology and technology of FFR-guided PCI may push adoption of its use even further. For example, it will be interesting to see the role that FFR-guided PCI will play once more widely adapted. While FFR-guided PCI may become a powerful noninvasive tool for predicting hemodynamically significant coronary lesions, we anticipate a continued role for traditional FFR for a large proportion of patients who may not receive cCTA imaging before angiogram or have calcified vessels that preclude accurate CT imaging. With continued innovation, a host of FFR modalities will offer options for the modern interventionalist’s toolkit; and in the setting of skyrocketing healthcare costs, it will be important to continue to focus on the cost–effectiveness of each of these options.

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Executive summary

- There is strong evidence to support the use of fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) of moderate coronary lesions. Economic modeling as well as clinical data from large trials show cost savings.
- FAME I compared FFR-guided PCI to angiography and showed that FFR-guided PCI was cost-effective at a threshold of US $50,000/quality-adjusted life-years (QALY).
- FAME II compared FFR-guided PCI to optimal medical therapy and showed that FFR-guided PCI had a cost–effectiveness ratio of $36,000/QALY.
- Newer, less invasive FFR technologies have the potential to expand interventionalists’ options for cost-effective hemodynamic assessment of moderate coronary lesions in the near future.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest
• Provides a historical perspective.

•• Landmark clinical trial.

Figure 4. Bootstrap replications of the incremental cost–effectiveness of the strategy of percutaneous coronary intervention in the setting of an abnormal fractional flow reserve compared with best medical therapy. Each of the 10,000 points represents the results of one bootstrap replication. The difference in cumulative costs is displayed in the vertical axis, and the difference in QALYs is displayed on the horizontal axis. Willingness-to-pay thresholds of $50,000 per QALY added (solid line), $100,000 per QALY added (dashed line), and $150,000 per QALY added (dotted line) are indicated in the plane. The fractions of replications in each sector of the plane are indicated (e.g., 0.0023 of the replications had a cost difference <0 and QALY difference >0). Adapted with permission from Fearon et al. [14].

QALY: Quality-adjusted life-years.


**Analysis from a landmark clinical trial.**


**Analysis from landmark clinical trial.**


**Analysis looking at promising novel technology.**
