Coronary Artery Disease, Current controversies in mgmt. of SIHD; ORBITA & ISCHEMIA

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• No financial disclosure.
• Not smart enough to be one of the interventional cardiologists.
The 10 Leading Causes of Death, Global, 2000 and 2012

<table>
<thead>
<tr>
<th>No</th>
<th>Causes of death, 2000</th>
<th>Deaths (million)</th>
<th>% of deaths</th>
<th>No</th>
<th>Causes of death, 2012</th>
<th>Deaths (million)</th>
<th>% of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ischaemic heart disease</td>
<td>5.0</td>
<td>11.3</td>
<td>1</td>
<td>Ischaemic heart disease</td>
<td>7.4</td>
<td>13.2</td>
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<tr>
<td>2</td>
<td>Stroke</td>
<td>5.7</td>
<td>10.7</td>
<td>2</td>
<td>Stroke</td>
<td>6.7</td>
<td>11.9</td>
</tr>
<tr>
<td>3</td>
<td>Lower respiratory infections</td>
<td>3.5</td>
<td>6.6</td>
<td>3</td>
<td>COPD</td>
<td>3.1</td>
<td>5.6</td>
</tr>
<tr>
<td>4</td>
<td>COPD</td>
<td>3.1</td>
<td>5.8</td>
<td>4</td>
<td>Lower respiratory infections</td>
<td>3.1</td>
<td>5.5</td>
</tr>
<tr>
<td>5</td>
<td>Diarrhoeal diseases</td>
<td>2.2</td>
<td>4.1</td>
<td>5</td>
<td>Trachea, bronchus, lung cancers</td>
<td>1.6</td>
<td>2.9</td>
</tr>
<tr>
<td>6</td>
<td>HIV/AIDS</td>
<td>1.7</td>
<td>3.2</td>
<td>6</td>
<td>HIV/AIDS</td>
<td>1.5</td>
<td>2.8</td>
</tr>
<tr>
<td>7</td>
<td>Tuberculosis</td>
<td>1.3</td>
<td>2.5</td>
<td>7</td>
<td>Diarrhoeal diseases</td>
<td>1.5</td>
<td>2.7</td>
</tr>
<tr>
<td>8</td>
<td>Prematurity</td>
<td>1.3</td>
<td>2.5</td>
<td>8</td>
<td>Diabetes mellitus</td>
<td>1.5</td>
<td>2.7</td>
</tr>
<tr>
<td>9</td>
<td>Trachea, bronchus, lung cancers</td>
<td>1.2</td>
<td>2.2</td>
<td>9</td>
<td>Road injury</td>
<td>1.3</td>
<td>2.3</td>
</tr>
<tr>
<td>10</td>
<td>Diabetes mellitus</td>
<td>1.0</td>
<td>2.0</td>
<td>10</td>
<td>Hypertensive heart disease</td>
<td>1.1</td>
<td>2.0</td>
</tr>
<tr>
<td>11</td>
<td>Road injury</td>
<td>1.0</td>
<td>1.9</td>
<td>11</td>
<td>Prematurity</td>
<td>1.1</td>
<td>2.0</td>
</tr>
<tr>
<td>12</td>
<td>Hypertensive heart disease</td>
<td>0.8</td>
<td>1.6</td>
<td>13</td>
<td>Tuberculosis</td>
<td>0.9</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Top 10 global causes of deaths, 2016

Deaths (millions)

1. Ischaemic heart disease
2. Stroke
3. Chronic obstructive pulmonary disease
4. Lower respiratory infections
5. Alzheimer disease and other dementias
6. Trachea, bronchus, lung cancers
7. Diabetes mellitus
8. Road injury
9. Diarrhoeal diseases
10. Tuberculosis

Cause Group
- Communicable, maternal, neonatal and nutritional conditions
- Noncommunicable diseases
- Injuries

SIHD

• the syndrome of recurrent, transient episodes of chest pain reflecting demand-supply mismatch, that is, angina pectoris.
SIHD

• the syndrome of recurrent, transient episodes of chest pain reflecting demand-supply mismatch, that is, angina pectoris.
• the syndrome of recurrent, transient episodes of chest pain reflecting demand-supply mismatch, that is, angina pectoris.
Case in your clinic

- 57 year M
- Not DM
- ?HTN
- DLP/ smoker
- BMI ~32

- Chest pain for 4-5 months.
- Especially on going upstairs.
- Associated with dyspnea
- Normal LV Fx.
- 8 min on Bruce.
Choices

- What would you do?
- GDMT?
- +/- CA?
- Is this evidence based?

- Will you control Sx?
- Prevent MI?
- Improve Mortality?
- Is it cost effective?
Choice 1
- No Chest pain.
- WMA
- 8 min

Choice 2
- Chest pain.
- No WMA
- 8 min

Choice 3
- Chest pain.
- WMA
- >8 min
<table>
<thead>
<tr>
<th>Choice 1</th>
<th>Choice 2</th>
<th>Choice 3</th>
<th>Choice 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No Chest pain.</td>
<td>• Chest pain.</td>
<td>• Chest pain.</td>
<td>• No Chest pain.</td>
</tr>
<tr>
<td>• WMA</td>
<td>• No WMA</td>
<td>• WMA</td>
<td>• No WMA</td>
</tr>
<tr>
<td>• 8 min</td>
<td>• 8 min</td>
<td>• &gt;8 min</td>
<td>• &gt;8 min</td>
</tr>
</tbody>
</table>
• Is INV strategy better than GDMT alone?
• Do you believe in “Placebo” Rx?
For diagnosis (and risk stratification) for patients with chest pain and an intermediate probability of coronary artery disease

OR

For risk stratification in patients with chest pain and a high probability of coronary artery disease:

Yes ⇓

Contraindications to stress testing?

Yes ⇓

Symptoms or clinical findings warranting angiography?

Yes

Consider coronary angiography

Yes ⇓

Patient able to exercise?

No

Pharmacologic imaging study

Yes

Previous coronary revascularization?

No

Exercise imaging study

No

Resting ECG interpretable?

Yes

Perform exercise test

Yes

Test results suggest high risk?

Yes

Consider coronary angiography/revascularization

No

Adequate information on diagnosis and prognosis available?

Yes

Consider imaging study/angiography

No

Consider coronary angiography

Enter treatment algorithm
For diagnosis (and risk stratification) for patients with chest pain and an intermediate probability of coronary artery disease

OR

For risk stratification in patients with chest pain and a high probability of coronary artery disease

Contraindications to stress testing?

Yes

Symptoms or clinical findings warranting angiography?

No

Patient able to exercise?

Yes

Previous coronary revascularization?

No

Resting ECG interpretable?

Yes

Perform exercise test

Yes

Test results suggest high risk?

Yes

Consider coronary angiography

No

Adequate information on diagnosis and prognosis available?

Yes

Consider imaging study/angiography

No

Consider coronary angiography

Enter treatment algorithm
<table>
<thead>
<tr>
<th>Extent of CAD</th>
<th>Prognostic Weight (0-100)</th>
<th>5-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-vessel disease, 75%</td>
<td>23</td>
<td>93</td>
</tr>
<tr>
<td>1-vessel disease, 50% to 74%</td>
<td>23</td>
<td>93</td>
</tr>
<tr>
<td>1-vessel disease, ≥95%</td>
<td>32</td>
<td>91</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>37</td>
<td>88</td>
</tr>
<tr>
<td>2-vessel disease, both ≥95%</td>
<td>42</td>
<td>86</td>
</tr>
<tr>
<td>1-vessel disease, ≥95% proximal LAD artery</td>
<td>48</td>
<td>83</td>
</tr>
<tr>
<td>2-vessel disease, ≥95% LAD artery</td>
<td>48</td>
<td>83</td>
</tr>
<tr>
<td>2-vessel disease, ≥95% proximal LAD artery</td>
<td>56</td>
<td>79</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>56</td>
<td>79</td>
</tr>
<tr>
<td>3-vessel disease, ≥95% in ≥1 vessel</td>
<td>63</td>
<td>73</td>
</tr>
<tr>
<td>3-vessel disease, 75% proximal LAD artery</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>3-vessel disease, ≥95% proximal LAD artery</td>
<td>74</td>
<td>59</td>
</tr>
</tbody>
</table>

*Assuming medical treatment only.
Contemporary Trials of OMT with or without Revascularization

- COURAGE (2007)
- BARI 2D (2009)
- FAME 2 (2012)
- Few Meta-analyses
Optimal Medical Therapy with or without PCI for Stable Coronary Disease

William E. Boden, M.D., Robert A. O’Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merrill Knudtson, M.D., Marcin Dada, M.D., Paul Casperson, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslee Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Title, M.D., Gerald Gau, M.D., Alvin S. Blaustein, M.D., David C. Booth, M.D., Eric R. Bates, M.D., John A. Spertus, M.D., M.P.H., Daniel S. Berman, M.D., G.B. John Mancini, M.D., and William S. Weintraub, M.D., for the COURAGE Trial Research Group*
COURAGE: Study design

AHA/ACC Class I/II indications for PCI, suitable coronary artery anatomy +
≥70% stenosis in ≥1 proximal epicardial vessel + objective evidence of ischemia
(or ≥80% stenosis + CCS class III angina without provocation testing)

Optimal medical therapy* + PCI (n = 1149)  Randomized  Optimal medical therapy (n = 1138)

Primary outcomes: All-cause mortality, nonfatal MI

Secondary outcomes: Death, MI, stroke; ACS hospitalization

Follow-up: Median 4.6 years

*Intensive pharmacologic therapy + lifestyle intervention
CCS = Canadian Cardiovascular Society

COURAGE: Treatment effect on hospitalization for ACS

Survival free of ACS

No. at risk
Medical therapy  PCI
0 1 2 3 4 5 6 7
1138 1149
1025 1027
956 957
833 835
662 667
418 431
236 246
127 134

HR 1.07 (0.84-1.37)
P = 0.56*

COURAGE
Clinical Outcomes Utilizing Revascularization and Aggressive Guideline-Driven Drug Evaluation

Trial tested whether PCI and optimal medical therapy or optimal medical therapy alone was superior in preventing death and nonfatal MI.

- Design: randomized
- Patients: 2,287
- Centers: 50
- Countries: United States and Canada

Results: No significant differences were found between the PCI and optimal medical therapy group (n=1,149) and optimal medical therapy alone group (n=1,138) in MI, death and stroke (20% vs. 19.5%, respectively; HR 1.05; 95% CI 0.87-1.27). There was no difference in hospitalization for ACS between the groups (12.4% PCI group vs. 11.8% medical therapy, HR 1.07; 95% CI 0.84-1.37) or MI (13.2% PCI vs. 12.3% medical therapy alone; HR 1.13; 95% CI 0.89-1.43).

Presented at ACC 2007.

A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

The BARI 2D Study Group

2368 Were enrolled

763 Were selected for CABG stratum

185 Were randomly assigned to medical therapy

194 Were randomly assigned to insulin provision

191 Were randomly assigned to insulin sensitization

378 Were randomly assigned to revascularization

190 Were randomly assigned to insulin provision

188 Were randomly assigned to insulin sensitization

807 Were randomly assigned to medical therapy

399 Were randomly assigned to insulin provision

408 Were randomly assigned to insulin sensitization

1605 Were selected for PCI stratum

798 Were randomly assigned to revascularization

402 Were randomly assigned to insulin provision

396 Were randomly assigned to insulin sensitization
A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

The BARI 2D Study Group
2011 ACCF/AHA/SCAI PCI Guideline

- "The findings from individual studies and systematic reviews of PCI vs medical therapy can be summarized as follows:
  - PCI reduces the incidence of angina
  - PCI has not been demonstrated to improve survival in stable patients
  - PCI may increase the short-term risk of MI
  - PCI does not lower the long-term risk of MI"
Coronary Revascularization: Factors to Consider in Evaluating Patients

- Assessment of clinical risk
- Consideration and integration of functional/imaging data
- Burden/extent of CAD
- Symptoms and medical therapy, including side effects and adherence
- Individual values and preferences
Principal hypothesis:
**Symptom relief in stable angina**

*PCI increases exercise time more than placebo procedure*

Primary endpoint

*Difference in exercise time increment between the arms*

For patients to be willing to participate in this first placebo-controlled trial of PCI, duration must long enough for full hemodynamic effect but not so long as to inhibit recruitment
Sample size calculation

To detect 30 sec, at 80% power, within-arm SD 75 sec, needs 200 randomized patients

Inclusion criteria

• Stable angina
• One or more $\geq 70$% stenosis in a single vessel
• Suitable for PCI

This sample size is comparable to other trials assessing *this question*.
Trial design

MEDICAL OPTIMIZATION PHASE
- Enrolment assessment
  - CCS
  - SAQ
  - EQ-5D-5L
- Pre-randomization assessment
  - CCS
  - SAQ
  - EQ-5D-5L
- Exercise test
- Stress echo

Six weeks

BLINDED FOLLOW UP PHASE
- Randomization
  - PCI
  - Placebo
- Research angiogram
  - iFR, FFR
  - Sedation
- Follow-up Assessment
  - CCS
  - SAQ
  - EQ-5D-5L
- Exercise test
- Stress echo

Six weeks
## Blinding techniques

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headphones and music</td>
<td>Standardised handover</td>
</tr>
<tr>
<td>Sedation</td>
<td>Ward team blinded</td>
</tr>
<tr>
<td>Minimum 15 min wait</td>
<td>Both arms:</td>
</tr>
<tr>
<td></td>
<td>Treated as if PCI</td>
</tr>
<tr>
<td>Both arms:</td>
<td>No access to cath report</td>
</tr>
<tr>
<td>DAPT</td>
<td>Same discharge letter</td>
</tr>
<tr>
<td>Same post-procedural instructions</td>
<td></td>
</tr>
<tr>
<td>Same discharge letter</td>
<td></td>
</tr>
</tbody>
</table>
ORBITA trial

230 enrolled Dec 2013 - Jul 2017 in 5 UK sites

Medical optimization phase

30 patients exited

200 patients randomized

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

Blinded follow-up phase

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

4 patients did not complete follow-up
# Stenosis severity

|                      | PCI  
|----------------------|------|
|                      | n = 105 | Placebo  
|                      | n = 95 |      |  P  |
| Area stenosis by QCA (%) | 84.6 (SD 10.2) | 84.2 (SD 10.3) | 0.781 |
| FFR                  | 0.69 (SD 0.16) | 0.69 (SD 0.16) | 0.778 |
| iFR                  | 0.76 (SD 0.22) | 0.76 (SD 0.21) | 0.751 |
Primary endpoint result

Change in total exercise time

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

Error bars are standard errors of the mean
Primary endpoint result

Change in total exercise time

- PCI: +16.6 sec (SD 86.3) p=0.200
- Placebo: +11.8 sec (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>
<tr>
<td>Difference in $\Delta$ between arms</td>
<td>-0.09 (-0.15 to -0.04)</td>
<td>p=0.0011</td>
</tr>
</tbody>
</table>

*The difference in $\Delta$ between arms is significantly different, p<0.0001.*
### Secondary endpoint results

**CCS class improved in both groups**

<table>
<thead>
<tr>
<th></th>
<th>CCS IV</th>
<th>CCS III</th>
<th>CCS II</th>
<th>CCS I</th>
<th>CCS 0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCI</strong></td>
<td>37%</td>
<td>61%</td>
<td>53%</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>40%</td>
<td>57%</td>
<td>43%</td>
<td>11%</td>
<td>3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCS class at enrolment</strong></td>
<td>24%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>CCS class at pre-randomization</strong></td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>CCS class at follow-up</strong></td>
<td>16%</td>
<td>34%</td>
</tr>
</tbody>
</table>

**PCI** indicates Percutaneous Coronary Intervention.
Conclusions

• ORBITA is the first placebo-controlled randomized trial of PCI in stable angina
• Area stenosis QCA 84.4%, FFR 0.69, iFR 0.76
• PCI was safe and physiologically effective
• PCI significantly reduced ischemic burden as assessed by stress echo
• In this single vessel, angiographically guided trial there was no difference in exercise time increment between PCI and placebo
ORBITA in context

- Single vessel
  - To allow complete revascularization
- PCI guided by angina + angiogram
  - In line with common practice
- Focus is on symptomatic relief
  - Not risk or events
- Intensive medical therapy
  - In line with Guidelines
blood, sweat, and tears of the actual people who do these trials and take care of the trials outside the whole procedure in the clinic.

"I think the most important point of this trial overall is that there is a powerful placebo effect to the procedure of PCI."

When you talk to the investigators, their intent was to prove the benefit of what happens in stable angina because it had not been carried out before. This is in
Does it reflect Real life?

- 6 weeks of intense follow up…
- 1-3 times/week access to Cardiologist…
- Intro/Increase of anti anginal agents to medications….
Stable IHD… What to do?

- Aggressive vs Conservative approach?
- Especially in “Moderate” ischemic burden…
- Do you start with Invasive and then medical strategy or vice versa….
• How about your usual patient in OD?
• Multivessel ….
• Moderate Ischemia…
ISCHEMIA
Trial

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

Ischemia Trial Version 04-14-2011
ISCHEMIA Overview

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

Chair - Judith Hochman, PI - David Maron
Co-PI's William Boden, Bruce Ferguson, Robert Harrington, Gregg Stone, David Williams

- Patients: at least moderate ischemia, EF ≥35%
- Hypothesis: an initial invasive strategy of cath and optimal revascularization (PCI or CABG) + OMT is superior to a conservative strategy of OMT alone with cath reserved for OMT failure
- Composite Primary Endpoint: CV death, MI, or hospitalization for UA, resuscitated cardiac arrest, or heart failure (adjudicated)
- Secondary Aim - Major: test hypothesis that invasive strategy improves angina-related QOL compared with OMT alone
- Sample Size: 8,000
- Follow-up: average 4 years

Ischemia Trial Version 04-14-2011
**ISCHEMIA Trial**
*International Study of Comparative Health Effectiveness with Medical & Invasive Approaches*

- **Patients:** Stable w/ at Least Moderate Ischemia (Core Lab)
  
  - SPECT \( \geq 10\% \) LV
  - Echo / CMR RWMA \( \geq 3/16 \) segments
  - New / Worse WMA
  - CMR Perfusion \( >12\% \) LV

  OR

  - Ex ECG
  - ST \( \geq 1.5 \) 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
Ischemia-Eligible Stable Patient
Meets all clinical and ischemia imaging criteria

Informed consent given?

yes

ENROLL

Blinded CCTA

Anatomy eligible?

yes

RANDOMIZE

INV Strategy
OMT + cath w/ plan for optimal revascularization

CON Strategy
OMT w/ cath only if 1° endpoint or refractory Sx

no

Registry

no

Ancillary study

1. CCTA will not be performed in patients with eGFR<60 ml/min
2. Exclude and register left main disease patients and <50% stenosis in all major epicardial coronary arteries
3. Funding for this ancillary study will be sought via a separate application

Ischemia Trial Version 04-14-2011
• Multi center, Intl. 300 centers. 30 countries.
• Follow up 3 years
Address previous limitations:

• Enroll pt BEFORE cath (not excluding high risk pt).
• Higher risk patient (moderate Ischemia).
• Minimize cross over.
• DES/FFR to resolve ischemia (not only stenosis).
• Adequately powered.
• Things did not go as planned.
• Lower than expected event rate in OMT group…
• 16% event rate DID NOT happen!
• What you do??
Cardiology World Erupts Into Controversy Over Change In Major Clinical Trial

Larry Husten  Contributor
Pharma & Healthcare
I'm a medical journalist covering cardiology news.
Stent trial researchers are accused of changing endpoints to suit results

BMJ 2018;360 doi: https://doi.org/10.1136/bmj.k1298 (Published 20 March 2018)
Cite this as: BMJ 2018;360:k1298
• 5179 recruited.
• $110 million and counting…….
• "Might not have an answer"
• CV death, MI → resust Cardiac Arrest, hosp for Angina, HF;
• Will this affect the credibility of the study?
• So for now,
• ORBITA is what we go with….
• “Placebo effect” is a reality…..
• We will discuss further with our panel
• Thank you......