Fractional Flow Reserve and the Results of the FAME Study

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Division of Cardiovascular Medicine
Stanford University Medical Center
46 year old diabetic woman with HTN and dyslipidemia presents to outside hospital with a NSTEMI in March 2009.

Cath reveals 3 vessel CAD and the patient is transferred to Stanford for CABG.

Cardiac surgeon reviews angiogram and asks for a second opinion.
Frequency of Stress Testing to Document Ischemia Prior to Elective Percutaneous Coronary Intervention

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R. Adams Dudley, MD, MBA
F. L. Lucas, PhD
David J. Malenka, MD
Erie Vittinghoff, PhD
Rita F. Redberg, MD, MSc

I n the United States, percutaneous coronary intervention (PCI) has become a common treatment strategy for patients with stable coronary artery disease (CAD) and such patients now account for the majority of PCIs performed.\(^1,2\) However, multiple studies have established that some important outcomes for patients with stable CAD (death and risk of future myocardial infarction) do not differ between patients treated with PCI plus optimal medical therapy and patients treated with optimal medical therapy alone.\(^3-10\) The addition of PCI does offer quicker relief of angina than medical therapy alone but also carries an increased risk of repeat revascularization, late-stent thrombosis, and a decreased

Context Guidelines call for documenting ischemia in patients with stable coronary artery disease prior to elective percutaneous coronary intervention (PCI).

Objective To determine the frequency and predictors of stress testing prior to elective PCI in a Medicare population.

Design, Setting, and Patients Retrospective, observational cohort study using claims data from a 20% random sample of 2004 Medicare fee-for-service beneficiaries aged 65 years or older who had an elective PCI (N=23,887).

Main Outcome Measures Percentage of patients who underwent stress testing within 90 days prior to elective PCI; variation in stress testing prior to PCI across 306 hospital referral regions; patient, physician, and hospital characteristics that predicted the appropriate use of stress testing prior to elective PCI.

Results In the United States, 44.5\% (n=10,629) of patients underwent stress testing within the 90 days prior to elective PCI. There was wide regional variation among the hospital referral regions with stress test rates ranging from 22.1\% to 70.6\% (national mean, 44.5\%; interquartile range, 39.0\%-50.9\%). Female sex (adjusted odds ratio [AOR], 0.91; 95\% confidence interval [CI], 0.86-0.97), age of 85 years or older (AOR, 0.83; 95\% CI, 0.72-0.95), a history of congestive heart failure (AOR, 0.85; 95\% CI, 0.79-0.92), and prior cardiac catheterization (AOR, 0.45; 95\% CI, 0.38-0.54) were associated with a decreased likelihood of prior stress testing. A history of chest pain (AOR, 1.28; 95\% CI, 1.09-1.54) and black race (AOR, 1.26; 95\% CI, 1.09-1.46) increased the likelihood of stress testing prior to PCI. Patients treated by physicians performing 150 or more PCIs per year were less likely to have stress testing prior to PCI (AOR, 0.84; 95\% CI, 0.77-0.93). No hospital characteristics were associated with receipt of stress testing.

Conclusion The majority of Medicare patients with stable coronary artery disease do not have documentation of ischemia by noninvasive testing prior to elective PCI.

JAMA 2008;300(15):1765-1773
Limitations of Noninvasive Imaging:

143 Patients with angiographically significant 3 vessel disease (> 70% diameter stenosis)

<table>
<thead>
<tr>
<th>Nuclear Scan Finding</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Defect</td>
<td>18%</td>
</tr>
<tr>
<td>Single Vessel Pattern</td>
<td>36%</td>
</tr>
<tr>
<td>Two Vessel Pattern</td>
<td>36%</td>
</tr>
<tr>
<td>Three Vessel Pattern</td>
<td>10%</td>
</tr>
</tbody>
</table>

Discordance occurred in 31% of vessels / territories, predominantly because of a low FFR and normal nuclear result.

Ragosta et al. Am J Cardiol 2007;99:896-902
Prognostic Importance of Ischemia

Nuclear perfusion scans in 718 patients followed for 5 years

Importance of Revascularization when Ischemia is Present

Nuclear perfusion scans performed in > 5000 patients

COURAGE Nuclear Substudy

Comparison of death/MI in patients with mod-severe pre-treatment ischemia

Shaw et al. Circulation 2008;117:1283
Limitation of Angiography

Comparison of QCA to FFR in over 3,000 lesions

Courtesy of Bernard De Bruyne, MD, PhD
FFR-Guided PCI in MVD

137 Patients, Non-Randomized

Fractional Flow Reserve versus Angiography for Multivessel Evaluation

HYPOTHESIS

FFR – guided Percutaneous Coronary Intervention (PCI) in multivessel disease is superior to current angiography – guided PCI
Participating Centers

EUROPE (14)

Cardiovascular Center Aalst \textit{(B. De Bruyne)}
Catharina Hospital Eindhoven \textit{(N. Pijls)}
Rigshospitalet, Copenhagen \textit{(T. Engstrom)}
Klinikum der Universitat Munchen \textit{(V. Klauss)}
Aarhus University Hospital \textit{(O. Frobert)}
University Hosp Bergmannsheil \textit{(W. Bojara)}
Sodersjukhuset, Stockholm \textit{(I. Herzfeld)}
Helsingborgs Lasarett \textit{(F. Schersten)}
Klinikum Darmstadt \textit{(Gerald Werner)}
Bristol Royal Infirmary \textit{(A. Baumbach)}
Staedt. Krankenhaus, Bogenhausen \textit{(G. Riess)}
Glasgow Western Infirmary \textit{(K Oldroyd)}
Royal Victoria Hosp, Belfast \textit{(G. Manoharan)}
King’s College Hosp, London \textit{(P. MacCarthy)}

USA (6)

Northeast Cardiology, Bangor, Maine \textit{(Peter N. Ver Lee)}
Stanford University \textit{(William F. Fearon)}
St Louis University \textit{(Michael Lim)}
University of Louisville \textit{(Massoud Leesar)}
University of South Carolina \textit{(Eric Powers)}
University of Virginia \textit{(Michael Ragosta)}
The FAME study was designed to reflect daily practice in performing PCI in patients with multivessel disease.

**Inclusion criteria:**
- **ALL** patients with multivessel disease
- At least 2 stenoses ≥ 50% in 2 or 3 major epicardial coronary artery disease, amenable for stenting

**Exclusion criteria:**
- Left main disease or previous bypass surgery
- Acute STEMI
- Extremely tortuous or calcified coronary arteries
Stanford Angiography-guided PCI

Indicate all stenoses ≥ 50% requiring stenting

Randomization

Patient with stenoses ≥ 50% in at least 2 of the 3 major epicardial vessels

Angiography-guided PCI

Stent all indicated stenoses

Follow-up

FFR-guided PCI

Measure FFR in all indicated stenoses

Stent only those stenoses with FFR ≤ 0.80

Patient with stenoses ≥ 50% in at least 2 of the 3 major epicardial vessels

Indicate all stenoses ≥ 50% requiring stenting

Randomization

Angiography-guided PCI

Stent all indicated stenoses

Follow-up

FFR-guided PCI

Measure FFR in all indicated stenoses

Stent only those stenoses with FFR ≤ 0.80
PRIMARY ENDPOINT

Composite of death, myocardial infarction, or repeat revascularization ("MACE") at 1 year
SECONDARY ENDPOINTS

- Individual components of MACE at 1 year
- Functional class
- Use of anti-anginal drugs
- Health-related quality of life (EuroQOL-5D)

- Procedure time
- Amount of contrast agent used during procedure
- Cost of the procedure
Assessed for eligibility N=1905

Randomized N=1005

Angiography-guided PCI N=496
- Lost to follow-up N=11
- Analyzed N=496

FFR-guided PCI N=509
- Lost to follow-up N=8
- Analyzed N=509

Not eligible N=900
- Left main stenosis N=157
- Extreme coronary tortuosity or calcification N=217
- No informed consent N=105
- Contra-indication for DES N=86
- Participation in other study N=94
- Logistic reasons N=210
- Other reasons N=31
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ANGIO-group N=496</th>
<th>FFR-group N=509</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>64±10</td>
<td>65±10</td>
<td>0.47</td>
</tr>
<tr>
<td>Male, %</td>
<td>73</td>
<td>75</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>25</td>
<td>24</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66</td>
<td>61</td>
<td>0.10</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>32</td>
<td>27</td>
<td>0.12</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>74</td>
<td>72</td>
<td>0.62</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>36</td>
<td>37</td>
<td>0.84</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>36</td>
<td>29</td>
<td>0.11</td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>26</td>
<td>29</td>
<td>0.34</td>
</tr>
<tr>
<td>LVEF, mean±SD</td>
<td>57±12</td>
<td>57±11</td>
<td>0.92</td>
</tr>
<tr>
<td>LVEF &lt; 50%, %</td>
<td>27</td>
<td>29</td>
<td>0.47</td>
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### Procedural Results (1)

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<tr>
<td><strong># indicated lesions per patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-70% narrowing, No (%)</td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 1.0</td>
<td>0.34</td>
</tr>
<tr>
<td>70-90% narrowing, No (%)</td>
<td>550 (41)</td>
<td>624 (44)</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 90% narrowing, No (%)</td>
<td>553 (41)</td>
<td>530 (37)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>247 (18)</td>
<td>260 (18)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Stents per patient</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lesions successfully stented (%)</td>
<td>92%</td>
<td>94%</td>
<td>-</td>
</tr>
<tr>
<td>DES, total, No</td>
<td>1359</td>
<td>980</td>
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<tr>
<td>Length of hospital stay (days)</td>
<td>3.7 ± 3.5</td>
<td>3.4 ± 3.3</td>
<td>0.05</td>
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## Adverse Events at 1 year

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<td>Total no. of MACE</td>
<td>113</td>
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<td>0.02</td>
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<td>76</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial infarction, specified</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All myocardial infarctions</td>
<td>43 (8.7)</td>
<td>29 (5.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Small periprocedural CK-MB 3-5 x N</td>
<td>16</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Other infarctions (“late or large”)</td>
<td>27</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>
**Event-free Survival**

**Absolute Difference in MACE-Free Survival**

- **30 days:** FFR-guided 2.9% vs. Angio-guided 90 days 3.8%
- **180 days:** FFR-guided 4.9% vs. Angio-guided
- **365 days:** FFR-guided 5.1% vs. Angio-guided
FAME 1 Year Economic Evaluation

Bootstrap Simulation

- Incremental QALY
- Incremental Cost [USD]

FFR Guidance Improves outcomes

FFR Guidance Saves Resources

AHA 2009
2 Year Survival Free of MACE

Late Breaking Trial, TCT 2009
## Adverse Events at 2 Years

<table>
<thead>
<tr>
<th></th>
<th>Angio-Guided n = 496</th>
<th>FFR-Guided n = 509</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total no. of MACE</strong></td>
<td>139</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td><strong>Individual Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>19 (3.8)</td>
<td>13 (2.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>48 (9.7)</td>
<td>31 (6.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>CABG or repeat PCI</td>
<td>61 (12.3)</td>
<td>53 (10.4)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Composite Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or Myocardial Infarction</td>
<td>63 (12.7)</td>
<td>43 (8.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death, MI, CABG, or re-PCI</td>
<td>110 (22.2)</td>
<td>90 (17.7)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Late Breaking Trial, TCT 2009
2 Year Outcome of Deferred Lesions

513 Deferred Lesions in 509 FFR-Guided Patients

2 Years

31 Myocardial Infarctions

9 Late Myocardial Infarctions

1 Myocardial Infarction due to an Originally Deferred Lesion

22 Peri-procedural

8 Due to a New Lesion or Stent-Related

Only 1/513 or 0.2% of deferred lesions resulted in a late myocardial infarction

Late Breaking Trial, TCT 2009
2 Year Outcome of Deferred Lesions

513 Deferred Lesions in 509 FFR-Guided Patients

2 Years

53 Repeat Revascularizations

16 Originally Deferred Lesions

10 Originally Deferred Lesions with Clear Progression

37 in a New Lesion or in a Restenotic One

6 Without FFR or Despite an FFR > 0.80

Only 10/513 or 1.9% of deferred lesions clearly progressed requiring repeat revascularization

Late Breaking Trial, TCT 2009
Post FAME Case Example

• 46 year old diabetic woman with HTN and dyslipidemia presents to outside hospital with a NSTEMI in March 2009.

• Cath reveals 3 vessel CAD and the patient is transferred to Stanford for CABG.

• Cardiac surgeon reviews angiogram and asks for a second opinion.
FFR of Ramus = 0.97
FFR of RCA = 0.87
Summary of Case

• Anatomic 3V CAD, functional 1V CAD

• Successfully treated with single stent

• 130 cc contrast, < 1 hour procedure

• Remains event free at 8 months
 Patients with angiographically 3VD (N=115), proportions per number of diseased vessels after assessment by FFR

Angiographic 3 Vessel Disease

Tonino et al., JACC 2009 (submitted)
Which Lesions Need FFR?

1329 lesions in the FFR-guided arm

~65%

Stenosis classification by angiography

Tonino et al., JACC 2009 (submitted)
Implications of FAME

1 year MACE Rates

- PCI
  - SYNTAX: 19.1%
  - PCI - angiography: 18.3%

- PCI - FFR
  - SYNTAX: 11.2%
  - PCI - FFR: 13.2%
Implications of FAME

Death and MI in the COURAGE study

Conclusion:

- FFR-guided PCI in patients with multi-vessel CAD compared to angio-guided PCI:
  - Improves outcomes at 1 year
  - Saves money
  - Simplifies the procedure
  - Is durable out to two years with excellent outcomes in the deferred lesions