Optimal Medical Therapy with or without Revascularization for SIHD Patients with Moderate-Severe Ischemia: 
*Update on the ISCHEMIA Trial*

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Stable Ischemic Heart Disease (SIHD)

- What is the best initial management strategy for patients with SIHD?
- What is the evidence that early revascularization improves prognosis?

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Contemporary Era of Intensive Medical Therapy

- COURAGE
- BARI 2D
- FAME-2
- STICH
- ISCHEMIA

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Evidence That Coronary Stenoses Could Be Left Alone Without Adverse Events

RITA-2, 1018 patients (504 PTCA, 514 medical management)

No Difference in Outcome over Median of 7 Years

(Henderson, et al. JACC 2003;42:1161)

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What Was Achieved with Optimal Medical Therapy (OMT) in COURAGE...

*Primary Endpoint: Survival Free of Death or MI*

- Randomization to PCI + OMT vs OMT
- Intensive, Guideline-driven Medical Therapy & Lifestyle Intervention In Both Groups

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COURAGE Trial: Event-Free Survival

Hazard ratio: 0.87
99% CI (0.65-1.16)
P = 0.38

8.3% vs 7.6%
COURAGE: Extended Follow-Up: Median: 11.9 Years (0-15 Years)

Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease

Steven P. Sedlis, M.D., Pamela M. Hartigan, Ph.D., Koon K. Teo, M.B., B.Ch., Ph.D., David J. Maron, M.D., John A. Spertus, M.D., M.P.H., G.B. John Marcini, M.D., William Kostuk, M.D., Bernard B. Chatman, M.D., Daniel Berman, M.D., Jeffrey D. Lorin, M.D., Marcin Dada, M.D., William S. Weintraub, M.D., and William E. Boden, M.D., for the COURAGE Trial Investigators

- 1,211 patients (53\% of original study population)
- Primary endpoint: all-cause death only (n=561 deaths; 25\%)

Sedlis et al at NEJM 2015; 373: 1937-46

- Significant clinical co-morbidity: 67\% HTN; 34\% DM; 71\% dyslipidemic; 29\% smokers; 39\% prior MI
- Significant angina at baseline in 88\% (12\% had "silent ischemia"); 58\% were CCS Class II or III
- Significant ischemia at baseline in 95\% of patients; 85\% had inducible ischemia on stress testing (57\% ETT and 43\% stress MPI, of whom 67\% had multiple reversible ischemic defects
- 69\% of patients had multivessel CAD with at least a 70\% proximal visual stenosis in one or more epicardial coronary arteries

Are COURAGE Trial Patients Generalizable to Contemporary Clinical Practice?

Revascularization Did Not Improve Survival in SIHD Patients with Diabetes

BARI 2D Study: Medical Therapy Versus Revascularization

Principal Secondary Endpoint (Death, MI, or Stroke)

FAME 2 Trial

Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease

FAME 2: FFR-Guided PCI vs. Medical Therapy in CAD (Stable, >1 week Post-ACS) Patients Referred for Cath angiography

- Primary Outcome
  - All-Cause Death, MI, or Urgent Revascularization
  - Primary endpoint driven solely by urgent revascularization; 52% of pts undergoing urgent revascularization had no evidence of ischemia on ECG, and biomarkers of myocardial necrosis were negative

- No. at risk
  - 441 PCI
  - 441 Medical Therapy

- Months after randomization
  - No difference in death/MI during the original 7 month mean follow-up, nor at 2 years—a total of 14 all-cause deaths (0.8%/year) and only 6 cardiac deaths (0.3%/year) = very low risk group

- Success of medical therapy/risk factor control in FAME 2 has still never been reported

SYNTAX: OMT is Associated with Improved 5-Year Survival After Revascularization

- SYNTAX: N=1800 randomized to PCI or CABG
- OMT = antiplatelet drug+statin+BB+ACEI/ARB
- OMT was underused in all patients, especially those undergoing CABG
- There was a 36% relative risk reduction in mortality (HR 0.64, 95% CI 0.48-0.85, p=0.002 at 5 years with OMT (greater than the treatment effect of revascularization—26% relative reduction in mortality with CABG versus PCI over 5 years)
- Underscores the importance of providing OMT to all patients who undergo PCI or CABG

Use of OMT Post Revascularization in SYNTAX

- OMT = antiplatelet+statin+BB+ACEI/ARB

Perspective on Interpreting FAME 2 Results

- FAME 2 randomized patients after cath: physicians treating OMT-assigned patients knew the anatomy and FFR results
- If the primary endpoint of COURAGE and BARI 2D included revascularization procedures, there would have been a significant Δ between arms
- There was no difference in death or MI during the original 7 month mean follow-up, nor at 2 years—a total of 14 all-cause deaths (0.8%/year) and only 6 cardiac deaths (0.3%/year) = very low risk group
- Success of medical therapy/risk factor control in FAME 2 has still never been reported
Effect of OMT vs. No OMT on Survival in SYNTAX

OMT = antiplatelet+statin+BB+ACEI/ARB

Design Limitations of Prior Strategy Trials

- Low to intermediate risk patients included
- Referral bias by randomizing after cath
- Revascularization procedures not optimal across prior trials (inadequate use of DES, uneven use of 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 contemporary optimal medical therapy (OMT) that includes intensive lifestyle intervention and aggressive, multifaceted secondary prevention?

What About Significant Multivessel Angiographic CAD and/or Proximal LAD Stenosis?

Freedom from Death, MI, or Hospitalization for ACS in SIHD Patients with 3-V CAD and Low EF, Stratified by Initial Randomization to PCI + OMT or OMT Alone

P = .59
PCI for Proximal LAD Stenosis 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 reduced the risk of death or MI

Ischemia and Risk of MI/Death

- Moderate-to-severe ischemia has been thought to be a marker for higher risk of death
  - *Newer data in the era of more advanced medical therapy challenge this*
  - Risk prediction is not the same as prediction of benefit with revascularization
- Is more severe ischemia a marker of greater atherosclerotic burden with more vulnerable plaques?
- Is moderate-severe ischemia a principal driver of long-term CV events?

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: For both groups, combined ischemia reduction is associated with fewer CV events
B: PCI reduces ischemia better than OMT
C: But...Does PCI Reduce CV Events?
A 2nd COURAGE Nuclear Substudy of 1,431 Pts Showed PCI Did Not Reduce CV 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

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

Why Have Randomized Trials Not Demonstrated a Survival Benefit for “Fixing” Coronary Stenoses in SIHD?

- 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
- Intensive guideline-directed medical therapy and lifestyle intervention have changed the underlying biology and natural history of atherothrombotic disease

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 initiating an empiric 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
- **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

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**Primary Aim**

- To determine whether an invasive strategy of routine cardiac catheterization followed by optimal revascularization and OMT in SIHD patients with at least moderate ischemia on stress imaging reduces the incidence of CV death or MI compared with a conservative strategy of OMT alone with cardiac catheterization and revascularization reserved for patients with ACS or refractory angina

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**Ischemia Eligibility Criteria**

Fulfillment of one of the following ischemia eligibility criteria, reviewed by core lab:

<table>
<thead>
<tr>
<th>Nuclear Perfusion</th>
<th>Echo/CMR Wall Motion</th>
<th>CMR Perfusion</th>
<th>ETT</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 10% ) LV</td>
<td>( \geq 23/16 ) segments with stress-induced severe hypokinesis or akinesis</td>
<td>( \geq 12.5% ) LV</td>
<td>( \geq 1.5 ) mm ST ( \downarrow ) @ ( \leq 7 ) METS</td>
</tr>
</tbody>
</table>

Projected annual CV death/MI rate across modalities = 5%

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**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

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**ISCHEMIA Where We Are Today**

*Current Study Status*
Global Overview

316 active sites in over 36 countries

GOAL = 375 active sites

It’s not too late to identify promising new sites!

Revised Timelines and Sample Size

- Awaiting formal NHLBI approval from meeting on 5/3/16 for recommendations on:
  - Reduction in sample-size from 8000 to 5000-6000 participants.
  - Extension in enrollment period
  - Extension in follow up period

Enrollment & Randomization Status

4785 Enrolled

- Insufficient ischemia = 457/4785 (9.6%)
- No obstructive disease = 586/3198 (18.3%)
- Left Main disease = 301/3198 (9.4%)
- Incidental Findings = 16/3198 (0.5%)
- Other = 414/4785 (8.7%)

2824 Randomized

Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>OVERALL (N = 2735)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± sd)</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Female</td>
<td>23% (629/2717)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39% (1081/2718)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73% (1965/2718)</td>
</tr>
<tr>
<td>Smoking, current</td>
<td>11% (307/2718)</td>
</tr>
<tr>
<td>Smoking, former</td>
<td>42% (1144/2718)</td>
</tr>
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</table>

Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>OVERALL (N = 2735)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>21% (571/2716)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>21% (574/2677)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>6% (149/2676)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>None (64% (1716/2672))</td>
</tr>
<tr>
<td>NYHA Class I</td>
<td>18% (492/2672)</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>18% (473/2672)</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>&lt;0.5% (10/2672)</td>
</tr>
</tbody>
</table>
Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>OVERALL (N = 2735)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection Fraction (%)</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>Angina history</td>
<td>88% (2337/2669)</td>
</tr>
<tr>
<td>Current angina</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>24% (653/2671)</td>
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<tr>
<td>CCS Class I</td>
<td>25% (676/2671)</td>
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<tr>
<td>CCS Class II</td>
<td>44% (1187/2671)</td>
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<tr>
<td>CCS Class III</td>
<td>6% (155/2671)</td>
</tr>
<tr>
<td>CCS Class IV</td>
<td>0% (0/2671)</td>
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</table>

Baseline Stress Test

<table>
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<th>Variable</th>
<th>OVERALL (N = 2735)</th>
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<tr>
<td>Modality</td>
<td></td>
</tr>
<tr>
<td>Nuclear</td>
<td>53% (1442/2708)</td>
</tr>
<tr>
<td>Echo</td>
<td>20% (541/2708)</td>
</tr>
<tr>
<td>CMR</td>
<td>7% (182/2708)</td>
</tr>
<tr>
<td>ETT w/o imaging</td>
<td>20% (543/2708)</td>
</tr>
<tr>
<td>Interpretation (imaging)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>39% (828/2122)</td>
</tr>
<tr>
<td>Moderate</td>
<td>53% (1117/2122)</td>
</tr>
<tr>
<td>None/Mild</td>
<td>8% (177/2122)</td>
</tr>
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</table>

ETT Ischemia Severity (Randomized)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OVERALL (N = 2807*)</th>
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</thead>
<tbody>
<tr>
<td>Interpretation (ETT)</td>
<td></td>
</tr>
<tr>
<td>ETT eligibility criteria met</td>
<td>78% (436/562)</td>
</tr>
<tr>
<td>Among those not meeting criteria,</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>70%</td>
</tr>
<tr>
<td>Mild</td>
<td>12%</td>
</tr>
<tr>
<td>None</td>
<td>18%</td>
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Optimal Medical Therapy in ISCHEMIA and ISCHEMIA-CKD

LIPID THERAPY

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

- Atorvastatin 80 mg
- Rosuvastatin 40 mg

- If not at LDL goal after 3 months on appropriate statin therapy:
  - Add ezetimibe 10 mg

Contact CCC Risk Factor Management Team
- phone: 1-212.263-5225
- email: ischemia@nymc.org

*Where available

We are conducting individual case reviews with site teams to intensify LDL therapy.

LDL goal in ISCHEMIA

Total Participants not at LDL Goal < 70mg/dL
Revascularization vs. OMT as an Initial Strategy in SIHD & Multivessel Disease

16 RCTs to date in 8,820 patients (including diabetics with MVD) show no reductions in death, MI, stroke, or other “hard events” with PCI in the modern era of contemporary OMT.

OMT can be safely administered to the majority of SIHD pts.

OMT remains under-utilized in patients undergoing revascularization, where clinical outcomes can be enhanced.

Whether greater PCI benefit and CV event reduction exists in patients with more extensive ischemia remains unclear, and is currently under prospective study (ISCHEMIA Trial).