PCI for Stable Ischemic Heart Disease: What Happened in the Last Week?

Ajay J. Kirtane, MD, SM

Center for Interventional Vascular Therapy
Columbia University Medical Center / NewYork Presbyterian Hospital

@ajaykirtane
Disclosure Statement of Financial Interest

- Ajay J. Kirtane
  - Institutional grants to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical
Last Thursday Morning...
(at TCT)
Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA)

Rasha Al-Lamee, MA (Oxon) MB BS MRCP
Imperial College London
Inclusion criteria

- Stable angina
- One or more ≥ 70% stenosis in a single vessel
- Suitable for PCI
Trial design

Enrollment assessment
CCS SAQ EQ-5D-5L

MEDICAL OPTIMIZATION PHASE

Pre-randomization assessment
CCS SAQ EQ-5D-5L

Exercise test
Stress echo

Blinded procedure
Research angiogram:
  iFR, FFR
  Sedation

PCI
Placebo

Randomization

PCI
Placebo

BLINDED FOLLOW UP PHASE

Follow-up Assessment
CCS SAQ EQ-5D-5L

Exercise test
Stress echo

Six

Six
ORBITA trial

230 enrolled Dec 2013 - Jul 2017 in 5 UK sites

- 30 patients exited

200 patients randomized

- PCI (n=105)
- Placebo (n=95)

- Follow-up (n=105)
- Follow-up (n=91)

Blinded follow-up phase

Medical optimization phase

30 patients exited

4 patients did not complete follow-up
Medical therapy optimization

Number of anti-anginal drugs

<table>
<thead>
<tr>
<th></th>
<th>Enrolment</th>
<th>Pre-randomization</th>
<th>Follow-up</th>
<th>Placebo</th>
<th>Pre-randomization</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30.45%</td>
<td>1.90%</td>
<td>13.30%</td>
<td>2.10%</td>
<td>23.20%</td>
<td>18.90%</td>
</tr>
<tr>
<td>1</td>
<td>50.45%</td>
<td>24.80%</td>
<td>22.90%</td>
<td>38.90%</td>
<td>74.70%</td>
<td>71.60%</td>
</tr>
<tr>
<td>2</td>
<td>18.10%</td>
<td>60.90%</td>
<td>63.80%</td>
<td>24.20%</td>
<td>5.30%</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>1.00%</td>
<td>1.00%</td>
<td></td>
<td>5.30%</td>
<td>18.90%</td>
<td></td>
</tr>
</tbody>
</table>
## Stenosis severity

<table>
<thead>
<tr>
<th></th>
<th>PCI n = 105</th>
<th>Placebo n = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area stenosis by QCA (%)</td>
<td>84.6 (SD 10.2)</td>
<td>84.2 (SD 10.3)</td>
</tr>
<tr>
<td>FFR</td>
<td>0.69 (SD 0.16)</td>
<td>0.69 (SD 0.16)</td>
</tr>
<tr>
<td>iFR</td>
<td>0.76 (SD 0.22)</td>
<td>0.76 (SD 0.21)</td>
</tr>
</tbody>
</table>
Primary endpoint result

*Change in total exercise time*

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in exercise time (seconds)</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>28.4 (SD 86.3)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>11.8 (SD 93.3)</td>
<td>0.235</td>
<td></td>
</tr>
</tbody>
</table>

Error bars are standard errors of the mean.
Primary endpoint result

Change in total exercise time

PCI

Change in exercise time (seconds)

+16.6 sec
(-8.9 to 42.0)
p=0.200

PCI

28.4
(SD 86.3)
p=0.001

Placebo

11.8
(SD 93.3)
p=0.235

Error bars are standard errors of the mean
Secondary endpoint results

**Blinded evaluation of ischaemia reduction**

<table>
<thead>
<tr>
<th>Peak stress wall motion index score</th>
<th>PCI n = 80</th>
<th>Placebo n = 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-randomization</td>
<td>1.11 (0.18)</td>
<td>1.11 (0.18)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1.03 (0.06)</td>
<td>1.13 (0.19)</td>
</tr>
<tr>
<td>(\Delta) (Pre-randomization to follow-up)</td>
<td>-0.08 (0.17)</td>
<td>0.02 (0.16)</td>
</tr>
</tbody>
</table>

\[ p<0.0001 \]

Difference in \(\Delta\) between arms: 

-0.09 (-0.15 to -0.04)

\[ p=0.0011 \]
Secondary endpoint results: Quality of Life Scores

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 weeks</td>
<td>Baseline</td>
<td>6 weeks</td>
</tr>
<tr>
<td>SAQ Physical Limitation</td>
<td>71.3</td>
<td>78.6</td>
<td>69.1</td>
<td>74.1</td>
</tr>
<tr>
<td>SAQ Anginal Frequency</td>
<td>79.0</td>
<td>93.0</td>
<td>75.0</td>
<td>84.6</td>
</tr>
<tr>
<td>SAQ Angina Stability</td>
<td>64.7</td>
<td>60.5</td>
<td>68.5</td>
<td>63.5</td>
</tr>
</tbody>
</table>

Bold values represent significant changes from baseline. No between-group differences between arms were detected.
Secondary endpoint results

**CCS class improved in both groups**

<table>
<thead>
<tr>
<th>CCS class at enrolment</th>
<th>CCS class at pre-randomization</th>
<th>CCS class at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>Placebo</td>
<td>PCI</td>
</tr>
<tr>
<td>37%</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>61%</td>
<td>57%</td>
<td>12%</td>
</tr>
<tr>
<td>2%</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

**CCS IV**

- PCI: 37%
- Placebo: 40%

**CCS III**

- PCI: 24%
- Placebo: 33%

**CCS II**

- PCI: 53%
- Placebo: 43%

**CCS I**

- PCI: 14%
- Placebo: 11%

**CCS 0**

- PCI: 9%
- Placebo: 14%

**CCS class improved in both groups**

Secondary endpoint results

- CCS IV: PCI 37%, Placebo 40%
- CCS III: PCI 24%, Placebo 33%
- CCS II: PCI 53%, Placebo 43%
- CCS I: PCI 14%, Placebo 11%
- CCS 0: PCI 9%, Placebo 14%

**CCS class at follow-up**

- PCI: 0%
- Placebo: 1%

**CCS class at enrolment**

- PCI: 37%
- Placebo: 40%

**CCS class at pre-randomization**

- PCI: 24%
- Placebo: 33%

**CCS class at follow-up**

- PCI: 0%
- Placebo: 1%

**CCS class at enrolment**

- PCI: 61%
- Placebo: 57%

**CCS class at pre-randomization**

- PCI: 14%
- Placebo: 20%

**CCS class at follow-up**

- PCI: 13%
- Placebo: 20%
ORBITA Results Summary

- PCI relieved hemodynamic significance of stenoses by physiologic criteria and relieved ischemia by DSE (placebo did not)
- Exercise time increased by +28 seconds in PCI arm (but not significantly in placebo arm: +12 seconds)
  - Difference between arms (16 seconds) was not significant
- Most QoL Measures were no different between arms but improved in both (slightly greater with PCI)
The implications of ORBITA are profound and far-reaching. First and foremost, the results of ORBITA show unequivocally that there are no benefits for PCI compared with medical therapy for stable angina, even when angina is refractory to medical therapy.

Based upon these data, all cardiology guidelines should be revised to downgrade the recommendation for PCI in patients with angina despite medical therapy.”
Placebo Effect of the Heart

After 40 years, millions of procedures, and billions of dollars, doctors are questioning whether a common procedure is doing more harm than good. How much does heart disease depend on a patient's state of mind?
Two Goals of Therapy in Patients with Stable CAD

1. Improve Symptoms and Quality of Life
   - Measured by “soft” endpoints (i.e. angina/QOL scales)

2. Improve Prognosis
   - Measured by “hard” endpoints (i.e. death, MI)
“Studies using [the RAND] method have shown that overuse of invasive techniques in the management of coronary disease is uncommon, and attention has turned to the issue of underuse.”

### Appropriateness of Revascularization and Outcomes in the UK

<table>
<thead>
<tr>
<th>Appropriateness Category</th>
<th>Angina at Follow-up</th>
<th>Angina at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical Treatment</td>
<td>Revascularization</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>56/110</td>
<td>9/14</td>
</tr>
<tr>
<td>Uncertain</td>
<td>172/317</td>
<td>67/142</td>
</tr>
<tr>
<td>Appropriate</td>
<td>143/205</td>
<td>114/210</td>
</tr>
</tbody>
</table>

**Angina at 1 year**

<table>
<thead>
<tr>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical treatment better</td>
</tr>
<tr>
<td>PTCA better</td>
</tr>
<tr>
<td>CABG better</td>
</tr>
</tbody>
</table>

**Hemingway et al. NEJM 2001**
## COURAGE: Effect of Medical Therapy

**SAQ Freedom From Angina**

<table>
<thead>
<tr>
<th></th>
<th>PCI + OMT</th>
<th>OMT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21%</td>
<td>23%</td>
<td>NS</td>
</tr>
<tr>
<td>3 Months</td>
<td>53%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 Year</td>
<td>57%</td>
<td>50%</td>
<td>0.005</td>
</tr>
<tr>
<td>2 Years</td>
<td>59%</td>
<td>53%</td>
<td>0.010</td>
</tr>
<tr>
<td>3 Years</td>
<td>59%</td>
<td>56%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Minimal DES Use and 32% of Medically Treated Patients in the Trial Crossed Over to PCI

Weintraub et al, NEJM 2008
Freedom from Anti-anginal Meds
Despite 32% XO to PCI in the OMT group

PCI + OMT compared to OMT resulted in:

• Significantly less use of nitrates at:
  - 1 year (53% vs. 67%)
  - 3 years (47% vs. 61%)
  - 5 years (40% vs. 57%)

• Significantly less use of Ca$^{+2}$ channel blockers at:
  - 1 year (40% vs. 49%)
  - 3 years (43% vs. 50%)
  - 5 years (42% vs. 52%)

Boden WE et al. NEJM 2007;356:1503-16
In a matched analysis, MT with 1st yr x-over was not associated with death, MI, or SAQ but was associated with worse health status and unstable angina admissions (OR 2.78, 95% CI [1.1,7.5], p=0.04)
Additionally, among patients with angina at baseline, freedom from angina after randomization was higher among revascularized patients compared to medical therapy.
FAME-2: Stable CAD patients scheduled for 1, 2 or 3 vessel DES-PCI

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

When all FFR > 0.80 (n=332)

MT

27%

50% randomly assigned to FU

Follow-up after 1, 6 months, 1, 2, 3 and 5 years
FAME-2: Quality of Life

% of Patients with Class II-IV Angina at each Time Point

- Baseline: 70.2% (PCI+MT), 67.7% (MT alone)
- 1 Month: 10.2% (PCI+MT), 28.5% (MT alone)
- 6 Months: 7.5% (PCI+MT), 18.4% (MT alone)
- 1 Year: 5.9% (PCI+MT), 15.2% (MT alone)
- 2 Years: 5.9% (PCI+MT), 12% (MT alone)
- 3 Years: 5.2% (PCI+MT), 9.7% (MT alone)

P-values:
- Baseline: P=0.42
- 1 Month: P<0.001
- 6 Months: P<0.001
- 1 Year: P<0.001
- 2 Years: P=0.002
- 3 Years: P=0.015
FAME-2: Quality of Life

Mean Number of Antianginal Medications/Patient at each Time Point

<table>
<thead>
<tr>
<th>Time Point</th>
<th>PCI+MT</th>
<th>MT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.33</td>
<td>1.35</td>
</tr>
<tr>
<td>1 Month</td>
<td>1.36</td>
<td>1.79</td>
</tr>
<tr>
<td>6 Months</td>
<td>1.32</td>
<td>1.68</td>
</tr>
<tr>
<td>1 Year</td>
<td>1.35</td>
<td>1.62</td>
</tr>
<tr>
<td>2 Years</td>
<td>1.36</td>
<td>1.53</td>
</tr>
<tr>
<td>3 Years</td>
<td>1.29</td>
<td>1.52</td>
</tr>
</tbody>
</table>

P-values: P=0.63, P<0.001, P<0.001, P<0.001, P=0.003, P<0.001
Results: Clinical Outcome

Three Year Rate of Death, MI, or Urgent Revascularization

MT alone vs. PCI+MT:
Hazard ratio, 2.36 (95% CI, 1.66—3.36); P<0.001 by log-rank test

MT alone vs. Registry:
Hazard ratio, 1.89 (95% CI, 1.18—3.03); P=0.007 by log-rank test

PCI+MT vs. Registry:
Hazard ratio, 0.79 (95% CI, 0.47—1.33); P=0.38 by log-rank test

Cumulative MACE Incidence (%)
# Results: Clinical Outcome

## Three Year Rate of Death, MI, or Urgent Revascularization

<table>
<thead>
<tr>
<th>Event</th>
<th>Randomized trial N=888</th>
<th>Registry N=322</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI+MT=447</td>
<td>MT=441</td>
</tr>
<tr>
<td>MACE</td>
<td>10.1%</td>
<td>22%</td>
</tr>
<tr>
<td>Death</td>
<td>2.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Myocardial Infarction (MI)</td>
<td>6.3%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Death or MI</td>
<td>8.3%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>4.3%</td>
<td>17.2%</td>
</tr>
</tbody>
</table>

*P value compares PCI + MT patients with MT patients
FAME-2: Costs

- PCI+MT Cumulative Cost
- MT Cumulative Cost

Index: $9,944, $11,499, $13,372, $15,280, $16,737, $16,792

1 Year: $3,427, $7,059, $13,372

2 Years: $1,908, $2,987, $14,485

3 Years: $1,513, $2,252

PCI+MT Annual Follow-Up Cost
MT Annual Follow-Up Cost
Key Characteristics of the ORBITA Population

• Single vessel disease
  ▪ ~30% FFR negative
  ▪ But angiographically legitimate (real-world practice)

• Intense medical therapy prior to randomization

• At randomization, patients’ symptoms were well-controlled as assessed by SAQ
  ▪ Approximately monthly angina

• Good exercise tolerance by VO2Max

• Minimal ischemia by DSE and DTS
Algorithm for GDMT for SIHD

Guideline-Directed Medical Therapy with ongoing patient education

Anginal Symptoms?
- Yes
  - Sublingual NTG

Beta blocker if no contraindication (Espec. if prior MI, heart failure or other indication)
- Yes
  - Successful Treatment?
    - Yes
      - Successful Treatment?
        - Yes
          - Consider revascularization to improve symptoms
        - No
          - Persistent symptoms despite adequate trial of Guideline-Directed Medical Therapy
    - No
      - Successful Treatment?
        - Yes
          - Persistent symptoms despite adequate trial of Guideline-Directed Medical Therapy
        - No
          - Consider revascularization to improve symptoms

No

Add/substitute CCB and/or long-acting nitrate if no contraindication
- Yes
  - Successful Treatment?
    - Yes
      - Persistent symptoms despite adequate trial of Guideline-Directed Medical Therapy
    - No
      - Consider revascularization to improve symptoms

No

Add/substitute ranolazine
- Yes
  - Successful Treatment?
    - Yes
      - Persistent symptoms despite adequate trial of Guideline-Directed Medical Therapy
    - No
      - Consider revascularization to improve symptoms

No

No
SYNTAX: Generic QOL and Utilities

SF-36 Physical Component Summary

Baseline | 1 month | 6 months | 12 months
---|---|---|---
P<0.001 | P=0.50 | P=0.07

SF-36 Mental Component Summary

Baseline | 1 month | 6 months | 12 months
---|---|---|---
P<0.001 | P=0.23 | P=0.43

EQ-5D Utilities (US)

Baseline | 1 month | 6 months | 12 months
---|---|---|---
P<0.001 | P=0.16 | P=0.99

Quality Adjusted Life Years

$\Delta = 0.02$ (P<0.01)

Quality of Life

Angina frequency, physical limitations, and quality-of-life domains of the SAQ assessed at baseline, at 1, 6, and 12 months, and annually thereafter.

Adjusted:
* $P<0.05$ favoring PCI
* $P<0.05$ favoring CABG
SAQ-Angina Frequency

- PCI: Δ = 1.5, p = 0.03
- CABG: Δ = -0.3, p = 0.63
- PCI: Δ = -0.8, p = 0.21

Baron et al, JACC 2017
APPEAR: Under-recognition of Angina

Individual Physician Reporting compared with SAQ

Physicians in APPEAR: Number of Patients Seen

Rates of Under-recognition

Arnold, S. et al. *Circ Cardiovasc Qual Outcomes*. 2016; 9:00-00
How Do Our Patients with Real Symptoms Actually Feel After Revascularization?

I thank you for all your help. It is a great feeling to be angina free.

Your grateful patient,
### GDMT vs. Revasc for Stable Ischemic Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Factors favoring GDMT</th>
<th>Factors favoring Revasc + GDMT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms:</strong> None to mild</td>
<td>Moderate to severe</td>
<td></td>
</tr>
<tr>
<td><strong>Exercise capacity:</strong> Normal</td>
<td>Reduced</td>
<td></td>
</tr>
<tr>
<td><strong>Ischemia/Risk:</strong> None to mild</td>
<td>Moderate to severe</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-anginal drug tolerance:</strong> Good</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td><strong>Revasc. risk (pt factors, cor anat):</strong> High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>DAPT compliance:</strong> Poor</td>
<td>Good</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from G. Stone
“An Unnecessary Procedure?”

• “This is really American medicine at its worst”
  - Steven Nissen

• “He is the poster child for the inappropriate use of stenting”
  - David Brown

*G. W. Bush, CRT 2014