International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA):

Primary Report of Clinical Outcomes

Funded by the National Heart, Lung and Blood Institute
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NIH/NHLBI

DSMB
Biostatistics Vanderbilt

Leadership, Executive, Steering Committees
NYU School of Medicine

Clinical Coordinating Center (CCC)
NYU School of Medicine Cardiovascular Clinical Research Center, NYU Langone Health

Imaging Coordinating Center and Stress Core Labs
(Nuclear, Echo, CMR, ETT)

320 Sites* in 37 Countries

Country Leaders/ AROs

Core Labs
ECG, Angiographic, CCTA

Statistical and Data Coordinating Center (SDCC)
Duke Clinical Research Institute

Economics and Quality of Life Coordinating Center (EQOL CC)
Duke Clinical Research Institute
Mid-America Heart Institute

Independent Clinical Events Committee
St. Louis University
Duke Clinical Research Institute

*Specific PCI and CABG volume and quality criteria were required for site participation.
ISCHEMIA Research Question

• In stable patients with at least moderate ischemia on a stress test, is there a benefit to adding cardiac catheterization and, if feasible, revascularization to optimal medical therapy?
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?

RANDOMIZE

Screen failure

INVASIVE Strategy
OMT + Cath +
Optimal Revascularization

CONSERVATIVE Strategy
OMT alone
Cath reserved for OMT failure

Endpoints

Primary Endpoint:
• Time to CV death, MI, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest

Major Secondary Endpoints:
• Time to CV death or MI
• Quality of Life (separate presentation)

Other Endpoints include:
• All-Cause Death
• Net clinical benefit (stroke added to primary endpoint)
• Components of primary endpoint

Statistical Considerations

Power and Precision (N = 5,179)

• **Power**: >80% power to detect 18.5% relative reduction in primary endpoint assuming an aggregate 4-year cumulative rate of approximately 14%.

• **Precision**: 95% confidence interval around primary endpoint treatment effect hazard ratio will extend from 15% lower to 17% higher than point estimate.

Pre-Specified Statistical Analysis

• Intention-to-treat

• **Model-free**: Cumulative event rates accounting for competing risks

• **Model-based**: Cox regression (covariate adjusted)
  • Emphasize nonparametric event rates if proportional hazards assumption is violated

• Bayesian analysis of Cox model
  • Evaluate the probability of a small or large hazard ratio in light of minimally informative prior probabilities and the current study data.
### Eligibility Criteria

#### Clinical and Stress Test Eligibility 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

**Major 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

*Ischemia eligibility determined by sites. All stress tests interpreted at core labs.*

#### CCTA Eligibility Criteria

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

**Major Exclusion Criteria**
- ≥ 50% stenosis in unprotected left main

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MI Endpoint Definitions
Event Collection and Adjudication Process

- Many methods were used to assure complete ascertainment and reporting of events
- All 5 primary endpoint events and stroke were adjudicated by an independent CEC comprised of senior experts from around the world

Universal Definition of MI except
- Spontaneous MIs (types 1, 2, 4b, 4c)
  - site-reported MI decision limits for troponin (upper limit of normal [ULN], not 99th percentile URL)
- Procedural MI
  - more stringent biomarker and supporting criteria for procedural MI
Procedural Myocardial Infarction Definitions

**PCI-related MI (Type 4a)**

Markers: CK-MB preferred over troponin
- CK-MB >5X ULN
- Troponin >35X ULN when CK-MB is unavailable

*PLUS at least one of the following:*

New ECG changes
- ST segment elevation or depression >0.1 mV in 2 contiguous leads
- New pathologic Q-waves in ≥2 contiguous leads or
- New persistent LBBB

Angio
- Reduced flow in major coronary
- Type C or greater dissection

Or stand-alone biomarker definition
- CK-MB to >10-fold the ULN (or when CK-MB is unavailable, a rise in troponin to >70 fold the MI Decision Limit/ULN)

**CABG-Related MI (Type 5)**

Markers: CK-MB preferred over troponin
- CK-MB to >10X ULN
- Troponin to >70X ULN when CK-MB is unavailable

*PLUS at least one of the following:*

Imaging
- A new substantial wall motion abnormality by (CEC assessed), except new septal and apical abnormalities

New ECG changes
- New pathologic Q-waves in ≥2 contiguous leads or
- New persistent LBBB present on day 3 post CABG or hospital discharge

Or stand-alone biomarker definition
- CK-MB to >15-fold the ULN (or when CK-MB is unavailable a rise in troponin to >100 fold the MI Decision Limit/ULN)

Elements in common with SCAI definition of clinically relevant MI

### Endpoint Definitions

#### Unstable Angina
- Prolonged ischemic symptoms at rest or accelerating pattern resulting in hospitalization
- **AND at least 1 of the following (core laboratory assessed):**
  - New or worsening ST or T wave changes
  - Angiographic evidence of a ruptured/ulcerated plaque, or thrombus

#### Heart Failure
- **>24 hour hospitalization for HF**
- **AND all of the following:**
  - **Symptoms** New/worsening dyspnea, orthopnea, PND, fatigue, reduced exercise tolerance AND
  - **Signs** of HF AND
  - **Increased pharmacologic** Rx or initiation of mechanical or surgical intervention AND
  - No other cause identified

#### Resuscitated Cardiac Arrest
- Successful resuscitation for documented cardiac arrest **out-of-hospital** (or ER), discharged from hospital alive

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Study Flow

- **Enrolled (8518)**
- **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 CON (2591)**
    - Median follow-up for survivors 3.3 years (IQR 2.2 to 4.4 years)
    - Proportion of follow-up completed: 99.7%

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

- Ischemia, Symptoms + Non-Obstructive CAD
  - 66% Women
# 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></td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td></td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td></td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Prior Myocardial Infarction (%)</td>
<td></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></td>
<td>90%</td>
<td>89%</td>
</tr>
<tr>
<td>Angina Began or Became More Frequent Over the Past 3 Months</td>
<td></td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Stress Test Modality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress Imaging (%)</td>
<td>75</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Exercise Tolerance Test (ETT) (%)</td>
<td>25</td>
<td>25</td>
<td>24</td>
</tr>
</tbody>
</table>

Median values reported with 25th and 75th percentiles
# Qualifying Stress Test: Core Lab Interpretation

*Only severe qualified by ETT

<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>

Baseline Coronary Artery Anatomy by CCTA

# of Vessels with ≥50 % Stenosis (%)

<table>
<thead>
<tr>
<th></th>
<th>INV</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td>≥3</td>
<td>47</td>
<td>44</td>
</tr>
</tbody>
</table>

N=2982

Specific Vessels with ≥50% Stenosis (%)

<table>
<thead>
<tr>
<th>Vessel Type</th>
<th>INV</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Main</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Left Anterior Descending</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Proximal LAD</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Left Circumflex</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Right Coronary Artery</td>
<td>70</td>
<td>68</td>
</tr>
</tbody>
</table>

N=3739

Risk Factor Management
Baseline vs last visit
No between group differences INV vs CON

High Level of Medical Therapy Optimization is defined as a participant meeting all of the following goals: LDL < 70 mg/dL and on any statin, systolic blood pressure < 140 mmHg, on aspirin or other antiplatelet or anticoagulant, and not smoking. High level of medical therapy optimization is missing if any of the individual goals are missing.
**Medication Use Over Time**

**Beta Blocker**
- Proportion of Participants With Beta Blocker Use by Treatment Across Visit Intent-to-Treat Population

**Calcium Channel Blocker**
- Proportion of Participants With Calcium Channel Blocker Use

**Other Anti-Anginal Medication**
- Proportion of Participants With Other Anti-Anginal Medication Use

**Dual Antiplatelet (DAPT)**
- Proportion of Participants With Dual Antiplatelet (DAPT) Use

1 DAPT use is defined as the use of aspirin and another antiplatelet medication.
Cardiac Catheterization and Revascularization

Cardiac Catheterization

Indications for cath in CON
Suspected/confirmed event 13.8%
OMT Failure 3.9%
Non-adherence 8.1%

Revascularization

Indicators for cath in CON
Suspected/confirmed event 13.8%
OMT Failure 3.9%
Non-adherence 8.1%
# Mode of Revascularization

## First Procedure for Those Revascularized in Invasive Group (~80% of INV)

Of the ~20% with no revascularization:
- ~2/3 had insignificant disease on coronary angiogram
- ~1/3 had extensive disease unsuitable for any mode of revascularization

| First Procedure | PCI
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>74%</td>
</tr>
<tr>
<td>• Successful, stent able to be placed</td>
<td>93%</td>
</tr>
<tr>
<td>• Of stents placed, drug eluting</td>
<td>98%</td>
</tr>
</tbody>
</table>

| First Procedure | CABG
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>26%</td>
</tr>
<tr>
<td>• Arterial Grafts</td>
<td>93%</td>
</tr>
<tr>
<td>• IMA</td>
<td>92%</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%)

Follow-up (years)

Cumulative Incidence (%)
Major Secondary: CV Death or MI

Adjusted Hazard Ratio = 0.90 (0.77, 1.06)
P-value = 0.21

Cumulative Incidence (%)

6 months: Δ = 1.9% (0.9%, 3.0%)

4 years: Δ = -2.2% (-4.4%, -0.1%)

Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>INV</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>2591</td>
<td>2588</td>
</tr>
<tr>
<td>1 year</td>
<td>2453</td>
<td>2383</td>
</tr>
<tr>
<td>2 years</td>
<td>1933</td>
<td>1933</td>
</tr>
<tr>
<td>3 years</td>
<td>1325</td>
<td>1314</td>
</tr>
<tr>
<td>4 years</td>
<td>746</td>
<td>752</td>
</tr>
<tr>
<td>End of study</td>
<td>298</td>
<td>282</td>
</tr>
</tbody>
</table>
Net Clinical Benefit: CV Death, MI, UA, HF, RCA, Stroke

HR = 0.95 (0.82, 1.10)
P-value = 0.50
Cardiovascular Death

Adjusted Hazard Ratio = 0.87 (0.66, 1.15)
P-value = 0.33
The probability of at least a 10% relative risk reduction of INV on all-cause mortality is <10%, based on pre-specified Bayesian analysis.
Myocardial Infarction

Adjusted Hazard Ratio = 0.92 (0.76, 1.11)
P-value = 0.38
Procedural MI
*Type 4a or 5 MI*

Spontaneous MI
*Types 1, 2, 4b, or 4c MI*

Adjusted Hazard Ratio = 2.98 (1.87, 4.74)
P-value = <0.01

Adjusted Hazard Ratio = 0.67 (0.53, 0.83)
P-value = <0.01
Hospitalization for Unstable Angina

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

Hospitalization for Heart Failure

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

Resuscitated Cardiac Arrest

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

Stroke

Adjusted Hazard Ratio = 1.22 (0.79, 1.88)
P-value = 0.36
Primary endpoint

Pre-specified Important Subgroups

There was no heterogeneity of treatment effect

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Adjusted Hazard Ratio</th>
<th>Estimated 4-Yr Event Rate</th>
<th>Adjusted HR (95% CI)</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INV vs CON (95% CI)</td>
<td></td>
<td>INV</td>
<td></td>
</tr>
<tr>
<td>Core Lab Ischemia Eligibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (13.8%)</td>
<td>0.91</td>
<td>13.1%</td>
<td>15.4% 0.91 (0.77, 1.07)</td>
<td>0.44</td>
</tr>
<tr>
<td>Yes (86.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (58.2%)</td>
<td>0.93</td>
<td>14.0%</td>
<td>0.93 (0.75, 1.16)</td>
<td>0.93</td>
</tr>
<tr>
<td>Yes (41.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New or More Frequent Angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (73.8%)</td>
<td>0.92</td>
<td>16.2%</td>
<td>0.86 (0.72, 1.03)</td>
<td>0.15</td>
</tr>
<tr>
<td>Yes (26.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High degree of medical therapy optimization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (80.3%)</td>
<td>0.90</td>
<td>15.9%</td>
<td>0.90 (0.76, 1.07)</td>
<td>0.54</td>
</tr>
<tr>
<td>Yes (19.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD Severity Based on 50% Stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One Vessel Disease (23.3%)</td>
<td>0.95</td>
<td>18.2%</td>
<td>0.95 (0.73, 1.24)</td>
<td>0.99</td>
</tr>
<tr>
<td>Two Vessel Diseases (31.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three or More (45.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal LAD (&gt;=50%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (53.2%)</td>
<td>0.98</td>
<td>12.2%</td>
<td>0.98 (0.74, 1.28)</td>
<td>0.72</td>
</tr>
<tr>
<td>Yes (46.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of Baseline Ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or Mild (11.9%)</td>
<td>1.05</td>
<td>16.6%</td>
<td>1.05 (0.68, 1.64)</td>
<td>0.80</td>
</tr>
<tr>
<td>Moderate (33.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (54.8%)</td>
<td></td>
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</tr>
</tbody>
</table>

N=3739 for Prox LAD Y/N
N=2982 for # diseased vessels
Primary endpoint and major secondary endpoint (CV death or MI)

No heterogeneity of treatment effect based on any characteristic

- 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
- Prior CABG
- Ejection Fraction
- eGFR
Limitations

- Unblinded trial – no sham procedure
- Based on exclusion criteria, the trial results do not apply to patients with:
  - Acute coronary syndromes within 2 months
  - Highly symptomatic patients
  - Left main stenosis
  - LVEF <35%
- Trial findings may not be generalizable to centers with higher procedural complication rates
- Completeness of revascularization has not yet been assessed
- Women were enrolled in the trial but more often excluded from randomization compared to men due to less ischemia and more non-obstructive CAD
Summary

- The curves cross for the primary endpoint and the major secondary endpoint at approximately 2 years from randomization:
  - ~2 in 100 *higher* estimated rate with INV at 6 months
  - ~2 in 100 *lower* estimated rate with INV at 4 years

- Procedural MIs were increased with an invasive strategy

- Spontaneous MIs were reduced with an invasive strategy

- Low all-cause mortality in both groups despite high-risk clinical characteristics, high-risk ischemia and extensive CAD

- No heterogeneity of treatment effect, including by type of stress test, severity of ischemia or extent of CAD

- Very low rates of procedure-related stroke and death
Conclusions

- ISCHEMIA is the largest trial of an invasive vs conservative strategy for patients with SIHD
- Overall, an initial INV strategy as compared with an initial CON strategy did not demonstrate a reduced risk over median 3.3 years for
  - Primary endpoint - CV death, MI, hospitalization for UA, HF, RCA
  - Major Secondary endpoint - CV death or MI
- The probability of at least a 10% benefit of INV on all-cause mortality was <10%, based on pre-specified Bayesian analysis
Thank you

- To the thousands of investigators and coordinators
- The dedication of thousands of participants
- The NHLBI
- We are extremely grateful for their contribution to advance our understanding of the relative risks and benefits of two commonly used management strategies for stable ischemic heart disease

Slides at ischemiatrial.org
Simultaneous publication precluded by short time from last patient, last visit to database lock to AHA