Relationships of Ischemia Severity and Coronary Artery Disease Extent with Clinical Outcomes in the ISCHEMIA Trial

David Maron, MD on behalf of Harmony Reynolds, MD and the ISCHEMIA Investigators
Study Design

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

CCTA not required, e.g., eGFR 30 to <60 or coronary anatomy previously defined

Blinded CCTA

Core lab anatomy eligible?

YES
RANDOMIZE

NO
Screen failure

INVASIVE Strategy
OMT + Cath + Optimal Revascularization

CONSERVATIVE Strategy
OMT alone
Cath reserved for OMT failure
ISCHEMIA Primary Endpoint

CV Death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest

Subjects at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td>2591</td>
<td>2431</td>
<td>1907</td>
<td>1300</td>
<td>733</td>
<td>293</td>
</tr>
<tr>
<td>INV</td>
<td>2588</td>
<td>2364</td>
<td>1908</td>
<td>1291</td>
<td>730</td>
<td>271</td>
</tr>
</tbody>
</table>
### ACC/AHA Guidelines for Revascularization to Improve Survival

Adapted from ACCF/AHA Guidelines for PCI and CABG JACC 2011

<table>
<thead>
<tr>
<th>Revascularization Method*</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-vessel disease with or without proximal LAD artery disease</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>PCI</td>
<td>IIb–Of uncertain benefit</td>
<td>B</td>
</tr>
<tr>
<td><strong>2-vessel disease with proximal LAD artery disease</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>PCI</td>
<td>IIb–Of uncertain benefit</td>
<td>B</td>
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<tr>
<td><strong>2-vessel disease without proximal LAD artery disease</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>IIa–With extensive ischemia</td>
<td>B</td>
</tr>
<tr>
<td>IIb–Of uncertain benefit without extensive ischemia</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>IIb–Of uncertain benefit</td>
<td>B</td>
</tr>
<tr>
<td><strong>1-vessel proximal LAD artery disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>IIa–With LIMA for long-term benefit</td>
<td>B</td>
</tr>
<tr>
<td>PCI</td>
<td>IIb–Of uncertain benefit</td>
<td>B</td>
</tr>
</tbody>
</table>
Analysis of Outcomes by Severity of Ischemia and Anatomy

• Assess relationship of ischemia and anatomy to death and MI
  – Ischemia severity (core lab interpretation)
  – Modified Duke prognostic index (integrates extent and severity of CAD on CCTA, core lab interpretation)

• Test for heterogeneity of treatment effect using these measures
Ischemia Severity

**Severe:** nuclear ≥15% LV; echo ≥4 segments; CMR ≥25% LV; ETT ST depression 1.5 mm in 2 leads or 2 mm in 1 lead at ≤7 METs with angina

**Moderate:** nuclear 10-14% LV; echo 3 segments; CMR 12.5% LV; ETT either ECG or functional capacity criteria above

**Mild:** nuclear 5-9% LV; echo 1-2 segments; CMR 1-12.4% LV; ETT 1 mm ST depression

**None:** normal

Anatomic Severity of CAD*

**6:** 3-vessel severe stenosis (≥70%) or 2-vessel severe stenosis with proximal LAD

**5:** 2-vessel severe stenosis, 1-vessel severe proximal LAD, or 3-vessel moderate stenosis (≥50%)

**4:** 2-vessel moderate stenosis or 1-vessel severe stenosis other than proximal LAD

**3:** 1-vessel moderate stenosis (≥50%)

*(left main and no obstructive CAD were excluded)*

* Using the Modified Duke Prognostic Index Categories
Statistical Analysis

- Outcomes assessed:
  - All-Cause Death
  - Myocardial Infarction
  - Primary Trial Outcome (CV Death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest)

- Adjusted for age, sex, geographical region, diabetes, hypertension, smoking, eGFR, BMI, LVEF, prior MI, heart failure or NYHA class II, prior revascularization, SAQ angina frequency at randomization, new or increasing angina
Statistical Analysis

- The association between ischemia or anatomy and outcomes was assessed using a Cox proportional hazards model adjusted for randomized treatment and baseline characteristics.
- Heterogeneity of treatment effect was assessed by comparing 4-year cumulative rates of the study endpoints for INV vs. CON across levels of ischemia and anatomy severity.
Association Between Ischemia, Anatomy, and All-Cause Mortality

<table>
<thead>
<tr>
<th>Degree of Ischemia</th>
<th>N</th>
<th>4-Year Rate</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>2797</td>
<td>5.8%</td>
<td>0.83 (0.57, 1.21)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1702</td>
<td>6.6%</td>
<td>0.89 (0.61, 1.30)</td>
</tr>
<tr>
<td>None/Mild</td>
<td>606</td>
<td>9.1%</td>
<td>ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified Duke Prognostic Score</th>
<th>N</th>
<th>4-Year Rate</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 3V ≥70% or 2V ≥70% w/prox LAD</td>
<td>1261</td>
<td>7.0%</td>
<td>ref</td>
</tr>
<tr>
<td>5 2V ≥70% or 3V ≥50% or 70% prox LAD</td>
<td>1027</td>
<td>5.3%</td>
<td>0.62 (0.42, 0.91)</td>
</tr>
<tr>
<td>4 1 ≥70% or 2V ≥50%</td>
<td>474</td>
<td>1.9%</td>
<td>0.35 (0.19, 0.66)</td>
</tr>
<tr>
<td>3 1V ≥50%</td>
<td>147</td>
<td>5.8%</td>
<td>0.57 (0.24, 1.33)</td>
</tr>
</tbody>
</table>

P for trend 0.33

P for trend <0.001

Lower risk of death  Higher risk of death
Association Between Ischemia, Anatomy, and MI

### Degree of Ischemia

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</thead>
<tbody>
<tr>
<td>Severe</td>
<td>2797</td>
<td>9.4%</td>
<td>1.37 (0.98, 1.91)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1702</td>
<td>10.2%</td>
<td>1.20 (0.86, 1.69)</td>
</tr>
<tr>
<td>None/Mild</td>
<td>606</td>
<td>8.8%</td>
<td>ref</td>
</tr>
</tbody>
</table>

### Modified Duke Prognostic Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>N</th>
<th>4-Year Rate</th>
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<tbody>
<tr>
<td>6</td>
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<td>1261</td>
<td>10.9%</td>
<td>ref</td>
</tr>
<tr>
<td>5</td>
<td>2V ≥70% or 3V ≥50% or 70% prox LAD</td>
<td>1027</td>
<td>8.7%</td>
<td>0.71 (0.53, 0.94)</td>
</tr>
<tr>
<td>4</td>
<td>1 ≥70% or 2V ≥50%</td>
<td>474</td>
<td>7.6%</td>
<td>0.58 (0.39, 0.86)</td>
</tr>
<tr>
<td>3</td>
<td>1V ≥50%</td>
<td>147</td>
<td>3.3%</td>
<td>0.16 (0.05, 0.52)</td>
</tr>
</tbody>
</table>

P for trend 0.04

P for trend <0.001
Ischemia Severity and Primary Outcome by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any ischemia subgroup

4-year event rate interaction $P = 0.28$

Shading indicates half width of confidence bands for INV vs. CON difference
Ischemia Severity and Risk of MI by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any ischemia subgroup.

4-year event rate interaction $P = 0.15$

Shading indicates half width of confidence bands for INV vs. CON difference
Ischemia Severity and All Cause Mortality by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any ischemia subgroup.

Severe Ischemia (N=2797)

Moderate Ischemia (N=1702)

Mild/No Ischemia (N=606)

4-year event rate interaction P= 0.23

Shading indicates half width of confidence bands for INV vs. CON difference.
Anatomic Severity and Primary Outcome by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any anatomic subgroup.

4-year event rate interaction

\( p = 0.17 \)

Shading indicates half width of confidence bands for INV vs. CON difference.
Anatomic Severity and MI by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any anatomic subgroup.

- **Duke Score 6**
  - $N=1261$
  - $3V \geq 70\%$ or $2V \geq 70\%$ w/prox LAD

- **Duke Score 5**
  - $N=1027$
  - $2V \geq 70\%$ or $3V \geq 50\%$ or $70\%$ prox LAD

- **Duke Score 4**
  - $1 \geq 70\%$ or $2V \geq 50\%$
  - $N=474$

- **Duke Score 3**
  - $1V \geq 50\%$
  - $N=147$

4-year event rate interaction $P = 0.26$

Shading indicates half width of confidence bands for INV vs. CON difference.
Anatomic Severity and All Cause Mortality by Treatment Group

The difference in 4-year event rates between treatment groups was not statistically significant in any anatomic subgroup

DukeScore 6

3V ≥70% or 2V ≥70% w/prox LAD

N = 1261

Duke Score 5

2V ≥70% or 3V ≥50% or 70% prox LAD

N = 1027

Duke Score 4

1V ≥70% or 2V ≥50%

N = 474

Duke Score 3

1V ≥50%

N = 147

4-year event rate interaction

P = 0.83

Shading indicates half width of confidence bands for INV vs. CON difference
Limitations

- Limited duration of follow up, median 3.2 years
- Anatomy was defined by CCTA, not conventional invasive angiography
- Patients with very severe ischemia (e.g., fall in BP with exercise, very limited functional capacity) were not likely enrolled by sites
- Patients with an unacceptable degree of angina were excluded, as were patients with left main disease, recent ACS, HF, EF <35%
- No adjustment for multiple comparisons
Anatomy was More Predictive of Outcomes than Ischemia

- In these patients with site-determined moderate or severe ischemia, there was no association between core laboratory-determined ischemia severity and death, but there was a marginal association between ischemia severity and risk of MI.
- There was a strong association between extent and severity of CAD and risk of death and MI.
ISCHEMIA Main Trial Results Apply to All Ischemia and Anatomic Subgroups

- There was no statistically significant evidence of a benefit from the invasive strategy on 4-year event rates for any level of ischemia.
- More severe and extensive coronary disease increased risk for death and MI, but an invasive approach did not significantly lower that risk at 4 years.
- This includes the subgroup with severe 3-vessel disease or 2-vessel disease with proximal LAD.
Thank you
CVD/MI by Treatment Group – Ischemia Severity

Severe Ischemia

Moderate Ischemia

Mild/No Ischemia

Interaction P= 0.25

Shading indicates half width of confidence bands for INV vs. CON difference
CVD/MI by Treatment Group – Coronary Artery Disease

Interaction
P = 0.43

Shading indicates half width of confidence bands for INV vs. CON difference