Cost-Effectiveness of Percutaneous Coronary Intervention in Patients with Stable Coronary Disease and Abnormal Fractional Flow Reserve

Running title: Fearon et al.; Cost-effectiveness of FFR-guided PCI

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Abstract:

**Background**—The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 2 trial demonstrated a significant reduction in subsequent coronary revascularization among patients with stable angina and at least one coronary lesion with a fractional flow reserve (FFR) ≤0.80, who were randomized to percutaneous coronary intervention (PCI) as compared with best medical therapy. The economic and quality of life implications of PCI in the setting of an abnormal FFR are unknown.

**Methods and Results**—We calculated cost of the index hospitalization based on initial resource use and follow-up costs based on Medicare reimbursements. We assessed patient utility using the EQ-5D health survey with US weights at baseline and one month and projected quality adjusted life-years (QALY) assuming a linear decline over three years in the one month utility improvements. We calculated the incremental cost-effectiveness ratio based on cumulative costs over 12 months. Initial costs were significantly higher for PCI in the setting of an abnormal FFR compared with medical therapy ($9,927 vs. $3,900, p<0.001), but the $6,027 difference narrowed over one year follow-up to $2,883 (p<0.001), mostly due to the cost of subsequent revascularization procedures. Patient utility was improved more at one month with PCI compared with medical therapy (0.054 vs. 0.001 units, p<0.001). The incremental cost-effectiveness ratio of PCI was $36,000 per QALY, which was robust in bootstrap replications and in sensitivity analyses.

**Conclusions**—PCI of coronary lesions with reduced FFR improves outcomes and appears economically attractive compared with best medical therapy among patients with stable angina.

**Clinical Trial Registration Information**—ClinicalTrials.gov. Identifier: NCT01132495

**Key words:** percutaneous coronary intervention, medical therapy, stable coronary artery disease, Fractional Flow Reserve
The optimal management strategy of patients with stable angina and documented coronary artery disease (CAD) remains controversial. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation) trial randomized patients to percutaneous coronary intervention (PCI) or best medical therapy alone, and found that PCI reduced anginal symptoms and improved quality of life at three years, but did not reduce the rates of death or myocardial infarction (MI). The cost-effectiveness of PCI in the COURAGE study was not favorable, however, with an incremental cost-effectiveness ratio (ICER) of at least $168,000 per quality-adjusted life-year (QALY).

Fractional flow reserve (FFR) measured with a coronary pressure wire during cardiac catheterization can identify functionally important coronary narrowings more accurately than can visual assessment of the coronary angiogram. Use of FFR to guide PCI, and treat only flow limiting lesions, was shown in the randomized FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial to improve clinical outcomes and lower costs compared with angiography-guided PCI among patients with multivessel CAD. Subsequently, the FAME 2 trial randomized patients with stable angina, angiographically documented CAD, and one or more lesions with reduced FFR to either PCI or best medical therapy. The FAME 2 study was stopped early based on the recommendation of the Data Safety Monitoring Board because of a significant reduction in the rate of hospitalization for urgent revascularization among patients assigned to PCI in the setting of an abnormal FFR, although the rates of death and MI were similar between the two groups. In this study, we sought to evaluate the economic and quality of life outcomes in the FAME 2 trial.

Methods
Study Design

The design and major clinical outcomes of the FAME 2 trial have been published previously.\textsuperscript{7} Briefly, FAME 2 was a prospective, international, randomized controlled trial that enrolled patients with stable angina and CAD (one, two, or three vessel disease) amenable to PCI with a second generation drug-eluting stent. Prior to randomization, FFR was measured across all lesions that appeared significant on visual assessment. Patients with an FFR > 0.80 across all lesions were followed in a registry and not randomized. Patients with an FFR ≤ 0.80 across one or more lesions were randomly assigned to either PCI or to best medical therapy. The FAME 2 study population was therefore limited to patients with documented, significant myocardial ischemia due to a coronary lesion amenable to PCI. The primary endpoint was the composite of death, MI, or subsequent hospitalization with urgent coronary revascularization.

Costs

We calculated medical costs based on resource use and clinical events during the index procedure, hospitalization, and subsequent follow-up. We counted the number of guiding catheters, coronary guidewires, balloon catheters, stents, medications, adverse events and hospital days for each patient, as well as time in the cardiac catheterization laboratory, and applied cost weights in US dollars to calculate costs of the index procedure. We assigned costs to post-discharge events based on Medicare’s reimbursement rate per diagnosis related group (DRG) for hospitalizations, in-patient procedures, outpatient tests, and physician fees and internet pharmacy costs for cardiac medications.\textsuperscript{8} We calculated cumulative costs monthly for 12 months using an actuarial approach,\textsuperscript{8} and adjusted all costs to 2012 US dollars using the Consumer Price Index (\url{www.bls.gov}). We did not discount costs due to the limited follow-up period.
Health Outcomes

Angina and employment status were assessed at baseline, 1, 6, and 12 months. Patient utility was assessed using the EQ-5D health survey with US weights at baseline, 1 month and 12 months.\(^9\)

Framework of the Economic Evaluation

Analyses were performed from a societal perspective. We assessed the ICER as the difference in the cumulative costs of PCI in the setting of an abnormal FFR and medical therapy, divided by the difference in cumulative quality adjusted life years (QALY) of PCI in the setting of an abnormal FFR and medical therapy. Only 11% of patients provided 12 month EQ-5D scores because the trial was stopped early, so we used the baseline and one month EQ-5D data to calculate QALYs in the two treatment groups. Based on earlier data on the time course of angina relief and quality of life changes after coronary revascularization\(^2,8\), we assumed that the difference in the improvement from baseline in EQ-5D scores between the randomized groups would decline linearly to zero (i.e., to no difference) over three years of follow-up. We tested alternative QALY measures, including assumptions that the initial difference in utility would decline linearly to zero over two years or over four years. We also used an independent approach in which the change in utility from baseline to one month was assumed to last through the 12 months of in-trial follow-up in all patients, but follow-up was truncated at 12 months. In this approach we also assumed patient utility would improve among patients assigned to the medical therapy arm at the time they underwent PCI, and that the improvement would last for the remainder of the 12 month follow-up period.

In all analyses, we made the conservative assumption that the difference in cumulative costs at 12 months between the PCI in the setting of an abnormal FFR arm and the medical
therapy arm would not change further over subsequent follow-up. We performed sensitivity analyses to assess the impact of different costs of coronary stents, and by setting to zero the cost of the coronary pressure wire, the catheterization procedure, and the baseline hospital stay in the medical therapy arm.

**Statistical Analysis**

We report categorical data as frequencies, and continuous data as mean +/- standard deviation. We compared categorical data using the Chi-squared\(^2\) test, and continuous data (costs and QALYs) using the t-test. The comparisons between baseline and 1-month utilities were made by the paired t test, while comparisons of differences between groups were made by the two-sample t test. We computed confidence intervals for differences in costs and QALYs, and in the ICER using the bootstrap technique using the percentile-method with 10,000 replications.

**Results**

The FAME 2 trial was stopped after 888 patients had been randomized, with a median follow-up of 208 days (first, third quartiles: 103-312 days) in the PCI arm and 209 days (first, third quartiles: 106-314 days) in the medical therapy arm.\(^7\) The baseline characteristics were similar between the two groups (Table 1). The primary composite endpoint of death, myocardial infarction, and urgent revascularization occurred in 4.3% of the 447 patients randomized to PCI in the setting of an abnormal FFR and in 12.7% of the 441 patients randomized to medical therapy (p<0.001). There was no difference in the rate of death (0.2% vs. 0.7%, p=0.31) or myocardial infarction (3.4% vs. 3.2%, p=0.89), but a highly significant difference in the rate of urgent revascularization (1.6% vs. 11.1%, p<0.001).

The initial procedure and hospitalization cost was significantly greater among patients
randomized to PCI than among patients randomized to medical therapy ($9,927 vs. $3,900, p<0.001) (Figure 1). The $6,027 initial cost difference was driven primarily by the cost of the PCI procedure (Table 2). Over the subsequent year, follow-up costs were higher in the medical therapy arm, such that the cumulative costs at 12 months were $12,646 in the PCI arm, compared with $9,763 in the medical therapy arm (p<0.001). The higher follow-up costs in the medical therapy arm were driven primarily by the higher rate of revascularization (Table 3). The higher cost of antiplatelet therapy in the PCI arm was balanced by the higher cost of antianginal agents in the medical therapy arm (Table 3).

At 30 days, significantly fewer patients in the PCI arm had Canadian Cardiovascular Society Class 2 or greater angina (11.1% vs. 28.9%, p<0.0001) compared with those receiving medical therapy alone. The change in patient utility from baseline to 30 days was significantly greater in the PCI arm than in the medical therapy arm (0.054 vs. 0.001, p<0.0001) (Table 4). In the 11% of patients who achieved one year follow-up, there was a nonsignificant 0.02 decline in utility from one month to 12 months in both groups. There was little effect of either therapy on employment, with a 3.8% net change in work status among patients assigned to PCI (p=0.38), and a -4.4% net change in work status among patients assigned to medical therapy (p=0.18) between baseline and 6 months.

Assuming that the effect of PCI on utility would decline linearly over three years, and that the cost difference present at one year would not change, the ICER for PCI compared with medical therapy was $36,000/QALY. The ICER was below a willingness to pay threshold of $50,000/QALY in most (80%) of the 10,000 bootstrap replications, and was below the $100,000/QALY threshold in almost all (99.5%) replications (Figures 2 and 3).

The ICER for PCI was changed in several sensitivity analyses, but remained in the
$100,000/QALY range or less. When we arbitrarily assumed the cost of a drug-eluting stent was $400 higher than our base case estimate of $1,656 per stent, the ICER increased to $44,000/QALY, whereas if we assumed the stent cost was $400 lower than the base case, the ICER became $29,000/QALY. When we set the cost of the pressure wire to zero in the medical treatment arm, the ICER became $44,000/QALY. If we assumed the utility benefit of PCI dissipated over two years rather than the base case of three years, ICER became $54,000 QALY, whereas if we assumed the utility benefit would dissipate over four years the ICER changed to $27,000/QALY. If we set the cost of the non-urgent PCIs in follow-up to zero in the medical therapy arm, the ICER changed to $55,000/QALY. If we limited the follow-up period to 12 months, and assumed that medically treated patients after a subsequent PCI had an increase in utility of 0.053, the ICER for PCI became $60,000/QALY. Symptom status did have more of an effect on the ICER, when we analyzed the cost-effectiveness of patients with Canadian Cardiovascular Society Class 0/1 angina, it was $102,000/QALY, as compared to $26,000/QALY in those patients with Canadian Cardiovascular Society Class 2-4 angina. If Medicare costs were used for the index PCI and there was no change in the baseline costs in the medical therapy arm, the one year cost-differential would increase by approximately $2,000 and the ICER would increase to $63,000/QALY. Finally, if we excluded the baseline cost of the catheterization procedure and hospital stay in the medical therapy arm, the ICER for PCI became $63,000/QALY.

**Discussion**

Fractional flow reserve measured during coronary angiography accurately identifies flow limiting coronary lesions. The FAME 2 trial demonstrated that PCI of coronary lesions with an
FFR ≤ 0.80 improves clinical outcomes compared with best medical therapy. The present study shows that PCI in the setting of an abnormal FFR also reduces angina and improves patient utility significantly. While by design the PCI strategy had higher initial costs than the medical therapy strategy, the difference in cost between these strategies was cut by more than half over a year of follow-up (Figure 1). PCI in the setting of an abnormal FFR appears to provide good value for the added cost, with an ICER well below the standard willingness to pay threshold of $50,000 per quality-adjusted life-year, a finding that was robust in bootstrap replications (Figure 2) and several sensitivity analyses.

The COURAGE trial compared PCI with medical therapy in patients with stable CAD, but found PCI to be economically unattractive despite significant improvements in angina and quality of life, with ICERs ranging between $168,000 and $300,000 per QALY. By contrast, FAME 2 found an ICER of $36,000 per QALY for PCI in the setting of an abnormal FFR. The most likely explanation for these different results is that PCI in COURAGE was guided by the visual appearance of the lesion on coronary angiography, while PCI in FAME 2 was guided by identification of functionally significant lesions based on a measured FFR ≤ 0.80. The measurement of FFR in FAME 2 excluded 26% of otherwise eligible patients from PCI because they did not have a functionally significant lesion, despite angiographically significant CAD. Furthermore, 19% of patients in FAME 2 who had a lesion with an FFR ≤ 0.80 had another lesion with an FFR > 0.80. All of these patients and lesions presumably would have been treated with PCI in COURAGE, with little benefit and perhaps harm because of the absence of significant ischemia. Thus, the targeting of PCI in FAME 2 to the patients and lesions most likely to benefit may have reduced unnecessary procedures and increased the efficiency of PCI, and thereby led to a more favorable ICER compared with medical therapy.
There were other differences between the COURAGE and the FAME 2 trials that may have affected the economic evaluation. In COURAGE, a significant proportion of patients had few if any angina symptoms, which may explain in part the smaller utility change after PCI documented in the COURAGE trial. The higher initial difference in cost of $11,410 between the PCI arm and the medical therapy arm in COURAGE as compared to FAME 2 ($6,027) was due primarily to the much lower initial cost assigned to the medical therapy arm in COURAGE (only $752 per patient) compared with FAME 2 ($3,900 per patient). The cost of the PCI procedures in COURAGE was also higher than in FAME 2, perhaps because fewer stents were used with PCI in the setting of an abnormal FFR. The more striking difference between studies is that the initial cost difference between PCI and medical therapy in COURAGE was essentially unchanged over three years of follow-up, despite a 40% reduction in the rate of subsequent coronary revascularization procedures among patients assigned to the PCI strategy. By contrast, in FAME 2 the initial difference in cost between PCI in the setting of an abnormal FFR and medical therapy narrowed over follow-up (Figure 1) because of a significantly higher rate of hospitalizations for acute coronary syndromes and for revascularization. The follow-up costs in the PCI arm of FAME 2 may have been further lowered compared with the PCI arm in COURAGE by the use of second generation drug-eluting stents, which have had lower rates of restenosis than the bare-metal stents used in COURAGE.

The FAME 1 trial compared FFR-guided PCI with angiography-guided PCI, like that used in COURAGE, in patients with stable and unstable multivessel CAD. The economic evaluation of FAME 1 found that FFR-guided PCI led to improved clinical outcomes at lower costs (by $2,000 per patient at one year) than angiography-guided PCI. In the FAME 2 trial, application of FFR guidance may have allowed for more judicious stenting in those patients with
significant myocardial ischemia. By stenting only those lesions responsible for ischemia and medically treating the lesions that were not functionally significant, the benefit of PCI may have been maximized and the risks may have been minimized.

The main limitation of this study is that follow-up in FAME 2 was shorter than originally planned because of the premature discontinuation of the trial based upon the recommendation of the Data and Safety Monitoring Board. As a result of the limited time horizon, we had to make a number of assumptions regarding the follow-up costs and durability of the benefit from PCI. The key assumption was that the initial benefit of PCI seen at one month would gradually diminish to zero over three years of follow-up. This assumption is based on the results of COURAGE, and other studies in which the improvements in angina and quality of life from coronary revascularization declined over three years or more. Our results were similar, however, in various sensitivity analyses that varied the period of benefit between one and four years. Consequently, we believe that the projections of the durability of the benefit from PCI are reasonable. The early termination of the study may have also led to an overestimation of benefit by PCI. The other major limitation is that all patients in FAME 2 had FFR performed, so we cannot address directly the cost-effectiveness per se of using FFR. The initial FAME trial has previously shown the FFR-guided PCI strategy to have superior clinical outcomes and lower costs than standard, visually guided PCI.

Conclusion

In patients with symptomatic stable coronary artery disease, PCI in the setting of an abnormal FFR improves angina and quality of life, and appears to be economically attractive compared with best medical therapy assuming the benefit of PCI lasts longer than one year.
Funding Sources: This study was sponsored by St. Jude Medical.

Conflict of Interest Disclosures: Dr. Fearon receives institutional research support from St. Jude Medical. Dr. Pijls and Dr. De Bruyne are consultants for St. Jude Medical. No other authors have conflicts of interests relevant to this study.

References:


**Table 1: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FFR-guided PCI (n=447)</th>
<th>Medical Therapy (n=441)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.5 ±9.4</td>
<td>63.9 ±9.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Tobacco Use (%)</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Previous PCI (%)</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>≥ CCS II Angina (%)</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>Angiographically significant lesions (number per patient)</td>
<td>1.9 ±1.1</td>
<td>1.7 ±0.9</td>
</tr>
</tbody>
</table>
### Table 2. Resource Utilization at Initial Procedure

<table>
<thead>
<tr>
<th>Resource</th>
<th>FFR-guided PCI Mean cost/patient ($)</th>
<th>Medical Therapy Mean cost/patient ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheterization Laboratory</td>
<td>1209</td>
<td>709</td>
</tr>
<tr>
<td>Guide Catheter ($52)</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>Guidewire ($51)</td>
<td>49</td>
<td>15</td>
</tr>
<tr>
<td>Pressure Wire ($650)</td>
<td>650</td>
<td>603</td>
</tr>
<tr>
<td>Balloon Catheter ($166)</td>
<td>293</td>
<td>3</td>
</tr>
<tr>
<td>Drug-Eluting Stent ($1,656)</td>
<td>2,612</td>
<td>15</td>
</tr>
<tr>
<td>Bare-Metal Stent ($809)</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Adenosine ($150/vial)</td>
<td>87</td>
<td>67</td>
</tr>
<tr>
<td>GPI ($500/vial)</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>Hospital Day ($2,000)</td>
<td>3,067</td>
<td>2,018</td>
</tr>
<tr>
<td>Professional Fee ($796)</td>
<td>796</td>
<td>0</td>
</tr>
<tr>
<td>Staged PCI</td>
<td>567</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>414</td>
<td>367</td>
</tr>
<tr>
<td><strong>Total Baseline Costs</strong></td>
<td>$ 9,927</td>
<td>$3,900</td>
</tr>
</tbody>
</table>

### Table 3. Resource Utilization and Cumulative Costs During 12 Month Follow-Up

<table>
<thead>
<tr>
<th>Resource</th>
<th>FFR-guided PCI (n=447) #/group</th>
<th>Medical Therapy (n=441) #/group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>88</td>
<td>144</td>
</tr>
<tr>
<td>Hospital Days</td>
<td>446</td>
<td>861</td>
</tr>
<tr>
<td>Outpatient Visits</td>
<td>249</td>
<td>251</td>
</tr>
<tr>
<td>Exercise Tests</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>Coronary Angiograms</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>*Cost/Patient ($)</td>
<td>269</td>
<td>1,751</td>
</tr>
<tr>
<td>Non-Urgent PCI ($11,166)</td>
<td>193</td>
<td>1,248</td>
</tr>
<tr>
<td>Urgent PCI ($11,166)</td>
<td>70</td>
<td>1,099</td>
</tr>
<tr>
<td>CABG ($27,207)</td>
<td>942</td>
<td>874</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Platelet Therapy</td>
<td>229</td>
<td>111</td>
</tr>
<tr>
<td>Anti-Anginal Therapy</td>
<td>167</td>
<td>218</td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>283</td>
<td>371</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>962</td>
<td>520</td>
</tr>
<tr>
<td><strong>Total Follow-Up Costs</strong></td>
<td><strong>$2,719</strong></td>
<td><strong>$5,863</strong></td>
</tr>
<tr>
<td><strong>Total 12 Month Costs</strong></td>
<td><strong>$12,646</strong></td>
<td><strong>$9,763</strong></td>
</tr>
</tbody>
</table>

* The top portion of table 3 lists absolute counts of events during the observed follow-up, which gives a picture of the differences in medical utilization between the two groups. The bottom portion of the table lists the cumulative cost over 12 months in the two groups, which uses an actuarial technique to account for patients with less than the full 12 months follow-up.
Table 4. EQ-5D Health Utilities by Treatment Groups

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Baseline</th>
<th>1 Month</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR-Guided PCI</td>
<td>0.817 ±0.160</td>
<td>0.871 ±0.154</td>
<td>0.054</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medical Therapy</td>
<td>0.845 ±0.144</td>
<td>0.846 ±0.148</td>
<td>0.001</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. The cumulative medical costs (vertical axis) of the PCI in the setting of an abnormal FFR strategy (solid line) and the medical therapy strategy (dashed line) over 12 months of follow-up (horizontal axis).

Figure 2. Bootstrap replications of the incremental cost effectiveness of the PCI in the setting of an abnormal FFR strategy 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 quality-adjusted life-years (QALY) 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., 0.088 of the replications had a cost difference <0 and QALY difference >0).

Figure 3. Cost-effectiveness acceptability curve of the incremental cost-effectiveness of the FFR-guided strategy compared with best medical therapy, based on 10,000 bootstrap replications. The cumulative percentage of replications (vertical axis) below various willingness-to-pay thresholds (horizontal axis) in dollars per quality-adjusted life-years (QALYs). The
points on the curve indicate the cumulative proportion of replications below thresholds of $25,000/QALY (18%), $50,000/QALY (80%), $75,000/QALY (97%), $100,000/QALY (99.5%), $125,000/QALY (99.9%), and $150,000/QALY (99.97%).
Figure 1

![Graph showing cumulative cost over follow-up (months).]

- **Cumulative Cost**
  - $14,000
  - $12,000
  - $10,000
  - $8,000
  - $6,000
  - $4,000
  - $2,000
  - $0

- **Follow-up (Months)**
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
  - 10
  - 11
  - 12

- **Legend**
  - FFR-Guided PCI
  - Medical Therapy

Arrows indicate:
- Increase in cumulative cost for FFR-Guided PCI by $6,027 from 0 to 12 months.
- Increase in cumulative cost for Medical Therapy by $2,883 from 0 to 12 months.
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