International Study of Comparative Health Effectiveness with Medical and Invasive Approaches
Stable Ischemic Heart Disease

- What is the best initial management strategy for patients with SIHD?
- What is the evidence that early revascularization improves prognosis?
Why Do We Revascularize in Stable Ischemic Heart Disease?

- To improve survival
- To improve quality of life
Impact of Revascularization on Outcomes in SIHD: Review of Evidence
Randomized Clinical Strategy Trials of Revascularization in SIHD

- CABG vs. “Medical Therapy” (no CABG) 1970s-1980s
- PCI (BMS) vs. “Some” Medical Therapy 1990s-2000s
- PCI + “Optimal” Medical Therapy vs. OMT 2000s
CABG vs MED
CABG Surgery Trialists Collaboration; 10-year outcome

Extension of Survival (in months) at 10 Years After CABG in Various Subgroups

- Overall: N=150
- Vessel disease:
  - One/two vessels: N=550
  - Three vessels: N=1300
  - 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).

Subgroup conclusions are based on pooling of predominantly negative trials.

SIHD: PCI vs. Medicine Pre-COURAGE

Meta-analysis of 11 randomized trials; N = 2950

<table>
<thead>
<tr>
<th>Event</th>
<th>Favor PCI</th>
<th>Favor Medical Management</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td>0.68</td>
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<td>Cardiac death or MI</td>
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<td></td>
<td>0.28</td>
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<tr>
<td>Nonfatal MI</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
</tbody>
</table>

Risk ratio (95% CI)

Trials of Optimal Medical Therapy With or Without Revascularization

- COURAGE
- BARI 2D
- FAME 2
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*

- 2287 patients with SIHD randomized to PCI + OMT or OMT alone
- Primary endpoint: death or MI

Boden et al NEJM 2007
PCI Did Not Reduce Death or MI in SIHD Patients

Optimal Medical Therapy (OMT) vs PCI + OMT

Hazard ratio: 1.05
95% CI (0.87-1.27)
P = 0.62

Number at Risk
- Medical Therapy: 1138, 1017, 959, 834, 638, 408, 192, 30
- PCI: 1149, 1013, 952, 833, 637, 417, 200, 35

Boden et al. NEJM 2007
• 2368 patients with type 2 diabetes and SIHD randomized to prompt revascularization + OMT or OMT alone

• Primary endpoint: all-cause death
Revascularization Did Not Improve Survival in SIHD Patients with Diabetes

BARI 2D Survival by Revascularization Mode
PCI vs. CABG Selected by Treating Physicians

35% DES (after April 2003, 61% DES)
84% IMA grafts

FAME 2: FFR-Guided PCI versus Medical Therapy in Stable CAD

Stable CAD patients scheduled for 1, 2 or 3 vessel DES-PCI
N = 1220

FFR in all target lesions

Randomized Trial

At least 1 stenosis with FFR ≤ 0.80 (n=888)

Randomization 1:1

PCI + MT
MT

Registry

When all FFR > 0.80 (n=332)

MT

Follow-up after 1, 6 months, 1, 2, 3, 4, and 5 years

50% randomly assigned to FU

FAME 2 Halted in January 2012 for Difference in Primary Endpoint

- On recommendation of an independent Data & Safety Monitoring Board after randomizing 888 patients (54% of planned enrollment)
- Found a highly statistically significant reduction in the primary endpoint* in PCI group
- Average follow-up 7 months (planned follow-up 2 years)

*Death, MI, urgent revascularization
**FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD**

**Primary Outcome**

*All-cause death, MI, or urgent revascularization*

---

*FFR-Guided PCI vs. Medical Therapy*: HR 0.32 (0.19-0.53); p<0.001

*FFR-Guided PCI vs. No Flow-Limiting Stenosis*: HR 1.29 (0.49-3.39); p=0.61

*Medical Therapy vs. No Flow-Limiting Stenosis*: HR 4.32 (1.75-10.7); p<0.001

---

### FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD

**No Difference in All-Cause Mortality**

**FFR-Guided PCI vs. Medical Therapy:** HR 0.33 (0.03-3.17); p=0.31

**FFR-Guided PCI vs. No Flow-Limiting Stenosis:** HR 1.12 (0.05-27.33); p=0.54

**Medical Therapy vs. No Flow-Limiting Stenosis:** HR 2.66 (0.14-51.18); p=0.30

---

FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD
No Difference in Myocardial Infarction

**FFR-Guided PCI vs. Medical Therapy:** HR 1.05 (0.51-2.19); p=0.89

**FFR-Guided PCI vs. No Flow-Limiting Stenosis:** HR 1.61 (0.48-5.37); p=0.41

**Medical Therapy vs. No Flow-Limiting Stenosis:** HR 1.65 (0.50-5.47); p=0.41

**FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD**

Primary Endpoint Driven by Urgent Revasc

- **FFR-Guided PCI vs. Medical Therapy**: HR 0.13 (0.06-0.30); p<0.001
- **FFR-Guided PCI vs. No Flow-Limiting Stenosis**: HR 0.63 (0.19-2.03); p=0.43
- **Medical Therapy vs. No Flow-Limiting Stenosis**: HR 4.65 (1.72-12.62); p=0.009

Unstable angina only 51.8%

21.4% Myocardial Infarction

26.8% Unstable angina + evidence of ischemia on ECG

FAME 2 Perspective

- FAME 2 randomized patients after cath; physicians treating OMT-assigned patients knew the anatomy and FFR results
- If primary endpoint of COURAGE and BARI 2D included revascularization procedures, there would have been significant Δ between arms
- No difference in death or MI
- Success of medical therapy/risk factor control not reported
Revascularization to Improve Survival Compared With Medical Therapy

<table>
<thead>
<tr>
<th>3-vessel disease with or without proximal LAD artery disease*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CABG</strong></td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX score &gt;22) who are good candidates for CABG.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>IIb—Of uncertain benefit</td>
<td>B</td>
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<thead>
<tr>
<th>2-vessel disease with proximal LAD artery disease*</th>
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<tbody>
<tr>
<td><strong>CABG</strong></td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>IIb—Of uncertain benefit</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-vessel disease without proximal LAD artery disease*</th>
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</thead>
<tbody>
<tr>
<td><strong>CABG</strong></td>
<td>IIa—With extensive ischemia</td>
<td>B</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>IIb—Of uncertain benefit without extensive ischemia</td>
<td>C</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>IIb—Of uncertain benefit</td>
<td>B</td>
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<table>
<thead>
<tr>
<th>1-vessel proximal LAD artery disease</th>
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</thead>
<tbody>
<tr>
<td><strong>CABG</strong></td>
<td>IIa—With LIMA for long-term benefit</td>
<td>B</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>IIb—Of uncertain benefit</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1-vessel disease without proximal LAD artery involvement</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>CABG</strong></td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>III: Harm</td>
<td>B</td>
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</table>

<table>
<thead>
<tr>
<th>LV dysfunction</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>CABG</strong></td>
<td>IIa—EF 35% to 50%</td>
<td>B</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>IIb—EF &lt;35% without significant left main CAD</td>
<td>B</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>Insufficient data</td>
<td>B</td>
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</table>

<table>
<thead>
<tr>
<th>Survivors of sudden cardiac death with presumed ischemia-mediated VT</th>
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<tbody>
<tr>
<td><strong>CABG</strong></td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>I</td>
<td>C</td>
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</table>

<table>
<thead>
<tr>
<th>No anatomic or physiologic criteria for revascularization</th>
<th></th>
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<tbody>
<tr>
<td><strong>CABG</strong></td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>III: Harm</td>
<td>B</td>
</tr>
</tbody>
</table>

2011 ACCF/AHA/SCAI PCI Guidelines   *CABG for unprotected LM not shown (Class I)
Does Revascularization Improve Symptoms in SIHD?
Freedom from Angina: Coronary Artery Surgery Study (CASS)

Freedom from Angina: CASS vs. COURAGE

Freedom from angina rates have markedly increased with “optimal” medical therapy.

Freedom from Angina During COURAGE*

*by SAQ Angina Frequency Score
Freedom from Angina in BARI 2D: PCI

Dagenais et al. Circulation 2011;123:1492-1500
Freedom from Angina in BARI 2D: CABG

Dagenais et al. Circulation 2011;123:1492-1500
The Challenge with Angina Frequency as an Endpoint: Placebo Effect

Angina frequency was reduced by ranolazine but note the marked placebo effect

Kosiborod et al. JACC2013
Revascularization to Improve Symptoms

>1 significant stenosis amenable to revascularization and unacceptable angina despite guideline-directed medical therapy
Design Limitations of Prior Strategy Trials

- Low risk patients included
- Referral bias by randomizing after cath
- Revascularization procedures not optimal (little DES, no FFR)
- Underpowered (inadequate sample size)
Remaining Gap

- Is there any high risk group of SIHD patients in whom revascularization improves death/MI in the era of modern medical therapy?
**COURAGE Primary Endpoint by Angiographic Severity: No Difference**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>N</th>
<th>HR</th>
<th>[95% CI]</th>
<th>4.6 Year Rate</th>
<th>P value</th>
<th>P value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall treatment</td>
<td>2287</td>
<td>0.90</td>
<td>[0.73, 1.10]</td>
<td>16.2</td>
<td>0.30</td>
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<tr>
<td>Jeopardy Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥ 50% DS threshold)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0,1</td>
<td>589</td>
<td>0.99</td>
<td>[0.62, 1.58]</td>
<td>12.3</td>
<td></td>
<td>0.06</td>
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<tr>
<td>Score 2,3</td>
<td>989</td>
<td>0.66</td>
<td>[0.48, 0.92]</td>
<td>12.5</td>
<td></td>
<td></td>
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<tr>
<td>Score 4,5,6</td>
<td>454</td>
<td>1.27</td>
<td>[0.80, 1.82]</td>
<td>21.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeopardy Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥ 70% DS threshold)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Score 0,1</td>
<td>1562</td>
<td>0.85</td>
<td>[0.65, 1.10]</td>
<td>13.7</td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>Score 2,3</td>
<td>421</td>
<td>0.99</td>
<td>[0.63, 1.56]</td>
<td>17.6</td>
<td></td>
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<tr>
<td>Score 4,5,6</td>
<td>49</td>
<td>0.81</td>
<td>[0.21, 3.03]</td>
<td>16.2</td>
<td></td>
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<tr>
<td>Vessel Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0,1 VD</td>
<td>839</td>
<td>0.94</td>
<td>[0.64, 1.38]</td>
<td>12.4</td>
<td></td>
<td>0.96</td>
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<tr>
<td>2 VD</td>
<td>811</td>
<td>0.82</td>
<td>[0.59, 1.14]</td>
<td>15.0</td>
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<tr>
<td>3 VD</td>
<td>382</td>
<td>0.90</td>
<td>[0.64, 1.27]</td>
<td>24.1</td>
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</table>

**Figure 1.** Influence of angiographic burden of disease on the outcome of death and nonfatal MI, excluding periprocedural MI. The rates of death and nonfatal MI during 4.6 years of follow-up are provided to the right of the forest plots. HR indicates hazard ratio.

Proximal LAD and Risk of Death or MI

In COURAGE and BARI 2D:

- Proximal LAD >50% was *not* an independent predictor of death or MI
- The hazard ratio for PCI vs. OMT was similar for proximal LAD vs. other stenoses
- No suggestion that PCI of proximal LAD reduces the risk of death or MI

Mancini GBJ et al. *JACC* 2008; 51:A244
Chaitman BR et al. *Circulation*. 2010; 122: A10145
Observational study: Revascularization was associated with lower risk of cardiac death only in those with >10% ischemia on perfusion imaging.
COURAGE Serial Nuclear Substudy: Outcomes in 105 Patients with Moderate-to-Severe Baseline Ischemia Who Returned for 2nd Study @ 6-18 months

A: PCI reduces ischemia better than OMT alone

B: For both groups combined, ischemia reduction is associated with fewer events

C: Does PCI Reduce Events?

PCI did not Reduce Events
Subset with Moderate-to-Severe Ischemia at Baseline, with or without a 2nd scan during follow up

For 189 pts with core lab-interpreted moderate-severe ischemia, PCI vs. OMT 24% vs. 21%, HR 1.19 (95% CI 0.65-2.18)

Shaw et al. AHJ 2012
Survival in Ischemic vs. Non-Ischemic Patients in STICH

There was no difference between patients with vs. those without ischemia in all-cause mortality or other endpoints

Panza et al. JACC 2013
STICH: Survival by Presence of Ischemia and Treatment Group

There was no difference in the treatment effect between CABG and MED for mortality or any other clinical endpoint for those with and without ischemia.

Panza et al. JACC 2013
How Does Ischemia Confer Risk?

- Moderate-to-severe ischemia is a marker for high risk of death
- Unclear whether increased risk of death related to . . .
  - Adverse effects of ischemia
  - Occlusion of severe stenosis
  - Arrhythmias
  - More severe ischemia as a marker of atherosclerotic burden with more vulnerable plaques
Stenosis Severity ≠ Plaque Vulnerability

- Dissociation between the angiographic (or physiologic) severity of a stenosis and underlying atheroma and propensity to become a culprit lesion
- Atherosclerosis is a systemic disease, with diffuse coronary artery involvement
- Medical therapy has changed the underlying biology and natural history of atherothrombotic disease
Severe Obstruction (angina, no rupture) vs Mild Obstruction (no angina, likely to rupture)

Severe fibrotic plaque
- Severe obstruction
- No lipid
- Fibrosis, Ca²⁺

Exertional angina
• (+) ETT

Revascularization
Anti-anginal Rx

Vulnerable plaque
- Minor obstruction
- Eccentric plaque
- Lipid pool
- Thin cap

Plaque rupture
- Acute MI
- Unstable angina
- Sudden death

Pharmacologic stabilization
Early identification of high-risk?

Courtesy of PH Stone, MD.
Coronary Stenosis Severity Prior to MI

- Ambrose 1988
- Little 1988
- Nobuyoshi 1991
- Giroud 1992

- All 4 studies

<table>
<thead>
<tr>
<th>Coronary stenosis (%)</th>
<th>&lt;50%</th>
<th>50%-70%</th>
<th>&gt;70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrose 1988</td>
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<td></td>
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<tr>
<td>Little 1988</td>
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<td></td>
<td></td>
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<tr>
<td>Nobuyoshi 1991</td>
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<td></td>
<td></td>
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<tr>
<td>Giroud 1992</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All 4 studies</td>
<td>68%</td>
<td>18%</td>
<td>14%</td>
</tr>
</tbody>
</table>

A Fundamental Question

- If clinical trials in the OMT era show no clear death or MI benefit from an initial strategy of revascularization, do we need to cath and revascularize patients prior to a trial of OMT?
ISCHEMIA Overview

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

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

- **Patients**: stable, at least moderate ischemia (core lab)
- **Primary Aim**: to determine whether an initial invasive strategy of cath and 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 or MI
- **Major Secondary Endpoint**: angina-related QOL
- **Sample Size**: 8,000
- **Follow-up**: average ~4 years
Inclusion Criteria

- Men or women. *Emphasis on good representation of women and minorities*

- Fulfillment of one of the following ischemia eligibility criteria:

<table>
<thead>
<tr>
<th>Nuclear Perfusion via SPECT or PET</th>
<th>Echo</th>
<th>CMR</th>
<th>ETT (for Protocol v2.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10% myocardium ischemic</td>
<td>≥3/16 segments with stress-induced severe hypokinesis or akinesis</td>
<td>perfusion: ≥12% myocardium ischemic and/or wall motion: ≥3/16 segments with stress-induced severe hypokinesis or akinesis</td>
<td>See criteria on next slide</td>
</tr>
</tbody>
</table>
Inclusion Criteria

Exercise Testing without Imaging (all 4 criteria must be met)

1. Clinical history of typical angina or typical angina during the exercise test
2. Absence of resting ST segment depression $\geq 1.0$ mm or confounders that render exercise ECG non-interpretable (LBBB, LVH with repolarization, pacemaker, etc.)
3. As compared to the baseline tracing, additional exercise-induced horizontal or downsloping ST segment depression $\geq 1.5$ mm in 2 leads or $\geq 2.0$ mm in any lead; ST segment elevation $\geq 1$ mm in a non-infarct territory. Both the J-point and the ST segment need to meet criteria.
4. Either of the following:
   a. Workload at which ST segment criteria are met is not to exceed completion of stage 2 of a standard Bruce protocol or 7 METS if a non-Bruce protocol is used.  
      or
   b. ST segment criteria are met at $<75\%$ of the maximum predicted HR
Stable Patient Moderate or Severe Ischemia

Blinded CCTA

Core lab anatomy eligible?

no → Late screen failure

yes → RANDOMIZE

INVASIVE Strategy
OMT + Cath + Optimal Revascularization

CONSERVATIVE Strategy
OMT alone
Cath reserved for OMT failures

Average 4 Years of Follow-up
Primary Endpoint: Composite of CV Death and MI

1CCTA may not be performed, particularly in patients with eGFR < 60 mL/min; see MOO for details
2Exclude patients with LM disease or no obstructive disease
3OMT=Optimal Medical Therapy
Attempt to Avoid Prior Design Limitations

- Exclude low risk patients
- Reduce referral bias by randomizing prior to cath
- Optimize revascularization procedures (DES, FFR, Heart Team)
- Have sufficient power to detect a difference between treatment strategies
Primary Aim

- To determine whether an initial invasive strategy of cardiac catheterization and optimal revascularization, if feasible, in addition to OMT in SIHD patients with at least moderate ischemia on ischemia testing reduces the incidence of CV death or non-fatal MI compared with a conservative strategy of OMT alone with cardiac catheterization and revascularization reserved for failure of OMT.
Secondary Aims

- Major: Compare angina-related QOL between groups
- Also compare:
  - components of the primary endpoint
  - composite of CV death, MI, resuscitated cardiac arrest, or hospitalization for unstable angina or HF
  - other composite endpoints
  - health resource utilization, costs, and cost-effectiveness between groups
Composite Primary Endpoint

- CV Death
- Nonfatal MI

Secondary Endpoints

- Angina-related QOL
- CV death, MI, resuscitated cardiac arrest, or hospitalization for unstable angina or HF
- All cause mortality
- Stroke
Reasons for Blinded CCTA*

- Safety (exclude LM disease)
- Recruitment (reassure referring physicians without disclosing non-LM anatomy)
- Power (avoid dilution by patients with no obstructive CAD)

*If eGFR low, CCTA will not be performed and the patient will be excluded if LM disease is suspected by the treating physician.
Major Exclusion Criteria

- LVEF < 35%
- History of unprotected left main stenosis \( \geq 50\% \) on prior coronary computed tomography angiography (CCTA) or prior cardiac catheterization (if available)
- Finding of “no obstructive CAD” (<50% stenosis in all major epicardial vessels) on prior CCTA or prior catheterization, performed within 12 months
- Coronary anatomy unsuitable for either PCI or CABG
- Unacceptable level of angina despite maximal medical therapy
- Very dissatisfied with medical management of angina
- Canadian Cardiovascular Society Class III angina of recent onset, OR angina of any class with a rapidly progressive or accelerating pattern
- Canadian Cardiovascular Society Class IV angina, including unprovoked rest angina
Canadian Cardiovascular Society (CCS) Angina Classification

Class I
- Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.

Class II
- Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.

Class III
- Marked limitation of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.

Class IV
- Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest.

Exclusion: Participant-reported unacceptable level of angina despite maximal medical therapy

- Ask the question "Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or angina?"

- Potential responses:
  - 4 or more times per day
  - 1-3 times per day
  - 3 or more times per week but not every day
  - 1-2 times per week
  - Less than once a week
  - None over the past 4 weeks

At least daily angina without ability to further titrate medical or anti-anginal therapy excludes the participant.
Exclusion: Very dissatisfied with medical management of angina

- Ask the question "How bothersome is it for you to take your pills for chest pain, chest tightness, or angina as prescribed?"
- Potential responses:
  - Extremely bothersome
  - Quite a bit bothersome
  - Moderately bothersome
  - Slightly bothersome
  - Not bothersome at all
  - My doctor has not prescribed pills
  - “Extremely bothersome” excludes the participant
Angina and Noncompliance Exclusion Criteria

- The reason for these criteria is to exclude participants who, if randomized to CON, will need cardiac catheterization because their angina symptoms cannot be controlled with medical therapy because they are refractory to medications, dissatisfied with taking medications, or won’t take them.
Exclusion Criteria

- History of noncompliance with medical therapy
- Acute coronary syndrome within the previous 2 months
Exclusion: ACS syndrome within the previous 2 months

- Patients with acute coronary syndrome within the previous 2 months, defined as STEMI, non-STEMI, or rest angina subset of unstable angina, is excluded.

- Low risk unstable angina such as new onset angina or changing pattern that does not include rest angina or a rapid, high risk crescendo pattern on minimal exertion does NOT exclude patient.
Exclusion Criteria

- PCI within the previous 12 months
- Stroke within the previous 6 months or spontaneous intracranial hemorrhage at any time
- History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia, not due to a transient reversible cause.
Exclusion: Ventricular Tachycardia (VT)

- Patients cannot have any history of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia not due to a transient reversible cause

- Patients who have an ICD (implantable cardioverter defibrillator) to prevent VT are eligible to be enrolled in the trial
Exclusion Criteria

- NYHA Class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months
New York Heart Association (NYHA) Classification

**Exclusion: Class III-IV HF**

### Class I
- **No limitations.** Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnea.

### Class II
- **Slight limitation of physical activity.** They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnea. Ordinary physical activity includes walking more than two blocks on level ground, climbing more than one flight of stairs at normal pace, walking uphill, walking or climbing stairs rapidly, walking or stair climbing under adverse conditions (cold, wind, emotional stress).

### Class III
- **Marked limitation of physical activity.** They are comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnea. Less than ordinary activity includes walking one to two blocks on level ground or climbing one flight of stairs at a normal pace.

### Class IV
- **Inability to carry out any physical activity without symptoms of fatigue, palpitations, or dyspnea.** Symptoms may be present even at rest. If any physical activity is undertaken, these symptoms are increased.
Exclusion: Heart Failure

- Patients cannot have NYHA class III or class IV heart failure at study enrollment, or have been hospitalized within the past 6 months for worsening chronic heart failure.
- If they do not have chronic heart failure, but had transient HF complicating acute myocardial infarction (more than 2 months prior to enrollment) they are eligible to be enrolled in the trial.
Exclusion: Prior CABG

- Prior CABG, unless CABG was performed more than 12 months ago, and coronary anatomy has been demonstrated to be suitable for PCI or repeat CABG to accomplish complete revascularization of ischemic areas (CCC approval required)

- Rationale: patients with prior CABG initially permitted for enrollment, high rate of inability to revascularize in INV group
Additional Exclusion Criteria

- Non-ischemic dilated or hypertrophic cardiomyopathy
- End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30mL/min (not an exclusion for CKD ancillary trial)
- Severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial
- Allergy to radiographic contrast that cannot be adequately pre-medicated, or any prior anaphylaxis to radiographic contrast
- Planned major surgery necessitating interruption of dual antiplatelet therapy (note that patients may be eligible after planned surgery*)
- Life expectancy less than the duration of the trial due to non-cardiovascular comorbidity
- Pregnancy (known to be pregnant; to be confirmed before CCTA and/or randomization, if applicable)
- Patient who, in the judgment of the participant’s physician, is likely to have significant unprotected left main stenosis (Those who are able to undergo CCTA will have visual assessment of the left main coronary artery by the CCTA core lab)
- Enrolled in a competing trial that involves a non-approved cardiac drug or device
Exclusion Criteria

- Inability to comply with the protocol
- Exceeds the weight or size limit for CCTA or cardiac catheterization at the site
- High risk of bleeding which would contraindicate the use of dual antiplatelet therapy
- Cardiac transplant recipient
Optimal Medical Therapy

- Applied equally to CON and INV
- Based on guidelines
- Study team at each site is responsible for implementation of OMT, in conjunction with participant’s personal MD
- Local circumstances will dictate how study team collaborates with personal physician
## Behavioral Risk Factor Goals

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Cessation</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>&lt;7% calories</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>≥30 minutes of moderate intensity ≥5 times/week</td>
</tr>
<tr>
<td>Medication Adherence</td>
<td>100% adherence</td>
</tr>
<tr>
<td>Influenza Vaccination</td>
<td>Recommended to all patients annually</td>
</tr>
</tbody>
</table>
# Physiologic Risk Factor Goals

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body Weight by Body Mass Index (kg/m²)</strong></td>
<td><strong>Initial BMI</strong> Weight Loss Goal</td>
</tr>
<tr>
<td>25-27.5</td>
<td>BMI &lt;25</td>
</tr>
<tr>
<td>&gt;27.5</td>
<td>10% relative weight loss</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>&lt;140/90 mmHg</td>
</tr>
<tr>
<td><strong>LDL-C (primary goal)</strong></td>
<td>&lt;70 mg/dL (1.8 mmol/L)</td>
</tr>
<tr>
<td><strong>Non-HDL-C (secondary goal)</strong></td>
<td>&lt;100 mg/dL (2.6 mmol/L) if TG &gt;200 (2.3mmol/L)</td>
</tr>
<tr>
<td><strong>TC:HDL ratio (secondary goal)</strong></td>
<td>&lt;4.0</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>HbA1c &lt;8.0%*</td>
</tr>
</tbody>
</table>

*A more stringent HbA1c goal (such as <7%) may be appropriate for selected individuals*
Invasive Strategy

- Cath and revascularize all INV patients
- Revascularization method based on highest likelihood to safely and effectively relieve significant ischemia in viable myocardial territories
- FFR required per algorithm
PCI based on anatomic feasibility and clinical considerations
**For ETT Patients**

**Lesion Severity on Cath**

- **≥80%**
  - Consider FFR (not required but recommended)
  - PCI

- **50-79%**
  - Required
  - FFR <0.80 required if planning to perform PCI
  - PCI
  - >0.80
  - No PCI

- **<50%**
  - FFR <0.80 required if planning to perform PCI
  - No PCI

---

*PCI based on anatomic feasibility and clinical considerations
Cath in Patients Randomized to CON Strategy

- Cath will be reserved for patients with refractory angina, acute coronary syndrome, acute ischemic heart failure or resuscitated cardiac arrest

Cath in CON Patient

Hospitalization for ACS\(^1\)?

- Yes
  - Refractory symptoms? \(^2\)
    - Yes: Consistent with CON strategy, Adherent to Protocol
    - No: NOT consistent with CON strategy, NOT Adherent to Protocol

\(^1\)ACS=acute coronary syndrome, includes resuscitated cardiac arrest and hospitalization for acute ischemic heart failure

\(^2\)According to trial definition

**Determination of acute ischemic event and refractory symptoms will be confirmed centrally**
“The PCI and CABG guideline writing committees endorse the performance of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, which will provide contemporary data on the optimal management strategy (medical therapy or revascularization with CABG or PCI) of patients with SIHD, including multivessel CAD, and moderate to severe ischemia.”

2011 ACCF/AHA/SCAI PCI and CABG Guidelines
Extra Slides
Sample Size Considerations

- High power (≥ 90%) for testing the primary endpoint
- High precision for estimating unknown true effect size (margin of error ≤ 15%)
- Robust power and precision across a range of plausible assumptions

<table>
<thead>
<tr>
<th>CON 4-yr Event Rate</th>
<th>Estimated Power (%)</th>
<th>N = 8000</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>( \Delta = 13% )</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>( \Delta = 15% )</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>( \Delta = 17% )</td>
<td>89</td>
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<tr>
<td>20%</td>
<td>82</td>
<td>92</td>
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<tr>
<td></td>
<td>92</td>
<td>97</td>
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<tr>
<td>25%</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>≥99</td>
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<tr>
<td>30%</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥99</td>
</tr>
</tbody>
</table>
Secondary Endpoints

- The major secondary endpoint will be angina-related quality of life

- Other secondary endpoints:
  - All-cause mortality
  - Composite of CV death, nonfatal MI, hospitalization for unstable angina, resuscitated cardiac arrest or heart failure
  - Stroke
  - Composite of CV death, nonfatal MI, stroke, hospitalization for unstable angina, resuscitated cardiac arrest or heart failure
  - Individual components of above endpoint
  - Other definitions (to be used in secondary analyses) will include the universal definition of MI and criteria to categorize large MI
Risk and Anatomic Referral Bias in Revasc. vs. Medicine Strategy Trials

- All prior SIHD strategy trials randomized patients after cath (e.g., COURAGE, BARI 2D, FAME 2)
- Higher risk patients may not have been enrolled (cardiologist refusal after seeing the anatomy)
- To answer the question of who benefits from an invasive strategy, we need to randomize higher risk SIHD patients before cath
Referral Rates to Cath When Moderate or Severe Ischemia is Detected

- ~35-65% of patients with at least moderate ischemia on MPI are referred for cardiac catheterization (data from 9 reports with 5,833 patients at 51 centers)
  - Clinical equipoise
  - We don’t know what the appropriate referral rate should be

Bateman TM et al. J Nucl Cardiol 1995
Hachamovitch et al. JACC 2004
Hachamovitch et al. Circ 2009
Hachamovitch et al. JACC 2012
Reduction of Ischemia with PCI vs OMT

COURAGE Trial Substudy

PCI + OMT (n=159)

33.3% with ≥5% ischemia reduction (p=0.0004)

OMT (n=155)

18.9% with ≥5% ischemia reduction

N=105 with mod - severe ischemia

PCI vs. OMT
78% vs. 52 % reduction in ischemia

Index

Most Sites Have Multiple Physical Locations

- Office with Stress Lab
- CCTA/Revascularization Center
- Private Office
- Private Office w/ CCTA + Stress Lab
- Site B
- Office
- Stress Lab
An ISCHEMIA Site Has Many Parts

Stress Lab | Treating Physician

Coordinator, PI, Co PIs (Lead Interventionalist, Lead Surgeon, Lead Imager)

CCTA Laboratory | CATH/PCI Lab | Surgery Center
COURAGE: PCI Did Not Improve Survival

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Medical Therapy</td>
<td>1138</td>
<td>1073</td>
<td>1029</td>
<td>917</td>
<td>717</td>
<td>468</td>
<td>302</td>
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</tr>
<tr>
<td>PCI</td>
<td>1149</td>
<td>1094</td>
<td>1051</td>
<td>929</td>
<td>733</td>
<td>488</td>
<td>312</td>
<td>44</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.87
95% CI (0.65-1.16)
P = 0.38

Boden WE et al NEJM 2007
Freedom from Angina: From CASS to BARI 2D

CABG: additional anti-anginal benefit over 5yrs

CASS

- Baseline: P=NS
- Year 1: P<0.0001
- Year 5: P<0.0001

BARI 2D - CABG

- Year 1: P<0.001
- Year 3: P<0.001
- Year 4: P=0.004
- Year 5: P=0.021
- Year 6: P=0.005

CABG vs. Medical Rx
(beta blockers + nitrates; no severe angina at baseline)

CABG vs. OMT
(18% angina-free at baseline)

Dagenais et al. Circ 2011
Freedom from Angina: COURAGE and BARI 2D*

PCI: additional anti-anginal benefit over 1-3yrs

COURAGE

<table>
<thead>
<tr>
<th>Year</th>
<th>OMT</th>
<th>PCI + OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Year 1</td>
<td>50%</td>
<td>70%</td>
</tr>
<tr>
<td>Year 3</td>
<td>60%</td>
<td>75%</td>
</tr>
<tr>
<td>Year 5</td>
<td>70%</td>
<td>80%</td>
</tr>
</tbody>
</table>

P-values: P=NS, P<0.001, P=0.02, P=NS

BARI 2D - PCI

<table>
<thead>
<tr>
<th>Year</th>
<th>MED</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>Year 3</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>Year 5</td>
<td>40%</td>
<td>60%</td>
</tr>
</tbody>
</table>

P-values: P<0.001, P=0.107, P=0.112, P=0.361, P=0.69

(12% angina-free at baseline)

(18% angina-free at baseline)

*CCS Class 0
Dagenais GR et al. Circulation 2011