DEFER, SYNTAX, COURAGE and FAME’s

A Synthesis

W. Wijns, Aalst (B)
What is your conclusion from ...

- DEFER
- FAME 1
- SYNTAX

How does this trial influence your practice ...
DEFER Study: Impact on Symptoms

% of asymptomatic patients

- DEFER
- PERFORM
- REFERENCE

1 month 6 months 12 months 24 months

Bech et al. Circulation 2001
DEFER Study Results at 5 years

When FFR > 0.75 Death and MI rate is < 1% per year

What is your conclusion from ...

- DEFER
- FAME 1
- SYNTAX

How does this trial influence your practice ...
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
### FAME 1 study: Functional Class at 1 Year

<table>
<thead>
<tr>
<th></th>
<th>ANGIO-group</th>
<th>FFR-group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=496</td>
<td>N=509</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients without event and free from angina</strong></td>
<td>326 (68)</td>
<td>360 (73)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Patients free from angina, No. (%)</strong></td>
<td>374 (78)</td>
<td>399 (81)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Number of anti-anginal meds, No.</strong></td>
<td>1.2 ± 0.7</td>
<td>1.2 ± 0.8</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>EQ-5D visual analogue scale</strong></td>
<td>74 ± 16</td>
<td>75 ± 16</td>
<td>0.65</td>
</tr>
</tbody>
</table>
# FAME 1 study: Adverse Events at 1 year

<table>
<thead>
<tr>
<th>Events at 1 year, No (%)</th>
<th>ANGIO-group N=496</th>
<th>FFR-group N=509</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death, MI, CABG, or repeat-PCI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</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>
What is your conclusion from ...

- DEFER
- FAME 1
- SYNTAX

How does this trial influence your practice ...
Patient in SYNTAX
Randomized Controlled Trial Intent-to-Treat

**RCT: Enrolled**
N=1800

- CABG n=897
- PCI* n=903

**RCT: 1 Year Follow-up**
CABG 94.6%  PCI 98.7%

- CABG n=849
- PCI* n=891

**RCT: 2 Year Follow-up**
CABG 93.2%  PCI 98.0%

- CABG n=836
- PCI* n=885

**RCT: 3 Year Follow-up**
CABG 92.2%  PCI 98.0%

- CABG n=827
- PCI* n=885

**RCT: 4 Year Follow-up**
CABG 91.3%  PCI 97.3%

- CABG n=819
- PCI* n=879

*TAXUS Express
MACCE to 4 Years

CABG (N=897) vs TAXUS (N=903)

Before 1 year:
12.4% vs 17.8%, P=0.002

1–2 years:
5.7% vs 8.3%, P=0.03

2–3 years:
4.8% vs 6.7%, P=0.10

3–4 years:
4.2% vs 7.9%, P=0.002

Cumulative Event Rate (%)

P<0.001

Cumulative KM Event Rate ± 1.5 SE; log-rank P value; *Binary rates

ITT population
Linear Increase in MACCE by Number of Stents in the SYNTAX Trial

**1.5 Stents**
- "Typical" Real World Average
- 1 stent
  - 5.6%

**4.6 Stents**
- SYNTAX Average
  - 17.8%

**Avg. in pts with 5-8+ stents in SYNTAX**
- 19.6%

12m MACCE in TAXUS Arm

- Number of Stents Implanted
- 12m MACCE Probability
- 12m MACCE Rate
Definite plus probable per ARC definitions (Cutlip, et al. *Circulation* 2007;115:2344). 1PCI patient had an ST 1d and 6d post-procedure; therefore, counted in the ≤1d and 2–30d intervals but only once in the total.
We conclude that ...

Dual targeting (anatomy + function) is symptomatically equivalent and prognostically superior to single targeting (angio only)

Less is More (DEFER, FAME 1)
More is Less (SYNTAX)
What is your conclusion from ...

- COURAGE
- FAME 2

How does this trial influence your practice ...
COURAGE Trial

Clinical Outcome Utilising Revascularisation and Aggressive Drug Evaluation

Multicenter randomised trial testing the following hypothesis:

- the best clinical outcome can be achieved by combining PCI with intensive medical therapy
- primary endpoint: death, MI, ACS (Tn+)
- N = 2287 pts: medical vs PCI + medical
COURAGE: Study Overview

- 2287 patients randomised (after angiography) between BMS plus drug therapy vs. drug therapy alone
- The composite primary end point was all-cause death or acute MI
- Duration 2.5 - 7 years with on average 5 year follow-up

<table>
<thead>
<tr>
<th>cumulative event rate</th>
<th>PCI</th>
<th>Med Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI</td>
<td>19.0%</td>
<td>18.5%</td>
</tr>
<tr>
<td>Death, MI, stroke</td>
<td>20.0%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Hospitalization for ACS</td>
<td>12.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>MI</td>
<td>13.2%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

**Trial conclusion**

PCI did not reduce the risk of death or MI in this patient population
What is your conclusion from ...

- COURAGE
- FAME 2

How does this trial influence your practice ...
Study design of FAME II randomised clinical trial

Stable Patients scheduled for one-, two- or three vessel DES stenting

FFR in all indicated stenoses

There is at least one Stenosis with FFR ≤ 0.80

1:1 Randomization

PCI + OMT

Cohort A
N=1634

OMT

There is no Stenosis with an FFR ≤ 0.80

OMT

Cohort B
N=200 (matched)

Primary Endpoint at 2 years: Death + MI + Unplanned hospitalisation leading to urgent revascularisation

Follow-up after 1, 6 months, 1, 2, 3, 4 and 5 years
**Rate of Any Revascularisation**

- RCT: OMT vs. RCT: PCI+OMT = 12.1% vs. 1.7%
- HR (95% CI): 7.63 (3.24-18.0); logrank p<.0001

**Cumulative incidence (%)**

<table>
<thead>
<tr>
<th>Months after randomisation</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCT: OMT only</td>
</tr>
<tr>
<td>0</td>
<td>339</td>
</tr>
<tr>
<td>1</td>
<td>238</td>
</tr>
<tr>
<td>2</td>
<td>123</td>
</tr>
<tr>
<td>3</td>
<td>119</td>
</tr>
<tr>
<td>4</td>
<td>115</td>
</tr>
<tr>
<td>5</td>
<td>112</td>
</tr>
<tr>
<td>6</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

**RCT: PCI+OMT vs. REGISTRY: OMT, p=0.54**
DEFER, SYNTAX, COURAGE and FAME’s

Let’s attempt a Synthesis

W. Wijns, Aalst (B)
Benefit of revascularization for stable ischaemic heart disease: the jury is still out

Evidence for benefit
If moderate / large ischemia

1997: ACIP trial
2003: Nuclear imaging studies
2008: Nuclear substudy COURAGE
2009: Substudy of BARI 2 D
2012: FAME 2 randomised trial

Evidence for lack of benefit 
in the absence of ischemia

1998: Nuclear imaging studies
2005: Besançon randomised trial*
2007: Defer randomised trial
2010: FAME 1 randomised trial

*Legaery, EHJ 26:2623
Revascularisation versus Medical Therapy after Stress SPECT: Survival Analysis

These two lines intersect at a value of ~ 10% of ischaemic myocardium, above which the survival benefit for revascularization over medical therapy increases as a function of increasing amounts of inducible ischemia.

Figure 4. Log hazard ratio for revascularization (Revasc) vs medical therapy (Medical Rx) as a function of % myocardium ischemic based on final Cox proportional hazards model. Model, $P<0.0001$; interaction, $P=0.0305$.

## Indications for revascularisation in stable angina or silent ischaemia

### For symptoms

<table>
<thead>
<tr>
<th>Subset of CAD by anatomy</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stenosis &gt; 50% with limiting angina or angina equivalent, unresponsive to OMT</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Dyspnoea/CHF and &gt; 10% LV ischaemia/viability supplied by &gt; 50% stenotic artery</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>No limit symptoms with OMT</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

### For prognosis

<table>
<thead>
<tr>
<th>Subset of CAD by anatomy</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main &gt; 50%*</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Any proximal LAD &gt; 50%*</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>2VD or 3VD with impaired LV function*</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Proven large area of ischaemia (&gt; 10% LV)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Single remaining patent vessel &gt; 50% stenosis*</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>1VD without proximal LAD and without &gt; 10% ischaemia</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

* With documented ischaemia or Fractional Flow Reserve (FFR) < 0.80 for % diameter stenosis by angiography between 50 and 90%
Practical decision tree for the Management of patients with stable CAD

Two steps approach

1. Is there an indication for revascularisation on top of OMT? For symptomatic and/or prognostic reasons?

2. If so, which is more appropriate: CABG or PCI?
Watch for ...

New ESC Guidelines on Stable Angina (september 2013)

Upcoming ESC Guidelines on Myocardial Revascularization (2014)

Ongoing ISCHEMIA trial
ISCHEMIA Trial

Stable Patient
Moderate or Severe Ischemia

Blinded CCTA\(^1\)

Core lab anatomy eligible?\(^2\)

- no → Late screen failure
- yes → RANDOMIZE

INVASIVE Strategy
OMT\(^3\) + Cath + Optimal Revascularization

CONSERVATIVE Strategy
OMT\(^3\) alone
Cath reserved for OMT failures

Average 4 Years of Follow-up
Primary Endpoint: Composite of CV Death and MI

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\(^1\) CCTA will be performed in all patients with eGFR ≥60 mL/min
\(^2\) Exclude patients with LM disease or no obstructive disease
\(^3\) OMT=Optimal medical medical therapy
Angiographic guidance to revascularization results in inappropriate intervention in ~50% of cases.

Revascularization will only improve prognosis in patients with significant risk (ischemic burden).

Indications for OMT or OMT + revascularization should be based on combined anatomic and functional evaluation.

Diagnostic value of FFR has reached the highest level of evidence (class I A recommendation) but remains poorly adopted.
Disclosures for William Wijns
Cardiovascular Center Aalst, Belgium

Consulting Fees: on my behalf go to the Cardiovascular Research Center Aalst

Contracted Research between the Cardiovascular Research Center Aalst and several pharmaceutical and device companies, incl. St Jude and Volcano

Ownership Interest: Cardio³BioSciences, biotechnology start-up on regenerative medicine

Chairman of PCR, Co-Chairman of EuroPCR and Africa PCR
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFER</td>
<td>325</td>
<td></td>
</tr>
<tr>
<td>FAME 1</td>
<td>1.005</td>
<td></td>
</tr>
<tr>
<td>SYNTAX</td>
<td>1.800</td>
<td>100K+</td>
</tr>
<tr>
<td>COURAGE</td>
<td>2.287</td>
<td>?</td>
</tr>
<tr>
<td>FAME 2</td>
<td>691</td>
<td></td>
</tr>
<tr>
<td>ISCHEMIA</td>
<td>8.800</td>
<td>90K+</td>
</tr>
</tbody>
</table>
Clinical Indications for PCI
Euro Heart Survey

10,982 Patients across Europe

Elective
STABLE

NSTEMI
55%

STEMI
26%

10.982 Patients across Europe

Ramcharitar et al, EuroIntervention 2008;4:429-41

Appropriateness of elective PCI for stable CAD is being challenged while PCI for acute CAD is life-saving.
Prognostic Value of Stress $^{99m}$Tc-sestamibi Perfusion Imaging

Average Annual Hard Events (Death or MI) in > 12000 Patients

- Normal: 0.6%
- Abnormal: 7.4%

Iskander S, Iskandrian A E  JACC 1998
6107 Patients had FFR Measurements (1999-2008)

Angiography
1. Proximal LAD stenosis > 30%
2. Other vessel disease < 30%

852 patients with an isolated proximal LAD stenosis

- 35 patients had non-cardiac life-threatening disease
- 42 patients required valvular surgery
- 45 patients FFR not taken into account to guide the treatment

730 patients eligible for the study

564 patients with an FFR ≥ 0.80 and treated medically

166 patients with an FFR < 0.80 and treated by revascularization

Isolated Proximal LAD Stenosis
Proximal LAD Stenoses

Log Rank P = 0.039

564 Patients with a prox LAD stenosis FFR > 0.80
166 Patients with an isolated LAD stenosis FFR < 0.80

O. Muller et al. JACC CV Interv 2010
Is More Stents More Care?

in Left Main & Multivessel Stenting

1 Year Repeat Revascularization, %

Stent Number

SYNTAX: RCT (n=4.6)
SYNTAX: Registry (n=3.1)
AUTAX (n=3.2)
ASAN Multivessel Registry (n=2.8)
PRECOMBAT (n=2.7)
FAME, Angio guided, (n=2.7)
FAME, FFR guided (n=1.9)
Dejan et al. (n=3.3)
Li Y et al. (n=2.7)
What is the Next?
Suggested Randomized Study, FAME III

Stable Patients with Positive FFR (<0.80), 2-3 Vessel Disease

Primary Endpoint at 2 years: Death + MI + Stroke
Does post-PCI FFR value predict outcome?

FFR Post Stent Registry: 750 patients post BMS

<table>
<thead>
<tr>
<th>Post Stent FFR Value</th>
<th>% MACE at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.96-1.00</td>
<td>5</td>
</tr>
<tr>
<td>0.91-0.95</td>
<td>6</td>
</tr>
<tr>
<td>0.86-0.90</td>
<td>16</td>
</tr>
<tr>
<td>0.81-0.85</td>
<td>22</td>
</tr>
<tr>
<td>0.76-0.80</td>
<td>30</td>
</tr>
</tbody>
</table>

Pijls N.H.J. et al., Circulation 2002
Proportion of Functionally Significant Stenoses in Patients with 3- or 2- Vessel Disease by Angiography

Angiographic 3-VD

- 0-VD (9%)
- 3-VD (14%)
- 1-VD (34%)
- 2-VD (43%)

Angiographic 2-VD

- 0-VD (12%)
- 2-VD (43%)
- 1-VD (45%)
Comparison of MACE in FAME patients with and without ACS

Tonino et al, J Am Coll Cardiol 2011 (submitted)
Evidence basis for myocardial revascularisation vs. Optimal Medical Therapy

• Several meta-analyses since 2000
  2000  Bucher
  2004  Brener
  2005  Hannan
  2005  Katritsis
  2008  Hannan
  2008  Schomig
  2009  Hlatky
  2009  Trikalinos
  2009  Jeremias

• Survival benefit from CABG vs OMT only
  HR 0.62 (0.50 – 0.77)

• Survival benefit from PCI vs OMT only
  HR 0.82 (0.68 – 0.99)