FFR-guided PCI vs Medical Therapy in Pts with Stable IHD

... the “yes, but ...” tale!

Emanuele Barbato, MD, PhD, FESC
Cardiovascular Center Aalst, Belgium
Federico II University Naples, Italy
Conflict of Interest

- Institutional research grants and speaker's fee from St. Jude Medical and Boston Scientific to Cardiovascular Research Center Aalst
Annual risk of Cardiac Death and Myocardial Infarction

Metanalysis of SPECT MPI studies in nearly 70K patients

- Normal: 0.6%
- Abnormal: 5.9%

8-10 x higher risk for abnormal compared to normal
Extent of Functional Assessment abnormality and Cardiovascular Event Rate
Myocardial Perfusion Imaging and Clinical Outcome

- 314 patients with CAD
- After either PCI+OMT or OMT
- Myocardial perfusion imaging prior and again 6 months after treatment

![Bar graph showing total event rates after 6-18 months for different ischemia levels.]

9th Coronary Physiology in the CathLab Course, Nice 2015
Risk of MACE and TVF at 2 years
Sub-analysis of FAME 2 trial (MT+Registry pts)

<table>
<thead>
<tr>
<th>Fractional Flow Reserve</th>
<th>MACE</th>
<th>TVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Abnormal</td>
<td>14 %</td>
<td>37 %</td>
</tr>
</tbody>
</table>

Approximately 4 x higher risk for Abnormal Fractional Flow Reserve compared to Normal Fractional Flow Reserve for both MACE and TVF.

Barbato, Toth, De Bruyne. Unpublished data
Rate of TVF for each 0.05 FFR reduction

For each 0.05 FFR increase ≈ 20% decrease in TVF risk

OR: 0.81 (0.76-0.86), p<0.001*

Non-significant stenoses

Barbato, Toth, De Bruyne. Unpublished data
Yes, but ...

... these patients are better not treated with PCI!
Low-to-intermediate Risk

COURAGE
W.E. Boden et al NEJM 2007

Intermediate-to-high Risk

SYNTAX
F.W. Mohr et al Lancet 2013

9th Coronary Physiology in the CathLab Course, Nice 2015
Factors un-favouring PCI

- Revascularization was not targeting ischemia relief
- Low risk patients selected
- Early generation DES or even BMS implanted
Factors un-favouring PCI

- Revascularization was not targeting ischemia relief
- Low risk patients selected
- Early generation DES or even BMS implanted
SWISSI II Trial
201 patients with silent ischemia after a myocardial infarction
10 Year-Follow-Up

Percutaneous Coronary Intervention

Drug Therapy

Log-Rank $P < 0.001$

Event-Free Survival

Time From Randomization, y

9th Coronary Physiology in the CathLab Course, Nice 2015

P Erne et al, JAMA 2007
FAME 2 Primary Outcomes

PCI+MT vs. MT: HR 0.39 (95% CI 0.26-0.57) P<0.001

De Bruyne B et al. NEJM 2014
Factors un-favouring PCI

• Revascularization was not targeting ischemia relief

• Low risk patients selected

• Early generation DES or even BMS implanted
Revascularization benefit vs. extent of ischemic myocardium

9th Coronary Physiology in the CathLab Course, Nice 2015

Hachamovich et al, Circulation 2003
Revascularization benefit vs. extent of FFR abnormality

8,418 patients from 90 cohorts with a total of 458 deaths, 235 non-fatal MI, 326 revascularizations

Normalized 1-Year MACE (%) vs. Mean Cohort FFR

PCI/CABG vs. medically treated

Johnson NP et al. JACC 2014
Factors un-favouring PCI

- Revascularization was not targeting ischemia relief
- Low risk patients selected
- Early generation DES or even BMS implanted
Yes, but ...

... this clinical benefit of PCI is only driven by “soft endpoints” like urgent revasc
Patients with urgent revascularization

- Unstable angina only: 51.8%
- Myocardial Infarction: 21.4%
- Unstable angina + evidence of ischemia on ECG: 26.8%

9th Coronary Physiology in the CathLab Course, Nice 2015
Yes, but ...

... this clinical benefit of PCI is only driven by “soft endpoints” like urgent revascularization.

... and by the way these were over-inflated by patients’ fear!
<table>
<thead>
<tr>
<th>Variable</th>
<th>Randomly Assigned Groups</th>
<th>Registry Cohort</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI plus Medical Therapy</td>
<td>Medical Therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alone</td>
<td></td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographically significant lesions — no. per patient</td>
<td>1.87±1.05</td>
<td>1.73±0.94</td>
<td>1.32±0.59</td>
</tr>
<tr>
<td>Vessels with at least one significant lesion — no. of patients (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>251 (56.2)</td>
<td>261 (59.2)</td>
<td>136 (81.9)</td>
</tr>
<tr>
<td>2</td>
<td>156 (34.9)</td>
<td>146 (33.1)</td>
<td>26 (15.7)</td>
</tr>
<tr>
<td>3</td>
<td>40 (8.9)</td>
<td>34 (7.7)</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>At least one significant lesion in proximal or middle left anterior</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>descending artery — no. (%)</td>
<td>291 (65.1)</td>
<td>276 (62.6)</td>
<td>74 (44.6)</td>
</tr>
</tbody>
</table>

* Table 1. Baseline Clinical, Angiographic, and Fractional Flow Reserve (FFR) Characteristics.† P values are calculated using the two-sample t-test for continuous variables and Pearson's chi-squared test for discrete variables.
Primary Outcomes
In MT group vs. Registry

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

De Bruyne B et al. NEJM 2014
Yes, but ...

... there is no difference in death or MI
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-Winkler, 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., M.Sc., Peter Jüni, M.D., and William F. Fearon, M.D.,
for the FAME 2 Trial Investigators*

FAME 2 trial was not powered to show significant differences in death or MI!
PCI+MT vs MT

0-7 days: HR 9.01 (95%CI 1.13-72.0)  P for interaction 0.002
8 days-2 years: HR 0.56 (95%CI 0.32-0.97)

De Bruyne B et al. NEJM 2014
After 2 years, > 40% of patients treated by MT had crossed over i.e. had undergone any revascularisation

De Bruyne B et al. NEJM 2014
Revasc vs. MT

*a network metanalysis*

All cause mortality (95 trials; 93533 pts)
- CABG vs. MT: 0.80 (0.70 to 0.91)
- R-ZES vs. MT: 0.65 (0.42 to 1.00)
- EES vs. MT: 0.75 (0.59 to 0.96)

Death or MI (88 trials; 89373 pts)
- CABG vs. MT: 0.80 (0.70 to 0.91)
- R-ZES vs. MT: 0.65 (0.42 to 1.00)
- EES vs. MT: 0.75 (0.59 to 0.96)

*25-35% reduction in all-cause mortality*
*25% reduction in death or MI*

with new generation DES

Windecker S et al. BMJ 2014
Revasc vs. MT

Trials with objective evidence of ischemia

- 48% all-cause mortality reduction with PCI vs. MT

Gada H & Kirtane AJ, Am J Cardiol 2015
Conclusions

• Large myocardial ischemia is bad for the patient

• FFR is able to detect ischemia and can predict clinical outcome

• FFR-guided PCI by targeting ischemia-inducing coronary stenosis improve clinical outcome

• PCI (with last generation DES and when targeting objective ischemia) can reduce all-cause mortality
THANK YOU
Freedom from Chest-pain

Ischemic lesions (FFR < 0.75) treated by stenting

Pijls NH et al. JACC 1997

9th Coronary Physiology in the CathLab Course, Nice 2015
Yes, but ...

... there is no difference in death or MI
### 9th Coronary Physiology in the CathLab Course, Nice 2015

De Bruyne B et al. NEJM 2014

<table>
<thead>
<tr>
<th></th>
<th>Randomised trial</th>
<th>Randomised trial compared to registry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No CCS II-IV/No total</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI+MT</td>
<td>314/447</td>
<td>1.04 (0.95-1.13)</td>
</tr>
<tr>
<td>MT alone</td>
<td>298/440</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Registry</td>
<td>107/166</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td><strong>30 Days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI+MT</td>
<td>45/441</td>
<td>0.36 (0.26-0.49)</td>
</tr>
<tr>
<td>MT alone</td>
<td>123/431</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Registry</td>
<td>25/162</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td><strong>6 Months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI+MT</td>
<td>33/440</td>
<td>0.41 (0.28-0.60)</td>
</tr>
<tr>
<td>MT alone</td>
<td>80/434</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Registry</td>
<td>26/163</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td><strong>12 Months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI+MT</td>
<td>26/437</td>
<td>0.39 (0.25-0.61)</td>
</tr>
<tr>
<td>MT alone</td>
<td>65/429</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Registry</td>
<td>25/159</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td><strong>24 Months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI+MT</td>
<td>25/425</td>
<td>0.49 (0.31-0.77)</td>
</tr>
<tr>
<td>MT alone</td>
<td>51/424</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Registry</td>
<td>23/157</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

**Diagram Note:**
- Patients with CCS II to IV (%) range from 0 to 80.

**Legend:**
- PCI+MT: Percutaneous Coronary Intervention + Medical Treatment
- MT alone: Medical Treatment alone
- Registry: Baseline data from a registry.