ORBITA:
An Interventionalist’s Perspective

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Disclosures

No
- Speakers bureau
- Consultation to pharmaceutical companies
- Advisory board
- Individual stock in pharmaceutical or diagnostic testing company

Yes
- Institution has received funds for clinical trials
- Site PI for device trials
Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial

Rasha Al-Lamee, David Thompson, Hakim-Moulay Debbi, Sayan Sen, Kare Tang, John Davies, Thomas Keeble, Michael Mielewczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Suneel Talwar, Ravi Assomull, Jamil Mayet, Roland Wensel, David Collier, Matthew Shun-Shin, Simon A Thom, Justin E Davies, Darrel P Francis, on behalf of the ORBITA investigators*

Summary

Background Symptomatic relief is the primary goal of percutaneous coronary intervention (PCI) in stable angina and is commonly observed clinically. However, there is no evidence from blinded, placebo-controlled randomised trials to show its efficacy.
Comment

Last nail in the coffin for PCI in stable angina?

David L Brown a, Rita F Redberg b
Bruce W. Andrus, MD, MS
Cardiovascular Medicine

Areas of focus
- Preventive cardiology
- Clinical lipidology
- Pulmonary hypertension
- Valvular heart disease
- And 3 more areas of focus

Locations
Lebanon
Randolph

I’m Batman!
• What was so different about ORBITA?
• How does it shape our thinking about stable angina?
• How does it fit with current guidelines?
• Is there ever a time to consider stents for stable angina?
COURAGE Reshapes Role for PCI in Stable Angina

- COURAGE trial (2007)
  - Med Rx versus PCI for stable angina
  - All patients with catheterization
    - 70% stenosis with ischemia
    - 80% stenosis alone
  - No difference in event rates (death, MI, stroke)
  - High cross over to PCI for symptoms (1/3 over 4 years)
  - Less angina in PCI group despite using fewer medications
Role for Fractional Flow Reserve Assessment (FFR)

- FAME and FAME-2 Trials
  - Patients with angiographic CAD
  - Lesions assessed using flow wire
  - If FFR<0.8, randomized PCI vs Medical Therapy

- In FFR (+) lesions, PCI reduced cumulative endpoint of death, MI, and revascularization
- Trial showed value of physiologic (not occulostenotic) lesion assessment

\[
FFR = \frac{P_d}{P_a} \text{ (during hyperemia)} = \frac{58}{79} = 0.73
\]
Different Populations

Stable Angina ≠ Acute Coronary Syndrome (STEMI/NSTEMI)
ORBITA at a Glance

- ORBITA question: what is the added benefit of PCI in medically optimized stable angina?
- Enrollment at first angiogram
  - Single vessel stenosis
  - Taken off table and “medical optimization” pursued
- After 6 weeks, repeat angiogram, physiologic lesion assessment (blinded) and PCI or sham PCI performed
- Follow up at 6 weeks to re-assess
ORBITA Patient Flow

Enrolment assessment
- Demographics
- CCS
- Questionnaires
- Blood pressure, heart rate

Medical optimisation phase
- 6 weeks

Pre-randomisation assessment
- CCS
- Questionnaires
- CPET
- DSE
- Blood pressure, heart rate

Blinded procedure
- Research angiogram
- IFR, FFR
- Sedation
- PCI

Randomisation

Blinded follow-up phase
- Placebo
- 6 weeks

Follow-up assessment
- CCS
- Questionnaires
- CPET
- DSE
- Blood pressure, heart rate

BP/HR monitoring
24/7 direct Cardiologist contact for med titration
2.9 calls/week
After 6 weeks of Medical Therapy, prior to Randomization

- At the time of randomization to PCI or sham:
  - 23% of patients in PCI arm 0,1 angina
  - 25% of patients in sham arm 0,1 angina

- Physiologic lesion assessment in PCI:
  - 26% had NEGATIVE FFR
  - 34% had NEGATIVE IFR
## ORBITA Findings

<table>
<thead>
<tr>
<th>Exercise time (s)</th>
<th>PCI</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Patients assessed</td>
<td>104</td>
<td>90</td>
</tr>
<tr>
<td>Pre-randomisation</td>
<td>528.0 (178.7)</td>
<td>490.0 (195.0)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>556.3 (178.7)</td>
<td>501.8 (190.9)</td>
</tr>
<tr>
<td>Increment (pre-randomisation to follow-up)</td>
<td>28.4 (95% CI 11.6 to 45.1)</td>
<td>11.8 (95% CI -7.8 to 31.3)</td>
</tr>
<tr>
<td>Difference in increment between groups</td>
<td>16.6 (95% CI -8.9 to 42.0)</td>
<td>..</td>
</tr>
<tr>
<td>p value</td>
<td>0.200</td>
<td>..</td>
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</table>
ORBITA Findings

- Less ischemia on DSE after PCI
- Duke treadmill score not different

### Peak stress wall motion index score

<table>
<thead>
<tr>
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<th>Patients assessed</th>
<th>Pre-randomisation</th>
<th>Follow-up</th>
<th>Increment (pre-randomisation to follow-up)</th>
<th>Difference in increment between groups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80</td>
<td>1.11 (0.18)</td>
<td>1.03 (0.06)</td>
<td>-0.08 (0.17; 95% CI -0.11 to -0.04)</td>
<td>-0.09 (95% CI -0.15 to -0.04)</td>
<td>0.0011</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>1.11 (0.18)</td>
<td>1.13 (0.19)</td>
<td>0.02</td>
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</table>

### Duke treadmill score

<table>
<thead>
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<th></th>
<th>Patients assessed</th>
<th>Pre-randomisation</th>
<th>Follow-up</th>
<th>Increment (pre-randomisation to follow-up)</th>
<th>Difference in increment between groups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>104</td>
<td>4.24 (4.82)</td>
<td>5.46 (4.79)</td>
<td>1.22 (4.36; 95% CI 0.37 to 2.07)</td>
<td>1.12 (95% CI -0.23 to 2.47)</td>
<td>0.104</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>4.18 (4.65)</td>
<td>4.28 (4.98)</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Why did PCI not improve exercise capacity as expected?

Does baseline angiography influence the results?

Do baseline symptoms influence the results?

Why did symptoms not improve as much as expected?

Why was ischaemia reduction so clear in the absence of more symptom benefit?

Does baseline ischaemia influence the results?
Why were the ORBITA results not as we expected?

“The link between ischaemia and symptoms is complex?”

“The efficacy of PCI is truly small?”

“The trial design could have been different?”
1 in 5 more patients free from angina in PCI group

\[ p = 0.006^* \]
Pre-randomisation FFR and iFR predicted reduction in stress echo ischaemia with PCI
FFR and iFR did not predict change in freedom from angina
Our presumed paradigm for angina and CAD

PLACEBO
ORBITA in Balance

• Good question with radical design (Sham control)
• Good data collection
• Physiologic data and angiographic data
• Transparency with results

• Selected patient population
• Unrealistic medical titration?
• High percentage of patients with no symptoms
• Enrolled at angiogram
• Follow up short (6 weeks)
A word of caution:

53 yo with angina and positive stress test suggestive of single vessel disease with LAD ischemia, on medical therapy.
ORBITA-2

POPULATION

Symptom assessment phase
Single and multivessel disease
Ischaemia on non-invasive or invasive test
Real world anti-anginal therapy
More patients
ISCHEMIA Trial
International Study of Comparative Health Effectiveness with Medical & Invasive Approaches

- **Patients:** Stable w/ at least moderate ischemia (Core Lab)
  - SPECT
    - ≥10% LV
  - Echo / CMR RWMA
    - ≥3/16 segments
    - New / Worse WMA
  - CMR Perfusion
    - >12% LV
  - Ex ECG
    - ST ↓ ≥1.5 mm in 2 leads or
    - >2.0 mm in ≥1 lead OR
    - ST ↑ ≥1.0 mm in non-infarct territory

- **Primary Aim:** To determine if initial invasive strategy of cath & PCI / CABG + medical therapy will reduce events compared to a strategy of medical therapy alone (cath - reserved for failed medical therapy)
  - **Sample Size:** 5,000 followed for ~4 years

Chair – Judith Hochman, MD; Co-Chair / PI: David Maron, MD
Imaging Coordinating Center: Leslee Shaw, PhD

Dartmouth Geisel School of Medicine

ISCHEMIA TRIAL.org
Overall Thoughts

• Guidelines for stable angina- we already know how to manage this population- medical therapy works for many.

• Remember that ACS (NSTEMI/STEMI is different animal, not studied here!)

• Stents can reduce ischemia, and when used appropriately, can reduce angina. Stents are not right for every patient, nor are they wrong for every patient!

• Still need clinical judgement, equipoise

• ISCHEMIA trial results coming soon- stay tuned!
Thank You

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