ISCHEMIA

The ISCHEMIA Trial Findings and Practice Implications

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Disclosures

- Grant from NHLBI: U01HL105907
- I am a preventive cardiologist
Outline

- Background
- Design
- Findings
- Implications
Background
Extension of Survival (in months) at 10 Years After CABG in Various Subgroups

- Overall
- Vessel disease
  - One/two vessels
  - Three vessels
  - Left main
- LV function
  - Normal
  - Abnormal
- Exercise test
  - Normal
  - Abnormal
- Angina
  - Class O, I, II
  - Class III, IV
- VA risk score
  - Low
  - Moderate
  - High
- Stepwise risk score
  - Low
  - Moderate
  - High

Relevance today is unclear. There was minimal or no use of effective medical therapy (ASA, statins, beta-blockers, ACE inhibitors, lifestyle).

Randomized Clinical Strategy Trials of Revascularization in SIHD: OMT Era

- COURAGE
- BARI 2D
- FAME 2
2287 patients with SIHD underwent either PCI + OMT or OMT alone
Primary endpoint: death or MI
COURAGE

Survival Free of Death from Any Cause and Myocardial Infarction

Hazard ratio, 1.05; 95% CI (0.87–1.27); P=0.62

PCI
Medical therapy

Boden et al NEJM 2007
Freedom from Angina During COURAGE

Unadjusted hazard ratio for death, PCI plus medical therapy vs. medical therapy alone, 0.95 (95% CI, 0.79–1.13)
P = 0.53 by log-rank test

No. at Risk
Optimal medical therapy 598 569 533 500 455 403 280
PCI plus optimal medical therapy 613 589 561 529 486 416 302
2368 patients with type 2 diabetes and SIHD underwent either prompt revascularization + OMT or OMT alone.

Primary endpoint: all-cause death
Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Bindu Kalesan, M.P.H., Emanuele Barbato, M.D., Ph.D., Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D., Sven Mobius-Winkler, M.D., Gilles Rioufol, M.D., Ph.D., Nils Witt, M.D., Ph.D., Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engström, M.D., Keith G. Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D., Peter Verlee, M.D., Ole Frobert, M.D., Nick Curzen, B.M., Ph.D., Jane B. Johnson, R.N., B.S.N., Peter Jüni, M.D., and William F. Fearon, M.D., for the FAME 2 Trial Investigators*

- 888 SIHD patients scheduled for 1, 2 or 3 vessel DES-PCI
- Randomized to FFR-guided PCI + MT or MT alone
- Primary endpoint: death, MI, or urgent revascularization
**Primary Outcome**

All-cause death, MI, or urgent revascularization

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>MT</th>
<th>PCI+MT</th>
<th>Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>447</td>
<td>441</td>
<td>166</td>
</tr>
<tr>
<td>1</td>
<td>414</td>
<td>414</td>
<td>156</td>
</tr>
<tr>
<td>2</td>
<td>370</td>
<td>388</td>
<td>145</td>
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<tr>
<td>3</td>
<td>322</td>
<td>351</td>
<td>133</td>
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<tr>
<td>4</td>
<td>283</td>
<td>308</td>
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<td>253</td>
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<td>6</td>
<td>220</td>
<td>243</td>
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<td>7</td>
<td>192</td>
<td>212</td>
<td>74</td>
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<tr>
<td>8</td>
<td>162</td>
<td>175</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>127</td>
<td>155</td>
<td>52</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>117</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>92</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>53</td>
<td>13</td>
</tr>
</tbody>
</table>

- **PCI+MT vs. MT:** HR 0.32 (0.19-0.53); p<0.001
- **PCI+MT vs. Registry:** HR 1.29 (0.49-3.39); p=0.61
- **MT vs. Registry:** HR 4.32 (1.75-10.7); p<0.001

De Bruyne B et al. *NEJM* 2012: on-line
Death from any Cause

- PCI+MT vs. MT: HR 0.33 (0.03-3.17); p=0.31
- PCI+MT vs. Registry: HR 1.12 (0.05-27.33); p=0.54
- MT vs. Registry: HR 2.66 (0.14-51.18); p=0.30
FAME 2: FFR-Guided PCI versus Medical Therapy in Stable CAD

Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>PCI+MT vs. MT: HR 1.05 (0.51-2.19); p=0.89</th>
<th>PCI+MT vs. Registry: HR 1.61 (0.48-5.37); p=0.41</th>
<th>MT vs. Registry: HR 1.65 (0.50-5.47); p=0.41</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MT</td>
<td>441</td>
<td>421</td>
<td>386</td>
</tr>
<tr>
<td>PCI+MT</td>
<td>447</td>
<td>414</td>
<td>388</td>
</tr>
<tr>
<td>Registry</td>
<td>166</td>
<td>156</td>
<td>145</td>
</tr>
</tbody>
</table>

Cumulative incidence (%)
FAME 2 Five-Year Outcomes

**Table 2. Clinical End Points at 5-Year Follow-up.**

<table>
<thead>
<tr>
<th>End Points</th>
<th>PCI Group (N=447)</th>
<th>Medical-Therapy Group (N=441)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Registry Cohort (N=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no. of patients (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary composite end point</td>
<td>62 (13.9)</td>
<td>119 (27.0)</td>
<td>0.46 (0.34–0.63)</td>
<td>26 (15.7)</td>
</tr>
<tr>
<td>Components of primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>23 (5.1)</td>
<td>23 (5.2)</td>
<td>0.98 (0.55–1.75)</td>
<td>7 (4.2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>36 (8.1)</td>
<td>53 (12.0)</td>
<td>0.66 (0.43–1.00)</td>
<td>14 (8.4)</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>28 (6.3)</td>
<td>93 (21.1)</td>
<td>0.27 (0.18–0.41)</td>
<td>14 (8.4)</td>
</tr>
</tbody>
</table>

NEJM 2014;371:1208-17.
B  Myocardial Infarction

FAME 2
5-Year Outcomes

Hazard ratio, 0.66 (95% CI, 0.43–1.00)

Cumulative Incidence (%)

Years since Randomization

No. at Risk
Medical therapy  441  408  399  387  315  301
PCI  447  421  410  399  340  328

Xaplanteris et al.
NEJM 2018
Design Limitations of Previous Trials

- Low risk patients included (i.e., mild ischemia)
- Revascularization procedures not optimal in COURAGE and BARI 2D (little DES, no FFR)
- Referral bias by randomizing after cath
- Small sample size (FAME 2)
Relationship of Ischemia and Treatment to Risk of Cardiac Death

N=10,627 no known CAD
146 Cardiac deaths
F/U=2 yrs

Medical Rx

Revasc

p<0.001

What is the best *initial* management strategy for patients with stable ischemic heart disease (SIHD) and at least moderate ischemia?

**OMT + Cath & Revasc**

**OMT**

**OMT = optimal medical therapy**
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 (n=5179)

Screen failure

Exclusion Criteria
• LM >50%
• EF <35%
• eGFR <30 ml/min*
• ACS <2 months
• Severe valvular disease

Left Main 7.5%
No obstructive disease 21%

INVASIVE Strategy
OMT + Cath + Optimal Revascularization
(n=2588)

CONSERVATIVE Strategy
OMT alone
Cath reserved for OMT failure
(n=2591)


*referred for ISCHEMIA-CKD
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
• Angina-related Quality of Life

## Definition of OMT in ISCHEMIA

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>&gt;30 minutes &gt;5 times per week</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>&lt;7% calories</td>
</tr>
<tr>
<td><strong>Physiologic</strong></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Systolic BP &lt;140 mm/Hg (↓ to &lt;130 mmHg in April 2018)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>LDL &lt;70 mg/dl (1.8 mmol/L)</td>
</tr>
<tr>
<td>BMI</td>
<td>Initial BMI  Weight Loss Goal</td>
</tr>
<tr>
<td></td>
<td>25-27.5  BMI &lt;25</td>
</tr>
<tr>
<td></td>
<td>&gt;27.5  10% relative weight loss</td>
</tr>
<tr>
<td><strong>Pharmacologic Targets</strong></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Aspirin 75-162 mg daily</td>
</tr>
<tr>
<td>Statin</td>
<td>Maximum tolerated dose of high-intensity statin</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>If LDL-C &gt;70 on maximally tolerated statin</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>If hypertension, diabetes, eGFR &lt;60 or LVEF &lt;40%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>If history of MI or LVEF &lt;40%</td>
</tr>
</tbody>
</table>

**LIPID THERAPY**
Goal: LDLC <70 mg/dL (1.8 mmol/L)

- **Atorvastatin 80 mg**
- **Rosuvastatin 40 mg**

If not at LDL goal after 3 months, evolocumab not available

- Add ezetimibe
- Add evolocumab

If not at LDL goal after 3 months, evolocumab available

- Contact CCC Risk Factor Management Team
  1-212.263-4225
  ischemia@nyumc.org

**HYPERTENSION THERAPY**
Goal: BP <140/90

- Start β-blocker and ACE inhibitor

If needed to control BP

- Increase ACE inhibitor or ARB

If needed to control BP

- Add CCB and/or diuretic

- If BP not controlled

- Contact CCC Risk Factor Management Team

**ANGINA THERAPY**

- Sublingual NTG and β-blocker

If needed to relieve angina

- Add or substitute CCB, LAN or ranolazine

If needed to relieve angina

- Add or substitute drug class not already Rx'd

If angina not controlled

- Contact CCC Risk Factor Management Team

* Or ARB if appropriate

- Consider (not in order of preference) ivabradine, nicorandil, perhexiline, trimetazidine where approved.

LAN = long-acting nitrate.

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1 Maximum dose is 20 mg for Asian individuals

2 Where available
Baseline LDL = 83 mg/dL. Last visit LDL = 65 mg/dL.

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 mm/Hg, 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.
Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

Adjusted hazard ratio (HR\text{adj}) for invasive vs. conservative: 0.93 (95% CI: 0.80 to 1.08)


HR adjusted for age, sex, eGFR, LVEF, and diabetes.
Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>INV</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>2591</td>
<td>2588</td>
</tr>
<tr>
<td>1</td>
<td>2431</td>
<td>2364</td>
</tr>
<tr>
<td>2</td>
<td>1907</td>
<td>1908</td>
</tr>
<tr>
<td>3</td>
<td>1300</td>
<td>1291</td>
</tr>
<tr>
<td>4</td>
<td>733</td>
<td>730</td>
</tr>
<tr>
<td>5</td>
<td>293</td>
<td>271</td>
</tr>
</tbody>
</table>

Incidence of Procedural vs. Spontaneous MI by Treatment Group

Procedural MI  
Type 4a or 5

Spontaneous MI  
Type 1


Chaitman et al. ACC 2020.
All-Cause Death

Adjusted hazard ratio ($H_{\text{adj}}$) for invasive vs. conservative: 1.05 (95% CI: 0.83 to 1.32)

# Primary Endpoint

**Pre-specified Subgroups**

<table>
<thead>
<tr>
<th>Met ischemia eligibility criteria, according to core laboratory</th>
<th>Percent of Patients</th>
<th>Estimated 5-Yr Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Invasive Strategy</td>
<td>Conservative Strategy</td>
</tr>
<tr>
<td>No</td>
<td>13.8</td>
<td>24.4</td>
</tr>
<tr>
<td>Yes</td>
<td>86.2</td>
<td>16.0</td>
</tr>
<tr>
<td>Degree of baseline ischemia, according to core laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or mild</td>
<td>11.9</td>
<td>24.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>33.3</td>
<td>18.2</td>
</tr>
<tr>
<td>Severe</td>
<td>54.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>58.2</td>
<td>14.5</td>
</tr>
<tr>
<td>Yes</td>
<td>41.8</td>
<td>18.8</td>
</tr>
<tr>
<td>New or more frequent angina ≤3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>73.8</td>
<td>16.0</td>
</tr>
<tr>
<td>Yes</td>
<td>26.2</td>
<td>17.6</td>
</tr>
<tr>
<td>Guideline-based medical therapy at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>80.3</td>
<td>17.0</td>
</tr>
<tr>
<td>Yes</td>
<td>19.7</td>
<td>12.7</td>
</tr>
<tr>
<td>CAD severity based on 50% stenosis</td>
<td></td>
<td></td>
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<tr>
<td>One vessel</td>
<td>23.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Two vessel</td>
<td>31.4</td>
<td>10.2</td>
</tr>
<tr>
<td>Three or more vessels</td>
<td>45.1</td>
<td>20.7</td>
</tr>
<tr>
<td>Stenosis of the proximal LAD coronary artery (≥50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>53.2</td>
<td>13.4</td>
</tr>
<tr>
<td>Yes</td>
<td>46.8</td>
<td>15.5</td>
</tr>
</tbody>
</table>

Angina-Related Quality of Life Results

Angina at Baseline
- Invasive strategy better
- The worse the angina, the greater the benefit

No Angina at Baseline
- No difference between Invasive and Conservative
Some Practical Questions Raised by ISCHEMIA

- How should we diagnose obstructive coronary disease?
- Do we need to rule out left main on everyone with at least moderate ischemia on a stress test?
- When should we refer to the cath lab?
- How should we assess patient symptoms, since they should drive revascularization?
Implications for Method to Diagnose CAD

Stable patient with suspected CAD

Non-imaging exercise stress test

- Pros
  - Cost
  - Symptomatic response to exercise
  - Hemodynamic response to exercise
- Cons
  - No quantitation of ischemia
  - No localization of ischemia
  - Not interpretable if paced, LVH, etc.
  - Lower sensitivity
  - Cannot rule out LM disease

Stress imaging test (Nuclear, Echo, CMR)

- Pros
  - Ischemia severity quantitated
  - Ischemia localized
  - Interpretable if paced, LVH, etc.
  - Diagnostic accuracy
- Cons
  - Cost
  - Radiation (nuclear)
  - Cannot rule out LM disease

Coronary CT angiogram

- Pros
  - Anatomic diagnosis is made
  - Anatomic burden is prognostic
  - Can rule out LM disease
  - FFR measurement option
- Cons
  - Renal function contraindication
  - Cost
  - Radiation (only 1 mSv)
Implications for Practice

- No need to rush stable patients to the cath lab
- Prognosis depends on anatomy, not ischemia
- CCTA may be the best first test to evaluate suspected CAD
- Need better methods to achieve risk factor control
- Use a validated method to assess symptoms (e.g., SAQ)
- Share evidence with patients, share decision about revascularization
- Revascularize for unacceptable angina despite OMT
- Do not revascularize if there are no symptoms

1Does not apply to patients with left main disease, ischemic cardiomyopathy (CAD and LVEF <35%), or angina that cannot be controlled medically
Implications for Management of Stable CAD

Patients with Stable CAD

Optimal Medical Therapy

None or Satisfied

Symptoms? (SAQ)

Left Main Disease?

PCI

Multi-disciplinary Heart Team

CABG

Cath ± Revasc

Unsatisfied

Shared Decision-Making Values/Preferences/Goals

Newer Rx: PCSK9i, icosapent ethyl, SGLT2i, GLP-1 RA, low dose rivaroxaban, anti-inflammatory(?)

Adapted from John Spertus
Initial Invasive or Conservative Strategy for Stable Coronary Disease

Health-Status Outcomes with Invasive or Conservative Care in Coronary Disease


NEJM 2020
Discussion