ISCHEMIA Trial
A long-waited update for CAD management in 2020

Paul M. Johnson, MD, FACC
Piedmont Heart Institute - Athens
February 22, 2020
I have no relevant financial disclosures.
ISCHEMIA Trial

• In stable patients with at least moderate ischemia on stress test on optimal medical therapy, is there a benefit to an invasive strategy of cardiac catheterization and revascularization?

What is the best strategy?

PCI + OMT?    OMT alone?
Stable Angina vs. Acute Coronary Syndrome

Stable Angina
- Severe stenosis
- Less likely to rupture
- Fibrotic, 
- Calcification
- Abnormal stress test
- Treatment is medical therapy, and revascularization

Previous trials have failed to show a survival benefit to revascularization in stable ischemic heart disease.
Previous trials have failed to show a benefit to PCI over OMT.
Limitations of prior trials

- Selection bias: randomization after cath
- Drug eluting stents not used in COURAGE, BARI2D
- PCI not FFR-guided in COURAGE, BARI2D
- No minimum amount of ischemia
- CABG not done in COURAGE, FAME2

• ISCHEMIA Trial: A modern trial with higher risk patients, randomized prior to catheterization, and treated with newer stents.
ISCHEMIA Trial

- In stable patients with at least moderate ischemia on stress test on optimal medical therapy, is there a benefit to an invasive strategy of cardiac catheterization and revascularization?

What is the best strategy?

PCI + OMT?  OMT alone?
Trial Design

Narrowing(s)
coronary CT angiogram

Conservative
- medication (statins, BP), exercise, and diet
- Successful!
- Failure of conservative therapy

Invasive
- Angiogram confirmation
- + stents and/or CABG (open heart)

Stress Test
- Echo
- Nuclear
- MRI
- EKG
Trial Endpoints

Primary Endpoints

• Composite time to CV death, MI, hospitalization for unstable angina, heart failure, resuscitated cardiac arrest

Secondary Endpoints

• Time to CV death or MI
• Quality of Life

• Intention to treat analysis
• > 80% power to detect 18.5% relative reduction in primary endpoint assuming aggregate 4-year cumulative rate of approximately 14%
Inclusion/Exclusion Criteria

**Inclusion Criteria**

- Age ≥ 21 years
- Moderate or severe ischemia
  - Nuclear ≥10% LV ischemia (summed difference score ≥7)
  - Echo ≥3 segments stress-induced moderate or severe hypokinesis, or akinesis
- CMR
  - Perfusion: ≥12% myocardium ischemic, and/or
  - Wall motion: ≥3/16 segments with stress-induced severe hypokinesis or akinesis
- Exercise Tolerance Testing (ETT) >1.5mm ST depression in >2 leads or >2mm ST depression in single lead at <7 METS, with angina

**Exclusion Criteria**

- NYHA Class III-IV HF
- Unacceptable angina despite medical therapy
- EF < 35%
- ACS within 2 months
- PCI or CABG within 1 year
- eGFR <30 mL/min or on dialysis

**CCTA Criteria**

- **Inclusion Criteria**
  - ≥50% stenosis in a major epicardial vessel (stress imaging participants)
  - ≥70% stenosis in a proximal or mid vessel (ETT participants)
- **Exclusion Criteria**
  - ≥50% stenosis in unprotected left main

Enrolled (8518)

Screen Failure (3339)
Major Reasons:
- Insufficient ischemia (N = 1350)
- No obstructive CAD (N = 1218)
- Unprotected LMD (N = 434)

Randomized (5179)
Study CCTA in 73% of randomized participants

Randomized to INV (2588)
Median follow-up for survivors 3.3 years (IQR 2.2 to 4.3 years)
Proportion of follow-up completed: 99.4%

Randomized to OMT (2591)
Median follow-up for survivors 3.3 years (IQR 2.2 to 4.4 years)
Proportion of follow-up completed: 99.7%
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>INV</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Enrollment (yrs.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64 (58, 70)</td>
<td>64 (58, 70)</td>
<td>64 (58, 70)</td>
</tr>
<tr>
<td>Female Sex (%)</td>
<td>23</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>73</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>42</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Prior Myocardial Infarction (%)</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Ejection Fraction, Median (%) (n=4637)</td>
<td>60 (55, 65)</td>
<td>60 (55, 65)</td>
<td>60 (55, 65)</td>
</tr>
<tr>
<td>Systolic Blood Pressure, Median (mmHg)</td>
<td>130 (120, 142)</td>
<td>130 (120, 142)</td>
<td>130 (120, 142)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, Median (mmHg)</td>
<td>77 (70, 81)</td>
<td>77 (70, 81)</td>
<td>77 (70, 81)</td>
</tr>
<tr>
<td>LDL Cholesterol, Median (mg/dL)</td>
<td>83 (63, 111)</td>
<td>83 (63, 111)</td>
<td>83 (63, 109.5)</td>
</tr>
<tr>
<td>History of Angina</td>
<td>90%</td>
<td>90%</td>
<td>89%</td>
</tr>
<tr>
<td>Angina Began or Became More Frequent Over the Past 3 Months</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
</tbody>
</table>

### Stress Test Modality

| Stress Imaging (%)                                      | 75             | 75             | 76             |
| Exercise Tolerance Test (ETT) (%)                       | 25             | 25             | 24             |

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>INV</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Inducible Ischemia*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>54%</td>
<td>53%</td>
<td>55%</td>
</tr>
<tr>
<td>Moderate</td>
<td>33%</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>Mild/None</td>
<td>12%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Uninterpretable</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Only severe qualified by ETT

80% in the INV group received revascularization

<table>
<thead>
<tr>
<th>First Procedure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>74%</td>
</tr>
<tr>
<td>• Successful PCI</td>
<td>93%</td>
</tr>
<tr>
<td>• Drug eluting stents</td>
<td>98%</td>
</tr>
<tr>
<td>CABG</td>
<td>26%</td>
</tr>
</tbody>
</table>

Coronary CCTA

# of Vessels with ≥50% Stenosis (%)
N=2982

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>22</td>
<td>47</td>
</tr>
</tbody>
</table>

Specific Vessels with ≥50% Stenosis (%)
N=3739

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87</td>
<td>46</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>1</td>
<td>87</td>
<td>47</td>
<td>67</td>
<td>68</td>
</tr>
</tbody>
</table>
Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

Adjusted Hazard Ratio = 0.93 (0.80, 1.08)
P-value = 0.34

Absolute Difference INV vs. CON

6 months:  
Δ = 1.9% (0.8%, 3.0%)

4 years:  
Δ = -2.2% (-4.4%, 0.0%)

Subjects at Risk

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>CON</th>
<th>INV</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>2591</td>
<td>2588</td>
</tr>
<tr>
<td>4 years</td>
<td>2431</td>
<td>2364</td>
</tr>
</tbody>
</table>

Judith Hochman, AHA Conference, 2019
Hospitalization for Unstable Angina

Adjusted Hazard Ratio = 0.50 (0.27, 0.91)
P-value = 0.02

Resuscitated Cardiac Arrest

Adjusted Hazard Ratio = 1.01 (0.29, 3.49)
P-value = 0.98

Hospitalization for Heart Failure

Adjusted Hazard Ratio = 2.23 (1.38, 3.61)
P-value = <0.01

Stroke

Adjusted Hazard Ratio = 1.22 (0.79, 1.88)
P-value = 0.36
No heterogeneity of treatment effect (CV death or MI)

• Age
• Sex
• Ethnicity
• Race
• Geographic region
• Stress test, imaging vs. no imaging
• Stress imaging modality

• Moderate or severe anterior ischemia
• Prior MI
• Prior cardiac cath
• Prior PCI or CABG
• Ejection fraction
• eGFR
ISCHEMIA Trial - Angina assessment

Stable Patient
Moderate or severe ischemia
(determined by site; read by core lab)

INVASIVE Strategy + OMT

CONSERVATIVE OMT alone (Cath if needed)

Brief QoL Assessment:
- Seattle Angina Questionnaire – 7
  - Angina Frequency **
  - Quality of Life **
  - Physical Limitations

SAQ Summary Score*

*Primary QoL Outcome
**Secondary QoL Outcome

Completion Rates

Con: 91% 88% 94% 93% 92% 90% 91% 89%
Inv: 88% 89% 93% 92% 92% 91% 90% 88%

John Spertus, AHA Conference, 2019
Interpreting and Stratifying SAQ Scores

**SAQ Angina Frequency Scale:**

Over the past 4 weeks, how often have you had angina?

- Daily/Weekly
- Monthly
- Not at All
- <1X/week
- 1-2X/week
- ≤3X/week
- 1-3X/day
- ≥4X/day

John Spertus, AHA Conference, 2019
Primary Outcome: Benefit of Invasive Rx on SAQ Summary Score

Typical Patient in ISCHEMIA

Month 3

Posterior Mean = 4.1 (3.2, 5.0)*

Month 12

Posterior Mean = 4.2 (3.3, 5.1) *

Month 36

Posterior Mean = 2.9 (2.2, 3.7)*

*95% Highest Posterior Density Interval

John Spertus, AHA Conference, 2019
Primary Outcome: Benefit of Invasive Rx on SAQ Summary Score

Typical Patient with Daily to Weekly Angina

Posterior Mean = 8.5 (5.8, 11.1)*
Posterior Mean = 7.3 (4.8, 9.9)*
Posterior Mean = 5.3 (3.4, 7.5)*

*95% Highest Posterior Density Interval

John Spertus, AHA Conference, 2019
Primary Outcome: Benefit of Invasive Rx on SAQ Summary Score

Typical Patient with at least Monthly Angina

**Month 3**
- Posterior Mean = 5.5 (4.3, 6.9)*

**Month 12**
- Posterior Mean = 4.8 (3.4, 6.1)*

**Month 36**
- Posterior Mean = 3.1 (2.0, 4.2)*

*95% Highest Posterior Density Interval

John Spertus, AHA Conference, 2019
Typical Patient with No Angina

Primary Outcome: Benefit of Invasive Rx on SAQ Summary Score

*95% Highest Posterior Density Interval

John Spertus, AHA Conference, 2019
In patients with at least some angina (daily, weekly, monthly) there were significant and durable improvements in quality of life with revascularization.
In patients with at least some angina (daily, weekly, monthly) there were significant and durable improvements in quality of life with revascularization.
ISCHEMIA Trial- Key Limitations

• Unblinded trial

• The results do not apply to these patients:
  • Acute coronary syndromes within two months
  • Highly symptomatic patients
  • Left main stenosis
  • LVEF < 35%

• Women were enrolled but more often excluded from randomization compared to men due to less ischemia and more non-obstructive CAD
An invasive strategy compared with initial conservative strategy did not reduce the risk for the primary endpoint of CV death, MI, hospitalization for unstable angina, or resuscitated cardiac arrest.

Patients with stable CAD and at least moderate ischemia have significant and durable improvement in angina and quality of life if they have angina.

In patients with stable ischemic heart disease, shared decision making should occur to align treatment with patient’s expectations and goals of care.
ISCHEMIA Trial
Application of Results in Athens, Ga

• This study does not apply to patients with acute coronary syndrome or stable patients with left main stenosis.

• Aggressive medical therapy for stable ischemic heart disease remains the cornerstone of treatment.
  • Risk factor modification
  • Anti-anginal therapy

• Physicians should educate patients about these outcomes so that informed treatment decisions can be made.
Learning Objectives

• The participants should be able to discuss the rationale for the ISCHEMIA trial, the study question, and the key findings of the trial.

• Participants will recognize the various patient populations they may see in practice that were included or excluded from the trial.

• Participants should feel comfortable discussing the expected outcomes for management of patients with stable ischemic heart disease treated with medical therapy alone versus medical therapy plus revascularization.
Competency Questions

• There many presentations of ischemic heart disease. The results of the ISCHEMIA trial are applicable to which of the following patients:
  A. A 43 year old female with NYHA III dyspnea and recently diagnosed LVEF of 30%.
  B. A 60 year old male with stable CCS II angina on optimal medical therapy and moderate ischemia on stress testing.
  C. A 72 year old male with PCI one month ago admitted with chest pain and elevated troponin.
  D. A 65 year old female with ESRD and CCS II angina on optimal medical therapy and moderate ischemia on stress testing.

• Based on results of the ISCHEMIA trial, a 60 year old male with stable CCS II angina on optimal medical therapy and moderate ischemia on stress test can expect the following with revascularization:
  A. A reduction in cardiovascular mortality.
  B. An increased risk of stroke.
  C. A significant reduction in angina symptoms compared to medical therapy alone.

The ISCHEMIA trial has not yet been published. For more information, visit www.ischemiatrial.org.