FFR in multivessel disease & FAME study

Coronary Physiology in the Catheterization Laboratory
European Heart House
April 7-9, 2011
Pim A.L. Tonino, MD, PhD
A rather common patient in our cath lab today…….

- 72-year-old male, stable angina class 3
- small non-STEMI 3 weeks earlier, no diagnostic Δ-ECG
- residual angina class 2-3
- positive exercise stress test

Coronary angiography
LCA

FAME STUDY patient # 1249
June 25th, 2007
RCA

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June 25th, 2007
A rather common patient in our cath lab today……

- 72-year-old male, stable angina class 3
- small non-STEMI 3 weeks earlier, no diagnostic Δ-ECG
- residual angina class 2-3
- positive exercise stress test

Coronary angiography

- 50% LAD artery
- 50% Intermediate branch
- 90% LCX artery
- 70% RCA proximal
- 50% RCA mid
How to proceed?
It is not the question **IF** stenting is indicated, but **WHERE** and **HOW MANY**
Ischemia-producing coronary lesions cause symptoms and cardiac events

Hachamovitch et al., Circulation 1998
PCI of ischemic lesions → better outcome

Shaw et al. COURAGE trial nuclear substudy. Circulation 2008
Ischemic lesions (FFR < 0.75) treated by stenting

freedom from chest pain

DEFER-study, JACC 2007; 49: 2105-2111
Functionally NON-significant stenoses

a functionally non-significant stenosis (“non-ischemic stenosis”) generally gives no complaints

So, from the symptomatic point of view there is no reason to stent such lesion
Cardiac Death And Acute MI After 5 Years: \textit{functionally non-significant stenoses}

Defer, JACC, 2008
So, functionally significant (= ischemic) lesions should be revascularized, ..... 

...........whereas it makes no sense to stent non-ischemic lesions

So, if we are able to accurately discriminate ischemic from non-ischemic lesions we can selectively treat the ischemic lesions by PCI and the non-ischemic lesions by medical treatment
Particularly in multivessel disease we often have insufficient information about stenosis-related myocardial ischemia.
The angiogram poorly predicts presence of myocardial ischemia related to a specific coronary stenosis.

Tonino et al., JACC, June 2010
Because ...

Non-invasive tests aren’t always performed pre-PCI

Only 44.5% (20.1% - 70.6%) of Medicare patients undergoing elective PCI, underwent stress-testing < 90 days before PCI
Non-invasive tests are frequently inaccurate in multivessel disease:

- **Excercise test**: non-conclusive, information per patient

- **Nuclear scan**: inaccurate in MVD (balanced ischemia, serial stenosis)
So ..... we need FFR
verifying equal pressures before entering the coronary artery
intermediate branch
PW (Certus wire) in intermediate branch
intermediate branch

resting         adenosine                pull-back

resting         adenosine                pull-back

intermediate branch
PW in LAD artery
Pressure Wire back to ostium of LCA
resting  adenosine  LCX
LCX

Pull-back & Advance
LCX after stenting (Endeavour 3.5 x 12)
LCX after stenting

resting

adenosine

LCX after stenting
verifying equal pressures before entering RCA
Pressure Wire in RCA
hyperemic pull-back recording RCA

distal stenosis  proximal stenosis
LESSONS FROM THIS PATIENT:

• only 1 stent necessary ; cost-savings!

• if treatment was based upon angio and performed by “more agresssive” interventionalist (or had been randomized to angio-guided arm of FAME study), at least 3 and maybe 4 or 5 stents would have been placed
FFR-guided vs. Angio-guided multivessel PCI (125 patients) (event-free survival after 30 months)

Leesar et al, JACC 2005
But, ….. does it matter to selectively stent ischemic stenoses? Does routine use of FFR in MVD impact prognosis? What about functional class? Procedure time?

The windtunnel for testing such an FFR-guided PCI strategy is a randomized trial
Lesions warranting PCI identified

PCI performed on indicated lesions only if FFR < 0.80

Randomized

Primary Endpoint

Composite of death, MI and repeat revasc. (MACE) at 1 year

Key Secondary Endpoints

Individual rates of death, MI, and repeat revasc., MACE, and functional status at 2 years

FFR-Guided

PCI performed on indicated lesions

Angio-Guided

PCI performed on indicated lesions
Participating Centers

USA (6)
Stanford University (William F. Fearon)
Northeast Cardiology, Bangor, Maine (Peter N. Ver Lee)
University of Louisville (Massoud Leesar)
St Louis University (Michael Lim)
University Hospital Virginia (Michael Ragosta)
University of South Carolina (Eric Powers)

EUROPE (14)
Cardiovascular Center Aalst (B. De Bruyne)
Catharina Hospital Eindhoven (N.Pijls)
Rigshospitalet, Copenhagen (T.Engstrom)
Klinikum der Universitat Munchen (V.Klauss)
Aarhus University Hospital (Ole Frobert)
University Hospital Bergmannsheil (Waldemar Bojara)
Sodersjukhuset, Stockholm (I Herzfeld)
Helsingborgs Lasarett (F Schersten)
Klinikum Darmstadt (Gerald Werner)
Bristol Royal Infirmary (A.Baumbach)
Staedt. Krankenhaus, Bogenhausen (G.Riess)
Glasgow Western Infirmary (Keith Oldroyd)
Royal Victoria Hospital, Belfast (Ganesh Manoharan)
1905 Patients were assessed for eligibility

900 Were not eligible
157 Had left main artery stenosis
217 Had extreme vessel tortuosity or calcification
105 Did not provide consent
86 Had contra-indication for drug-eluting stent
94 Participated in another study
210 Had logistic reasons
31 Had other reasons

> 50%

1005 Underwent randomization

496 Were assigned to angiography-guided PCI
36 Were lost to follow-up
496 Were included in intention-to-treat analysis

509 were assigned to FFR-guided PCI
29 Were lost to follow-up
509 Were included in intention-to-treat analysis
## Baseline

<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>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>
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<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>
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<td>Hyperlipidemia, %</td>
<td>73</td>
<td>72</td>
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<td>Previous MI, %</td>
<td>36</td>
<td>37</td>
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<tr>
<td>NSTE ACS, %</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>
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*Tonino et al. N Engl J Med. 2009*
## Procedural data

<table>
<thead>
<tr>
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<th>Angio-Guided (n = 496)</th>
<th>FFR-Guided (n = 509)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated lesions / patient</td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 1.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Stents / patient</td>
<td>2.7 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>70 ± 44</td>
<td>71 ± 43</td>
<td>0.51</td>
</tr>
<tr>
<td>Contrast agent used (ml)</td>
<td>302 ± 127</td>
<td>272 ± 133</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Equipment cost (US $)</td>
<td>6007</td>
<td>5332</td>
<td>&lt;0.001</td>
</tr>
<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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</tbody>
</table>
# Adverse events after 1 year

<table>
<thead>
<tr>
<th>Event</th>
<th>Angio-Guided n = 496</th>
<th>FFR-Guided n = 509</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Total no. of MACE</td>
<td>113</td>
<td>76</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>Myocardial Infarction</td>
<td>43 (8.7)</td>
<td>29 (5.7)</td>
<td>0.07</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>Death or Myocardial Infarction</td>
<td>55 (11.1)</td>
<td>37 (7.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death, MI, CABG, or re-PCI</td>
<td>91 (18.3)</td>
<td>67 (13.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
1 year event-free survival

Absolute Difference in MACE-Free Survival

- 30 days: 2.9%
- 90 days: 3.8%
- 180 days: 4.9%
- 360 days: 5.1%

Survival Free of MACE

Days since Randomization
1 year economic evaluation

Bootstrap Simulation

Fearon et al. Circulation, December, 2010
# Adverse events after 2 years

<table>
<thead>
<tr>
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<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>0.01</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><strong>Myocardial Infarction</strong></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 MI</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>

*Tonino et al. N Engl J Med. 2009*
Freedom from angina

- Angiography-guided
- FFR-guided

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 Year</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angio-guided</td>
<td>23.2</td>
<td>77.9</td>
<td>75.8</td>
</tr>
<tr>
<td>FFR-guided</td>
<td>25.9</td>
<td>81.3</td>
<td>79.9</td>
</tr>
</tbody>
</table>

% Freedom from angina
Does this mean we really have to measure all lesions with FFR in MVD patients?

FAME angiographic substudy: FFR mandatory in all MVD PCI, in all stenoses of 50-90%
How does FAME fit with other recently performed RCT’s to (DES) stenting in Multivessel Disease?

⇒ Keynote lecture
Why is outcome of FFR guided procedures so good?
Intrinsic risk of death and myocardial infarction?
Ischemic lesion $\rightarrow$ intrinsic risk 5\% per year
Non-ischemic lesion $\rightarrow$ intrinsic risk 1\% per year
Stented stenosis $\rightarrow$ intrinsic risk 3\% per year

“stent ‘m all” $\rightarrow$ intrinsic risk 12\% $\rightarrow$ 12\%
“stent only the ischemic ones” $\rightarrow$ intrinsic risk 12 $\rightarrow$ 8\%
both strategies eliminate ischemia $\rightarrow$ similar functional class
FAME study: CONCLUSIONS (1)

Routine measurement of FFR during PCI with DES in patients with multivessel disease, when compared to current angiography guided strategy:

- Reduces the rate of the composite endpoint of death, myocardial infarction, re-PCI and CABG at 1 year by ~ 30%
- Reduces mortality and myocardial infarction at 1 year by ~ 35%
FAME study: CONCLUSIONS (2)

Routine measurement of FFR during PCI with DES in patients with multivessel disease, when compared to current angiography guided strategy

- *Is cost-saving and does not prolong the procedure*
- *Reduces the number of stents used*
- *Decreases the amount of contrast agent used*
- *Results in a similar, if not better, functional status*
Routine measurement of FFR during DES-stenting in patients with multivessel disease is superior to current angiography guided treatment.

It improves outcome of PCI significantly

It supports the evolving paradigm of

“Functionally Complete Revascularization”, i.e. stenting of ischemic lesions and medical treatment of non-ischemic ones.
Routine measurement of FFR during DES-stenting in patients with multivessel disease is superior to current angiography guided treatment.

It improves outcome of PCI significantly.

It supports the evolving paradigm of

“Functionally Complete Revascularization”, i.e. stenting of ischemic lesions and medical treatment of non-ischemic ones.
FFR now Class I Level A in ESC guidelines!

Table 33  Recommendations for specific percutaneous coronary intervention devices and pharmacotherapy

<table>
<thead>
<tr>
<th>Description</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.</td>
<td>I</td>
<td>A</td>
<td>15, 28</td>
</tr>
<tr>
<td>DES(\text{\textsuperscript{a}}) is recommended for evaluation of coronary reserve (for preclinical testing important DAPT).</td>
<td>I</td>
<td>A</td>
<td>45, 46,</td>
</tr>
</tbody>
</table>
**What to do?**

1. CABG anyway (3-vessel disease)
2. PCI of RCA lesions only
3. Nuclear test (MIBI Spect)
4. PCI of all lesions (5 stents)
5. Further invasive diagnostic testing (FFR)
Start of procedure:
sensor close to tip of JR guiding catheter to verify equal pressures at that point
resting  adenosine  pullback

RCA:

FFR = 0.34
RCA after one stent:

FFR = 0.74
Why do we find gradient across proximal stenosis after having stented the distal one?

recording before any stent

recording after stenting distal stenosis

distal stenosis

proximal stenosis
RCA after 2 stents:

FFR = 0.87

adenosine pullback
Before entering into LCA:
verify again equal pressures when sensor at tip of the guiding catheter
LCX:
FFR = 0.94

adenosine
Diag branch:

FFR = 0.49

hyperemia     stop adenosine
Diag branch after stenting: FFR = 0.81
(no recording found)
LAD:

FFR = 0.83
In summary:

- RCA (2 stenoses) : FFR 0.34 $\rightarrow$ 0.74 $\rightarrow$ 0.84 (2 stents)
- MOCX : FFR 0.94 $\rightarrow$ no stent
- Diag branch: FFR 0.49 $\rightarrow$ 0.81 (1 stent)
- LAD: FFR 0.83 $\rightarrow$ no stent

Total time of procedure: 21.26 h $\rightarrow$ 22.12 h = 46 min

Case performed by Guus Brueren

Patient participated in FAME study
What about ref diameter, vessel size?

Reference diameter:

- FAME 2.5mm
- Pivotal DES trials 2.6-2.8mm

selection bias

single vessel disease
excluding lesions <2.5mm
less extensive disease

→ Most studies on PCI in MVD: no QCA
(MASII, ARTS, SYNTAX)
What about ref diameter, vessel size?

<table>
<thead>
<tr>
<th></th>
<th>Angio-guided group</th>
<th>FFR-guided group</th>
</tr>
</thead>
<tbody>
<tr>
<td>% lesions proximal</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td>% lesions prox or mid</td>
<td>71%</td>
<td>73%</td>
</tr>
</tbody>
</table>

So, FAME does not represent ‘smaller’ vessels, but the early DES trials represent ‘larger’ vessels.
MACE in SYNTAX – 3VD and FAME

- **PCI**
  - SYNTAX – 3VD: 19.1%
  - FAME: 18.3%

- **CABG**
  - SYNTAX – 3VD: 11.2%
  - FAME: 13.2%
MACCE in SYNTAX – 3VD and FAME

similar definition of MACCE, including CVA and excluding CKMB 3-5 x N

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI TERCILE</td>
<td>19.1</td>
<td>21.5</td>
</tr>
<tr>
<td>PCI LOWER</td>
<td>18.6</td>
<td>17.2</td>
</tr>
<tr>
<td>PCI ALL</td>
<td>11.2</td>
<td>8.8</td>
</tr>
<tr>
<td>PCI FAME</td>
<td>14.7</td>
<td>11.0</td>
</tr>
<tr>
<td>CABG TERCILE</td>
<td></td>
<td></td>
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FUNCTIONAL CLASS
in COURAGE - SYNTAX – 3VD and FAME

% free of angina at 1 year

<table>
<thead>
<tr>
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<th>COURAGE MEDICAL</th>
<th>SYNTAX</th>
<th>FAME PCI-angio</th>
<th>FAME PCI-FFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>58</td>
<td>71</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Medical</td>
<td>50</td>
<td>76</td>
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TREATMENT OPTIONS FOR MVD

R/x          PCI         CABG

FAME

COURAGE → PCI ← SYNTAX
TREATMENT OPTIONS FOR MVD

R/x  PCI  CABG