Coronary Physiology In The Cathlab

FAME STUDY: 2-year Follow-Up & CLINICAL SUBGROUP ANALYSIS

Educational Training Program ESC
European Heart House
april 7th – 9th 2011

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The Netherlands,
FAME study: **HYPOTHESIS**

FFR – guided Percutaneous Coronary Intervention (PCI) in multivessel disease, is superior to current angiography – guided PCI
FAME study: DESIGN

Randomized multicenter study in 1005 patients undergoing DES-stenting for multivessel disease in 20 US and European centers

- independent core-lab
- independent data analysis
- blinded adverse event committee

Multivessel disease:
Stenoses of > 50% in at least 2 of the 3 major coronary arteries
FAME study: Study Population

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

**Note:** patients with previous PCI were not excluded
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

FFR-guided PCI

Measure FFR in all indicated stenoses

Stent only those stenoses with FFR ≤ 0.80

Follow-up at 1, 2, 5 years
FAME study: PRIMARY ENDPOINT

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

- MACE at 2 and 5 years
- Individual components of MACE at 1,2,5 years
- 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
FAME study: Treatment

- PCI according to local routine
- Only drug-eluting stents (DES)
- FFR measured by Pressure Wire (Certus wire, RADI Medical Systems)
- Hyperemia induced by i.v. adenosine 140 µg/kg/min in femoral vein
- Follow-up visits at 1 and 6 months and 1, 2, and 5 years
## FAME study: Baseline Characteristics (1)

<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>
</tr>
<tr>
<td></td>
<td>ANGIO-group N=496</td>
<td>FFR-group N=509</td>
<td>P-value</td>
</tr>
<tr>
<td>---------------------------------</td>
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</tr>
<tr>
<td># indicated lesions per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-70% narrowing, No (%)</td>
<td>550 (41)</td>
<td>624 (44)</td>
<td>-</td>
</tr>
<tr>
<td>70-90% narrowing, No (%)</td>
<td>553 (41)</td>
<td>530 (37)</td>
<td>-</td>
</tr>
<tr>
<td>90-99% narrowing, No (%)</td>
<td>207 (15)</td>
<td>202 (14)</td>
<td>-</td>
</tr>
<tr>
<td>Total occlusion, No (%)</td>
<td>40 (3)</td>
<td>58 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Patients with ≥1 total occlusion (%)</td>
<td>7.5</td>
<td>10.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Patients with prox LAD involved, No (%)</td>
<td>186 (38)</td>
<td>210 (41)</td>
<td>0.39</td>
</tr>
<tr>
<td>% lesions in segment 1,2,6,7,or 11</td>
<td>960 (71)</td>
<td>1032 (73)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
## FAME study: Procedural Results (1)

<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># indicated lesions per patient</td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 1.0</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**FFR results**

- Lesions succesfully measured, No (%)  
  - ANGIO-group: -  
  - FFR-group: 1329 (98%)  

- Lesions with FFR ≤ 0.80 , No (%)  
  - ANGIO-group: -  
  - FFR-group: 874 (63%)  

- Lesions with FFR > 0.80 , No (%)  
  - ANGIO-group: -  
  - FFR-group: 513 (37%)  

**Stents per patient**

- 2.7 ± 1.2  
  - ANGIO-group: 1359  
  - FFR-group: 980  
  - P-value: <0.001

- Lesions succesfully stented (%)  
  - ANGIO-group: 92%  
  - FFR-group: 94%  
  - DES, total, No  
  - ANGIO-group: 1359  
  - FFR-group: 980  
  - P-value: -
## FAME study: Procedural Results (2)

<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>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>Materials used at procedure (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>
</tr>
</tbody>
</table>
### FAME study: Adverse Events at 1 year

<table>
<thead>
<tr>
<th>Event Description</th>
<th>ANGIO-group N=496</th>
<th>FFR-group N=509</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events at 1 year, No (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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 myocardial infarction</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><strong>Total no. of MACE</strong></td>
<td>113</td>
<td>76</td>
<td>0.02</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>
Complete follow-up at 2 years in 93.7% of all patients.
## FAME study: Adverse Events at 2 years

### Individual endpoints, No (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>ANGIO-group N=496</th>
<th>FFR-group N=509</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

### Composite endpoints, No(%) 

<table>
<thead>
<tr>
<th>Event</th>
<th>ANGIO-group N=496</th>
<th>FFR-group N=509</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<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>

### Total No of MACE

<table>
<thead>
<tr>
<th></th>
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<th>FFR-group N=509</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>139</td>
<td>105</td>
<td>0.01</td>
</tr>
</tbody>
</table>
FAME study: Event-free Survival 24 months

Absolute Difference in MACE-Free Survival

<table>
<thead>
<tr>
<th>Time</th>
<th>Event-free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>2.9%</td>
</tr>
<tr>
<td>6 months</td>
<td>4.9%</td>
</tr>
<tr>
<td>12 months</td>
<td>5.1%</td>
</tr>
<tr>
<td>24 months</td>
<td>4.7%</td>
</tr>
</tbody>
</table>
Freedom from Angina (\%)

<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>

Angio-guided vs. FFR-guided
Outcome of Deferred Lesions (1):

513 Deferred Lesions and 901 stented lesions in 509 FFR-Guided Patients

2 Years

31 Myocardial Infarctions

- 22 Peri-procedural

9 Late Myocardial Infarctions

- 8 Due to a New Lesion or Stent Related

1 Myocardial Infarction due to an Originally Deferred Lesion

Only 1/513 or 0.2% of deferred lesions resulted in a late myocardial infarction
513 Deferred Lesions and 901 stented 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 and/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
Caveats in Subgroup Analysis:

- subgroup analysis is not trivial
- good study is underpowered for subgroups
- subgroups should be pre-defined beforehand, no “dredging” for subgroups afterwards
- co-variante adjustment & interaction testing
- if results of trial equally apply to all pre-defined subgroups → corroboration of main study (heterogeneity testing)
In the FAME study, 248 patients (24.7 %) had diabetes:

- 125 in the angio-guided group
- 123 in the FFR-guided group

How was outcome in these patients?
FAME study: Diabetes vs Non-Diabetes
In the FAME study, 328 patients (32.6 %) was admitted because of unstable angina or non-Stemi

- 178 in the angio-guided group
- 150 in the FFR-guided group

How was outcome in these patients?
FAME study: Unstable Angina & Non-STEMI
In the FAME study, 275 patients (27.9 %) had Previous PCI:

- 180 in the angio-guided group
- 187 in the FFR-guided group

How was outcome in these patients?
FAME study: Patients with Previous PCI
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 and 2 years by ~ 30%

- Reduces mortality and myocardial infarction at 1 and 2 years by ~ 35 %

- These effects were of equal order in all predefined subgroups without significant heterogeneity
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.
BACK UP SLIDES
How does FAME fit with other recently performed RCT’s to (DES) stenting in Multivessel Disease
MACE in SYNTAX – 3VD and FAME

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
<th>PCI - angio</th>
<th>PCI - FFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNTAX – 3VD</td>
<td>19.1</td>
<td>11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAME</td>
<td>18.3</td>
<td></td>
<td>13.2</td>
<td></td>
</tr>
</tbody>
</table>
MACE in SYNTAX – 3VD and FAME

Similar definition of MACE
FUNCTIONAL CLASS
in COURAGE - SYNTAX – 3VD and FAME

% free of angina at 1 year

COURAGE
SYNTAX
FAME

PCI MEDICAL PCI CABG PCI - angio PCI - FFR

58 71 78 82
50 76 82

%
FAME and SYNTAX in Perspective

2-Year MACE rate in SYNTAX 3VD versus FAME

Identical Definition of MACCE: i.e. Including CVA and Excluding CK-MB 3-5 x N
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

CONSORT-E CHART
MACCE in SYNTAX – 3VD and FAME

similar definition of MACCE, including CVA and excluding CKMB 3-5 x N
Catharina Hospital, Eindhoven, The Netherland
“FUNCTIONAL CLASS IS A SOFT ENDPOINT” ??

You are 50 years old and have “stable angina” cl 2:

- When playing tennis, you have to stop after 15 minutes.
- When running 2 stairs in a hurry, you feel your chest or has to take nitro.
- You are reminded twice a week that you are heart patient.

And now there is a highly effective sophisticated method, FFR-guided PCI, that not only decreases event rate but makes you forget about your heart troubles!

Quality of Life is important in today's world!!!
“I do not stent lesions of 50-70%”
Ischemic threshold 0.80

Stenosis classification by angiography
FAME study: Economic Evaluation (1)

- Angio better
- FFR better

- Angio cheaper
- FFR cheaper

- QALY
- USD
An FFR-guided strategy to multivessel PCI is one of those rare situations in medicine in which a new innovative treatment not only improves outcome but is also cost-saving.

Fearon et al, Circulation 2010
What are the consequences of the FAME study for the treatment of patients with multivessel disease?
TREATMENT OPTIONS FOR MVD

FAME

R/x  PCI  CABG

COURAGE  SYNTAX
TREATMENT OPTIONS FOR MVD

AFTER FAME

R/x → PCI → CABG