Use of FFR for Optimal Management of Multivessel Coronary Artery Disease

Richard G. Bach, MD
Associate Professor of Medicine
Washington University School of Medicine
Director of Cardiac Intensive Care Unit
Barnes-Jewish Hospital
St. Louis, Missouri
Disclosure:

• Research Support/Grants: Astra Zeneca, LP, Bristol-Myers Squibb Co, Eli Lilly & Co, and Merck/Schering-Plough Pharmaceuticals

• Consulting (Clinical Event Committees): F. Hoffman-La Roche and Wyeth/Pfizer
OUTLINE

- Case presentation
- Clinical trial data: Evidence
- Implications for clinical practice
Case Presentation:

HPI: 69 year-old woman

- 6-8 months vague chest discomfort and shortness of breath with exertion
- Remains active but more fatigued
- Definite decrease in exercise tolerance
Past Medical History

- Hyperlipidemia
- Hypertension
- Obstructive sleep apnea
- Endometrial cancer s/p hysterectomy
Nuclear stress test

• Completed at an outside facility
• Showed possible apical and inferolateral ischemia;
• Ejection fraction normal
• No discomfort during the test
• No ECG changes reported

Cardiac Catheterization done:
Coronary Angiography
Cardiac catheterization

- “Significant 3-vessel disease”
  - Proximal LAD: 60-70%
  - First OM: 95% at bifurcation
  - Proximal-mid RCA: diffuse 70%

- Referred for CABG
  - Patient hesitant and sought second opinion
  - Referred by new cardiologist for possible PCI
QUESTION: What is the best option for the management of this patient?

A. Medical Therapy (per COURAGE)
B. Calculate the SYNTAX Score to decide on PCI vs. CABG
C. Multivessel PCI based on angiogram
D. FFR-guided PCI
QUESTION: What is the best option for the management of this patient?

A. Medical Therapy (per COURAGE)
B. Calculate the SYNTAX Score to decide on PCI vs. CABG
C. Multivessel PCI based on angiogram
D. FFR-guided PCI
COURAGE: Optimal Medical Therapy

Survival Free from Death and MI (median FU 4.6 yrs)

Hazard ratio: 1.05
95% CI (0.87-1.27)
P = 0.62

Number at Risk
Medical Therapy 1138 1017 959 834 638 408 192 30
PCI 1149 1013 952 833 637 417 200 35

Boden WE et al. NEJM 2007;356:1503-16
Issues with ‘COURAGE’

• Randomization
  – only 6% of total 35,539 pts screened

• Crossover
  – 33% at median of 4.6 years

• Increased revascularization rate
  – 6% of PCI used no stents
  – 97% of stents used were BMS
QUESTION: What is the best option for the management of this patient?

A. Medical Therapy (per COURAGE)
B. Calculate the SYNTAX Score to decide on PCI vs. CABG
C. Multivessel PCI based on angiogram
D. FFR-guided PCI
• 1800 Patients with LM or 3V CAD
• Randomly assigned 1:1 to CABG vs. PCI
• RESULTS:
  1 Yr Mortality: No different
  MACCE @ 1yr favored CABG: 12.4% vs. 17.8%
SYNTAX Results

A. Low SYNTAX Score

B. Intermediate SYNTAX Score

C. High SYNTAX Score

Serruys PW et al. NEJM 2009;360:961-72
Our Patient

**Summary**

<table>
<thead>
<tr>
<th>Lesion 1</th>
<th>Lesion 2</th>
<th>Lesion 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(segment 1): 1x2=</td>
<td>(segment 2): 1x2=</td>
<td>(segment 12a): 1x2=</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Length &gt;20 mm</td>
<td></td>
<td>Angulation &lt;70°</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><em>Sub total lesion 1</em></td>
<td><em>Sub total lesion 2</em></td>
<td><em>Sub total lesion 3</em></td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

**SYNTAX Score = 19**

---

**MACCE by SYNTAX Score 0-22**

<table>
<thead>
<tr>
<th>SYNTAX Score</th>
<th>Mean baseline</th>
<th>CABG 16.6 ± 4.0</th>
<th>TAXUS 16.7 ± 4.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-22</td>
<td>P=0.98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The cumulative MACCE rate is displayed for the SYNTAX Trial group this score corresponds to.
QUESTION: What is the best option for the management of this patient?

A. Medical Therapy (per COURAGE)
B. Calculate the SYNTAX Score to decide on PCI vs. CABG
C. Multivessel PCI based on angiogram
D. FFR-guided PCI
Issues with SYNTAX
(Including Angiographic Assessment for Revascularization Decisions)

- Large number of stents implanted per patient: $4.6 \pm 2.3$
- Long length of stented segments: ave $86 \pm 48$ mm, with stent length $>100$mm in 33%
- High rate of definite stent thrombosis 3.3 - 4% at 1 year!
Limitations of Angiography
Physiologic Lesion Assessment

Adenosine IC

During Maximal Vasodilatation

\[
F FR = \frac{P_d}{P_a} = 0.55
\]

\[
F FR = \frac{100}{90} = 0.70
\]
Defer Study: Quantitative Coronary Angiography

N=325
Elective PTCA
No documented ischemia

Angio and FFR

FFR ≥ 0.75
FFR < 0.75

Randomization
PTCA

Decisions:
Defer PTCA n=89
Perform PTCA n=96
Reference Group n=141

Stenosis Severity

% 100
90
80
70
60
50
40
30
20

FFR ≥ 0.75
Defer Group
Perform Group
Reference Group

FFR < 0.75

DEFER: 5 Year Cardiac Death and MI

Cardiac Death and MI less than 1% per year!
in the DEFER group

P< 0.003

P< 0.005

15.7

3.1

0

DEFER
PERFORM
REFERENCE

FFR > 0.75
FFR < 0.75

Pijls, et al. JACC 2007
Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

Pim A.L. Tonino, M.D., Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Uwe Siebert, M.D., M.P.H., Sc.D., Fumiaki Ikeno, M.D., Marcel van ‘t Veer, M.Sc., Volker Klauss, M.D., Ph.D., Ganesh Manoharan, M.D., Thomas Engström, M.D., Ph.D., Keith G. Oldroyd, M.D., Peter N. Ver Lee, M.D., Philip A. MacCarthy, M.D., Ph.D., and William F. Fearon, M.D., for the FAME Study Investigators*
Patient with stenoses ≥ 50% in at least 2 of the 3 major epicardial vessels

Indicate all stenoses ≥ 50% considered for stenting

Randomization

Angiography-guided PCI

Stent all indicated stenoses

1-year follow-up

FFR-guided PCI

Measure FFR in all indicated stenoses

Stent only those stenoses with FFR ≤ 0.80
### FAME: Procedural Results

<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><strong>Mean # of Indicated Lesions per Patient</strong></td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 1.0</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>FFR results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions successfully measured (%)</td>
<td>-</td>
<td>1329 (98%)</td>
<td>-</td>
</tr>
<tr>
<td>Lesions with FFR ≤ 0.80 (%)</td>
<td>-</td>
<td>874 (63%)</td>
<td>-</td>
</tr>
<tr>
<td>Lesions with FFR &gt; 0.80 (%)</td>
<td>-</td>
<td>513 (37%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Stents per patient</strong></td>
<td>2.7 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lesions successfully stented (%)</td>
<td>92%</td>
<td>94%</td>
<td>-</td>
</tr>
<tr>
<td>Total DES</td>
<td>1359</td>
<td>980</td>
<td>-</td>
</tr>
</tbody>
</table>

★ FFR-guided group used 0.8 less stents per patient!

FFR-guided

30 days 2.9%

90 days 3.8%

180 days 4.9%

360 days 5.3%

Angio-guided

Absolute Difference in MACE-free survival

FAME study:
Event-free Survival
Angiographic Versus Functional Severity of Coronary Artery Stenoses in the FAME Study

Fractional Flow Reserve Versus Angiography in Multivessel Evaluation

Pim A. L. Tonino, MD,* William F. Fearon, MD,† Bernard De Bruyne, MD, PhD,‡
Keith G. Oldroyd, MD,§ Massoud A. Leesar, MD,¶ Peter N. Ver Lee, MD,F
Philip A. MacCarthy, MD, PhD,# Marcel van’t Veer, MSC, PHD,* Nico H. J. Pijls, MD, PHD*

Eindhoven, the Netherlands; Stanford, California; Aalst, Belgium; Glasgow and London, United Kingdom;
Cincinnati, Ohio; and Bangor, Maine

FAME:
Angiographic vs. Functional NDV

Pts with angiographic 3VD (%DS >50%)
N=115
QUESTION:
What is the best option for the management of this patient?

A. Medical Therapy (per COURAGE)
B. Calculate the SYNTAX Score to decide on PCI vs. CABG
C. Multivessel PCI based on angiogram
D. FFR-guided PCI
FFR Assessment: LAD

- Eccentric, calcified, hazy 70% lesion
  - Pressure wire (Volcano Prestige) equalized in the left main and passed into the mid LAD
  - Resting FFR decreased to 0.95

- Adenosine 60mcg and 120mcg
  - FFR 0.89, 0.91

- Final result
  - Lesion physiologically not significant…
  - PCI Deferred
Coronary Angiography: LCA
PCI of Bifurcating OM with JBT
Coronary Angiography: RCA
FFR Assessment: RCA

- Eccentric, hazy, long 70% lesion
  - Volcano Prestige wire equalized in the proximal RCA and passed distally into the PDA
- Adenosine 30 mcg
  - FFR 0.72

- Final result
  - Physiologically significant
Follow-up…

• Patient with uncomplicated recovery…discharged in good condition
• ASA indefinitely
• Clopidogrel minimum one year
• Clinically improved…
  – No further chest tightness reported
  – Improved exercise tolerance
Conclusions

• In appropriately selected patients with multivessel CAD, a strategy of FFR-guided PCI can provide symptomatic benefit with strong evidence of superior outcomes, even at reduced cost.
### FAME: Patient Outcomes

| Events at 1 year, # (%) | ANGIO-Group  
  n = 496 | FFR-Group  
  n = 509 | P-value |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, CABG, or repeat-PCI</td>
<td>91 (18.4)</td>
<td>67 (13.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death</td>
<td>15 (3.0)</td>
<td>9 (1.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Death or MI</td>
<td>55 (11.1)</td>
<td>37 (7.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>CABG or repeat PCI</td>
<td>47 (9.5)</td>
<td>33 (6.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Total # of MACE</td>
<td>113</td>
<td>76</td>
<td>0.02</td>
</tr>
</tbody>
</table>

★ MACE rates in the FFR-guided group are 28% lower than the Angio-guided group!

★ Death or MI in the FFR-guided group is 34% lower than in the Angio-guided group!

Functional SYNTAX Score

![Graph A](Image)

- **Death or MI Rate at 1-year (%)**
  - **Low risk**
  - **Medium risk**
  - **High risk**

**Classic SYNTAX score**
- Low risk: 5.4%
- Medium risk: 6.0%
- High risk: 11.7%

**Functional SYNTAX score**
- Low risk: 4.8%
- Medium risk: 7.5%
- High risk: 15.8%

![Graph B](Image)

- **MACE rate at 1-year (%)**
- **Classic SYNTAX score**
  - Low risk: 8.4%
  - Medium risk: 10.2%
  - High risk: 20.9%
- **Functional SYNTAX score**
  - Low risk: 9.0%
  - Medium risk: 11.3%
  - High risk: 26.7%

*Statistical significance:
- *p < 0.05
- **p < 0.01

Nam CW et al. JACC 2011; 58(12):1211-1218
FAME vs. SYNTAX

Implications of FAME

1 year MACE Rates

PCI
SYNTAX: 19.1%
FAME: 18.4%

CABG
SYNTAX: 11.2%
FAME: 13.2%

PCI - angio
SYNTAX: 11.2%
FAME: 13.2%

PCI - FFR
SYNTAX: 13.2%
FAME: 18.4%
Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D.,
Bindu Kalesan, M.P.H., Emanuele Barbato, M.D., Ph.D.,
Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D.,
Sven Mobius-Winckler, M.D., Gilles Rioufol, M.D., Ph.D., Nils Witt, M.D., Ph.D.,
Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engström, M.D.,
Keith G. Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D.,
Peter Verlee, M.D., Ole Frobert, M.D., Nick Curzen, B.M., Ph.D.,
Jane B. Johnson, R.N., B.S.N., Peter Jüni, M.D., and William F. Fearon, M.D.,
for the FAME 2 Trial Investigators*
FAME 2: Trial Design

Stable patients with 1, 2, or 3 vessel CAD evaluated for PCI with DES
n=1220

FFR in all target lesions

Randomized Trial

At least 1 stenosis with FFR ≤ 0.80 (n=888)

Randomization 1:1

PCI + MT
MT

73%

Registry

All FFR > 0.80 (n=322)

MT
50% randomly assigned to follow-up

27%

Primary Endpoint: Death, MI, Urgent Revascularization at 2 years

De Bruyne B et al. NEJM 2012;367:991-1001
FAME 2: Primary Outcome:
Death, MI, Unplanned Hospitalization with Urgent Revascularization

Cumulative incidence (%)

PCI+MT vs. MT: HR 0.32 (0.19-0.53); p<0.001
PCI+MT vs. Registry: HR 1.29 (0.49-3.39); p=0.61
MT vs. Registry: HR 4.32 (1.75-10.7); p<0.001

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>MT</th>
<th>PCI+MT</th>
<th>Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>441</td>
<td>447</td>
<td>166</td>
</tr>
<tr>
<td>1</td>
<td>414</td>
<td>414</td>
<td>156</td>
</tr>
<tr>
<td>2</td>
<td>370</td>
<td>388</td>
<td>145</td>
</tr>
<tr>
<td>3</td>
<td>322</td>
<td>351</td>
<td>133</td>
</tr>
<tr>
<td>4</td>
<td>283</td>
<td>308</td>
<td>117</td>
</tr>
<tr>
<td>5</td>
<td>253</td>
<td>277</td>
<td>106</td>
</tr>
<tr>
<td>6</td>
<td>220</td>
<td>243</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>192</td>
<td>212</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>162</td>
<td>175</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>127</td>
<td>155</td>
<td>52</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>117</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>92</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>53</td>
<td>13</td>
</tr>
</tbody>
</table>

De Bruyne B et al. NEJM 2012;367:991-1001
FAME 2: Urgent Revascularization

PCI+MT vs. MT: HR 0.13 (0.06-0.30); p<0.001
PCI+MT vs. Registry: HR 0.63 (0.19-2.03); p=0.43
MT vs. Registry: HR 4.65 (1.72-12.62); p=0.009

De Bruyne B et al. NEJM 2012;367:991-1001
FAME 2: Conclusions

- In patients with stable coronary artery disease, FFR-guided PCI, improves patient outcome as compared with medical therapy alone.

- This improvement is driven by a dramatic decrease in the need for urgent revascularization for ACS.

- In patients with functionally non-significant stenoses medical therapy alone resulted in an excellent outcome, regardless of the angiographic appearance of the stenoses.

De Bruyne B et al. NEJM 2012;367:991-1001