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

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29th Annual Cardiology for Clinicians Spring Symposium
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Stable Ischemic Heart Disease (SIHD)

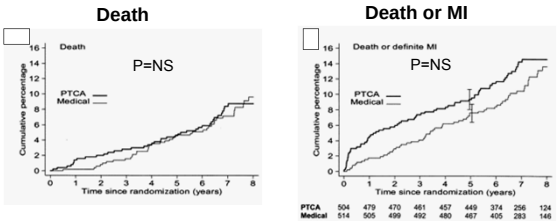
- What is the best initial management strategy for patients with SIHD?
- What is the evidence that early revascularization improves prognosis?

Contemporary Era of Intensive Medical Therapy

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

Evidence That Coronary Stenoses Could Be Left Alone Without Adverse Events

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



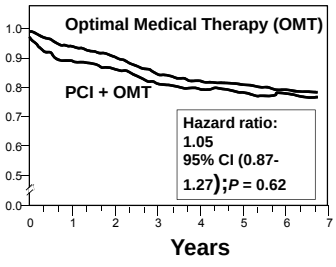
No Difference in Outcome over Median of 7 Years

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

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

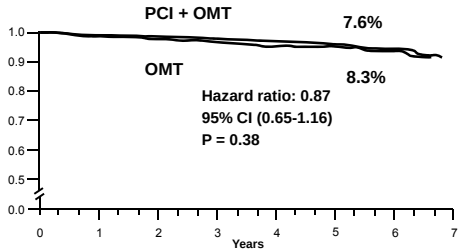
Primary Endpoint: Survival Free of Death or MI

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



Boden WE et al. *N Engl J Med.* 2007; 356:1503-1516.

COURAGE Trial: Event-Free Survival



Number at Risk

Medical Therapy	1138	1073	1029	917	717	468	302	38
PCI	1149	1094	1051	929	733	488	312	44

COURAGE: Extended Follow-Up:
Median: 11.9 Years (0-15 Years)

The NEW ENGLAND JOURNAL of MEDICINE

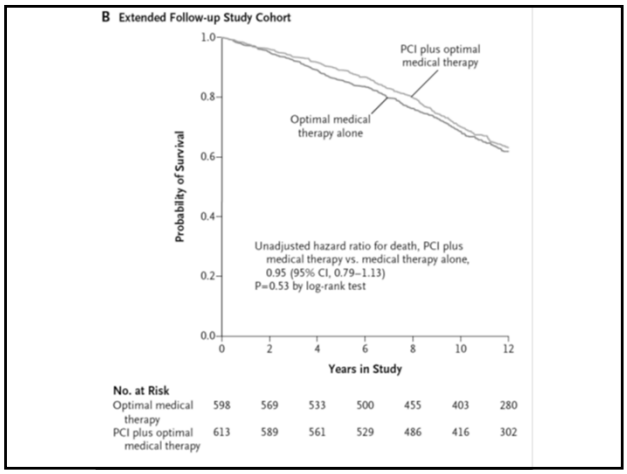
ORIGINAL ARTICLE

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 Mancini, M.D., William Kostuk, M.D., Bernard R. Chaitman, 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%)

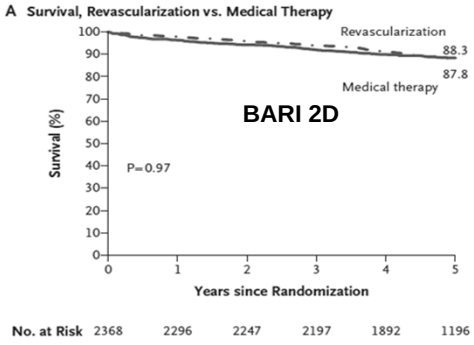
Sedlis et al NEJM 2015; 373: 1937-46



Are COURAGE Trial Patients Generalizable to Contemporary Clinical Practice?

- 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 <u>at least a 70% proximal visual stenosis</u> in one or more epicardial coronary arteries

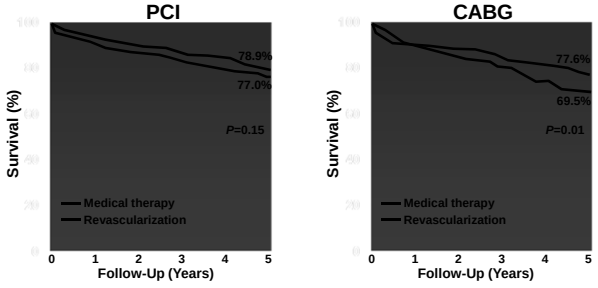
Revascularization Did Not Improve Survival in SIHD Patients with Diabetes



BARI 2D Study Group. *N Engl J Med* 2009;360:2503-2512.

BARI 2D Study: Medical Therapy Versus Revascularization

Principal Secondary Endpoint (Death, MI, or Stroke)



BARI 2D Study Group. *N Engl J Med.* 2009;360:2503-2512.

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FAME 2 Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 13, 2012 VOL. 367 NO. 11

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-Winckler, 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*

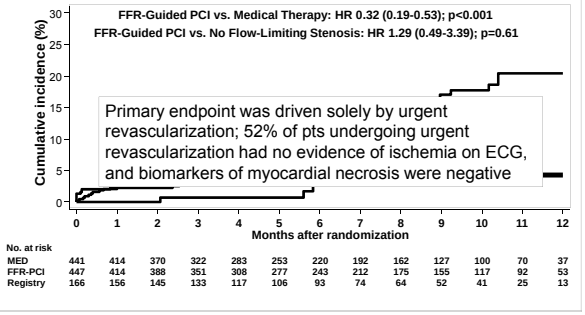
- 888 SIHD patients scheduled for 1, 2 or 3 vessel DES-PCI
- Randomized to FFR-guided PCI + MT or MT alone
- Primary endpoint: death, MI, or urgent revascularization

De Bruyne et al. *N Engl J Med* 2012;367:991-1001.

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

Primary Outcome

All-Cause Death, MI, or Urgent Revascularization



No. at risk													
MED	441	414	370	322	283	253	220	192	162	127	100	70	37
FFR-PCI	447	414	388	351	308	277	243	212	175	155	117	92	53
Registry	166	156	145	133	117	106	93	74	64	52	41	25	13

De Bruyne et al. NEJM 2012;367:991-1001.

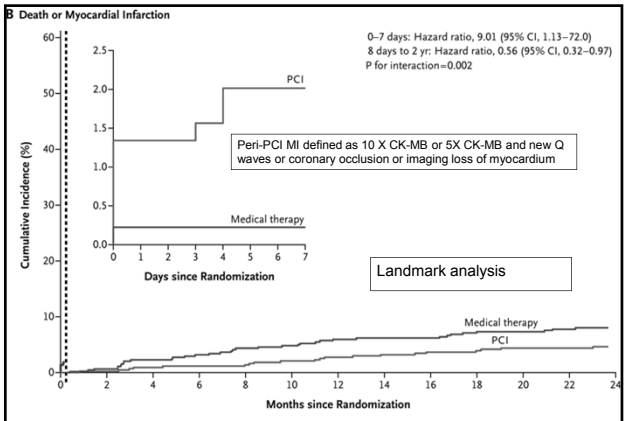
Baseline Class III-IV angina in ~23%

FAME 2 Two-Year Clinical Events: Still No Difference in Death/MI

Variable	PCI (N=447)	Medical Therapy (N=441)	Hazard Ratio (95%CI)*	P Value
	no. (%)			
Primary End Point	36 (8.1)	86 (19.5)	0.39 (0.26-0.57)	<0.001
Death from any cause	6 (1.3)	8 (1.8)	0.74 (0.26-2.14)	0.58
Myocardial Infarction	26 (5.8)	30 (6.8)	0.85 (0.50-1.45)	0.56
Urgent revascularization	18 (4.0)	72 (16.3)	.23 (0.14-0.38)	<0.001
Death or myocardial infarction	29 (6.5)	36 (8.2)	.79 (0.49-1.29)	0.35
Other End Points				
Death from cardiac causes	3 (0.7)	3 (0.7)	0.99 (0.20-4.90)	0.99

*Hazard ratios: PCI vs Med

•NEJM 2014;371:1208-17.



NEJM 2014;371:1208-17.

Perspective on Interpreting FAME 2 Results

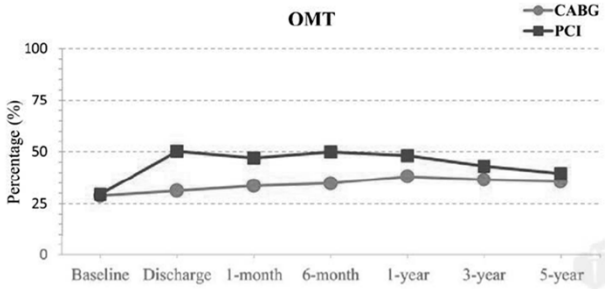
- FAME 2 randomized patients *after* cath; physicians treating OMT-assigned patients knew the anatomy and FFR results
- If the primary endpoint of COURAGE and BARI 2D included revascularization procedures, there would have been a significant Δ between arms
- There was no difference in death or MI during 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

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

Iqbal et al. Circulation 2015.

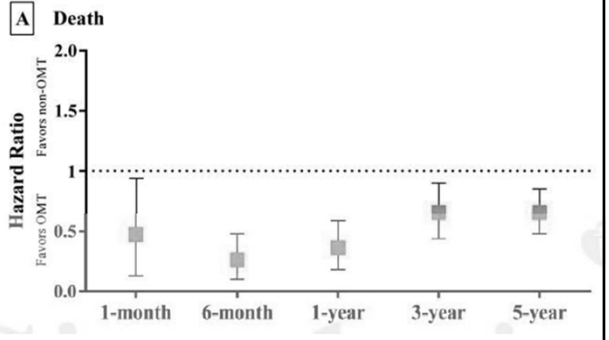
Use of OMT Post Revascularization in SYNTAX



OMT = antiplatelet+statin+BB+ACEI/ARB

Iqbal et al. Circulation 2015.

Effect of OMT vs. No OMT on Survival in SYNTAX



OMT = antiplatelet+statin+BB+ACEI/ARB

Iqbal et al. Circulation 2015.

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EDITORIAL COMMENT

Why Optimal Medical Therapy Should Be a Universal Standard of Care*

David J. Maron, MD,† William E. Boden, MD‡

A wise man, therefore, proportions his belief to the evidence.
–David Hume (1).

trial that used a creative method to evaluate the relationship between risk factor control, survival, and the composite endpoint of death, MI, or stroke,

Design Limitations of Prior Strategy Trials

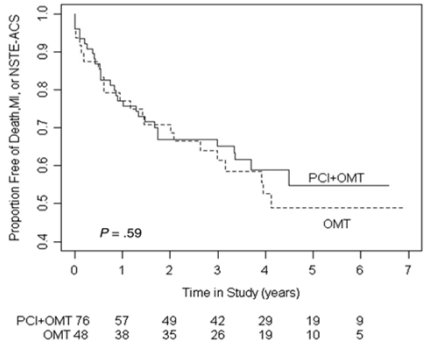
- Low to intermediate risk patients included
- Referral bias by randomizing after cath
- Revascularization procedures not optimal across prior trials (inadequate use of DES, uneven use of FFR)
- Underpowered (inadequate sample size)

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?

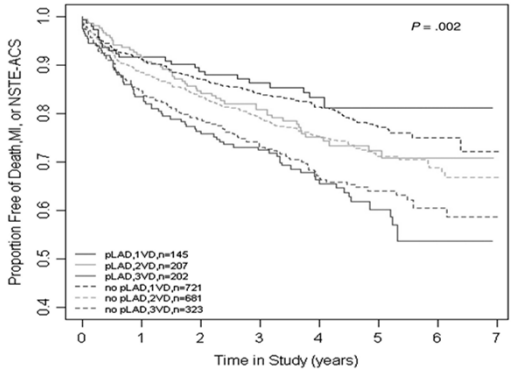
What About Significant Multivessel Angiographic CAD and/or Proximal LAD Stenosis?

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



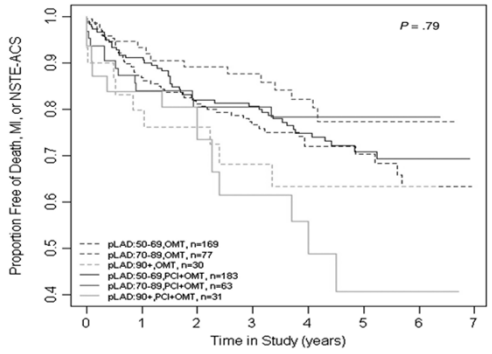
American Heart Journal 2013, http://dx.doi.org/10.1016/j.ahj.2013.07.007

Freedom from Death/MI/ACS According to Presence or Absence of Prox LAD Stenosis in the Setting of 1-3V CAD



American Heart Journal 2013, http://dx.doi.org/10.1016/j.ahj.2013.07.007

Freedom from D/MI/ACS in SIHD Patients with Increasing Stenosis Severity of Prox LAD: PCI+OMT or OMT Alone



Mancini GBJ et al. Am Heart J; http://dx.doi.org/10.1016/j.ahj.2013.07.007

PCI for Proximal LAD Stenosis and Risk of Death or MI

In COURAGE and BARI 2D:

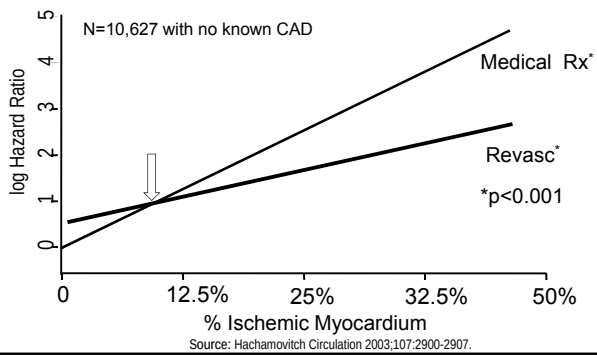
- Proximal LAD >50% was *not* an independent predictor of death or MI
- The hazard ratio for PCI vs. OMT was similar for proximal LAD vs. other stenoses
- No suggestion that PCI of proximal LAD reduced the risk of death or MI

Mancini GBJ et al. *JACC* 2008; 51:A244
Chaitman BR et a. *Circulation.* 2010; 122: A10145

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



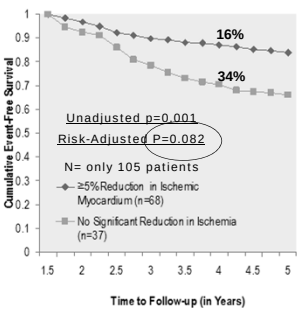
Source: Hachamovitch Circulation 2003;107:2900-2907.

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

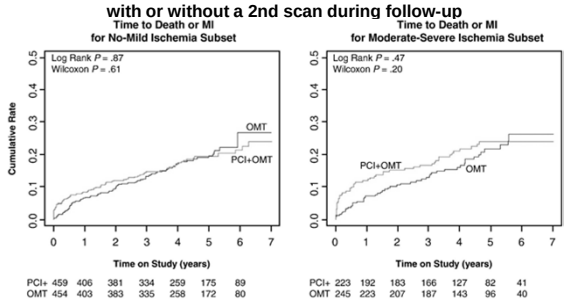
C: But…Does PCI Reduce CV Events?



Shaw et al. *Circulation*. 2008;117:1283-1291.

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

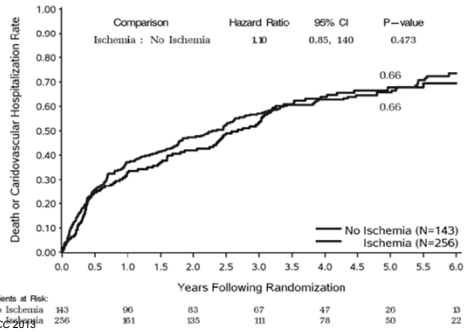


For 189 pts with *core lab-interpreted* moderate-severe ischemia, PCI vs. OMT: 24% vs. 21%, HR 1.19 (95% CI 0.65-2.18)

Shaw et al. AHJ 2012

Survival in Ischemic vs. Non-Ischemic Patients in STICH

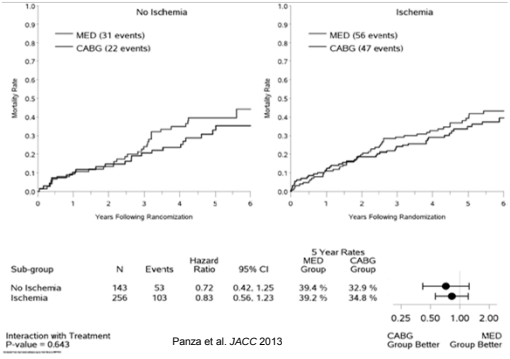
There was no difference between patients with vs. those without ischemia in all-cause mortality or other endpoints



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

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 thearpy 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 Trial

International **S**tudy of **C**omparative **H**ealth **E**ffectiveness with **M**edical and **I**nvasive **A**pproaches

Trial Update; ACC 2016

Investigator & Study Coordinator Meeting

April 3, 2016

ISCHEMIA Overview

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches

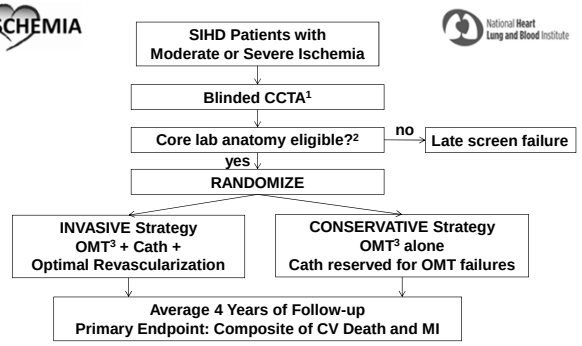
Chair - Judith Hochman, Co-Chair/PI - David Maron
Co-Pis: William Boden, Bruce Ferguson, Robert Harrington, Gregg Stone, David Williams

- 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

National Heart Lung and Blood Institute

ISCHEMIA

National Heart Lung and Blood Institute



[1]CCTA may **not** be performed**, particularly in patients with eGFR <**60 mL/min**; see MOO for details**
[2]Exclude patients with LM disease or no obstructive disease
[3]OMT=Optimal Medical Therapy

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

Ischemia Eligibility Criteria

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

Nuclear Perfusion	Echo/CMR Wall Motion	CMR Perfusion	ETT
≥10% LV	≥3/16 segments with stress-induced severe hypokinesis or akinesis	≥12.5% LV	≥1.5 mm ST ⇩ @ ≤7 METS

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

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

ISCHEMIA Where We Are Today

Current Study Status

Global Overview

316 active sites in over 36 countries

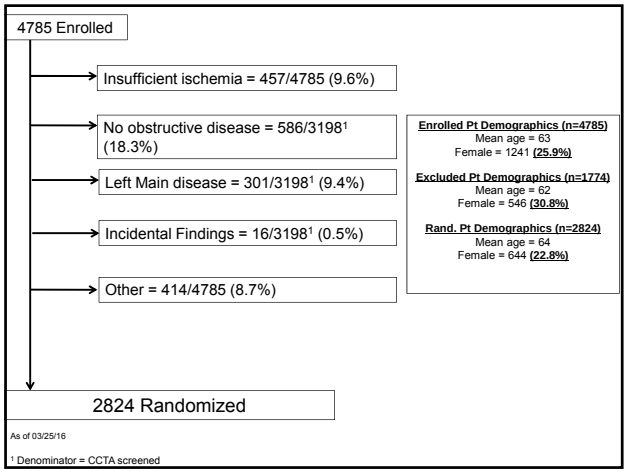
GOAL = 375 active sites

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



Baseline Characteristics

Variable	OVERALL (N = 2735)
Age (mean ± sd)	**64 ± 10**
Female	**23**% (629/2717)
BMI (kg/m^2) (mean ± sd)	**29 ± 6**
Diabetes	**39**% (1061/2716)
Hypertension	**73**% (1985/2716)
Smoking, current	**11**% (307/2716)
Smoking, former	**42**% (1144/2716)

Baseline Characteristics

Variable	OVERALL (N = 2735)
Prior MI	**21**% (571/2716)
Prior PCI	**21**% (574/2677)
Prior CABG	**6**% (148/2676)
Heart Failure	
None	**64**% (1716/2672)
NYHA Class I	**18**% (482/2672)
NYHA Class II	**18**% (473/2672)
NYHA Class III	**<0.5%** (1/2672)

Baseline Characteristics

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

Baseline Stress Test

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

ETT Ischemia Severity (Randomized)

Variable	OVERALL (N = 2807*)
Interpretation (ETT)	
ETT eligibility criteria met	**78%** (436/562)
Among those not meeting criteria,	
Moderate	**70%**
Mild	**12%**
None	**18%**

* As of 3/28/2016

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[1] 10 mg

If not at LDL goal after 3 months on combination therapy

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

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

[1]Where available

LDL goal in ISCHEMIA

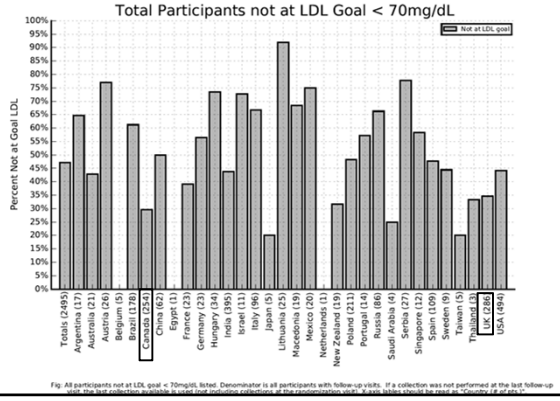


Fig. All participants not at LDL goal < 70mg/dL listed. Denominator is all participants with follow-up visits. If a collection was not performed at the last follow-up visit, the last collection available is used (not including collections at the randomization visit). X-axis labels should be read as "Country (# of pts)."

Systolic BP Goal in ISCHEMIA

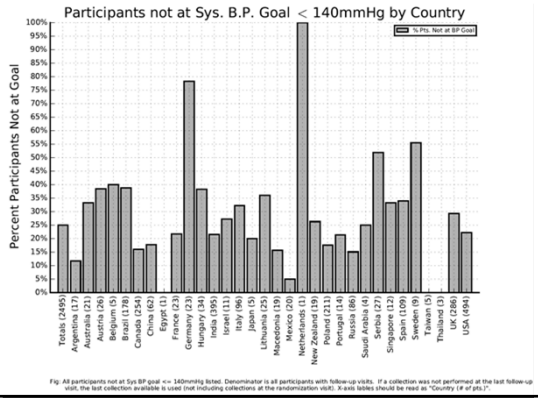


Fig. All participants not at Sys BP goal <= 140mmHg listed. Denominator is all participants with follow-up visits. If a collection was not performed at the last follow-up visit, the last collection available is used (not including collections at the randomization visit). X-axis lables should be read as "Country (# of pts.)".

Conclusions: 2016 Update

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)