Trial

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

Stable Ischemic Heart Disease

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

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Why Do We Revascularize in Stable Ischemic Heart Disease?

- To improve survival
- To improve quality of life

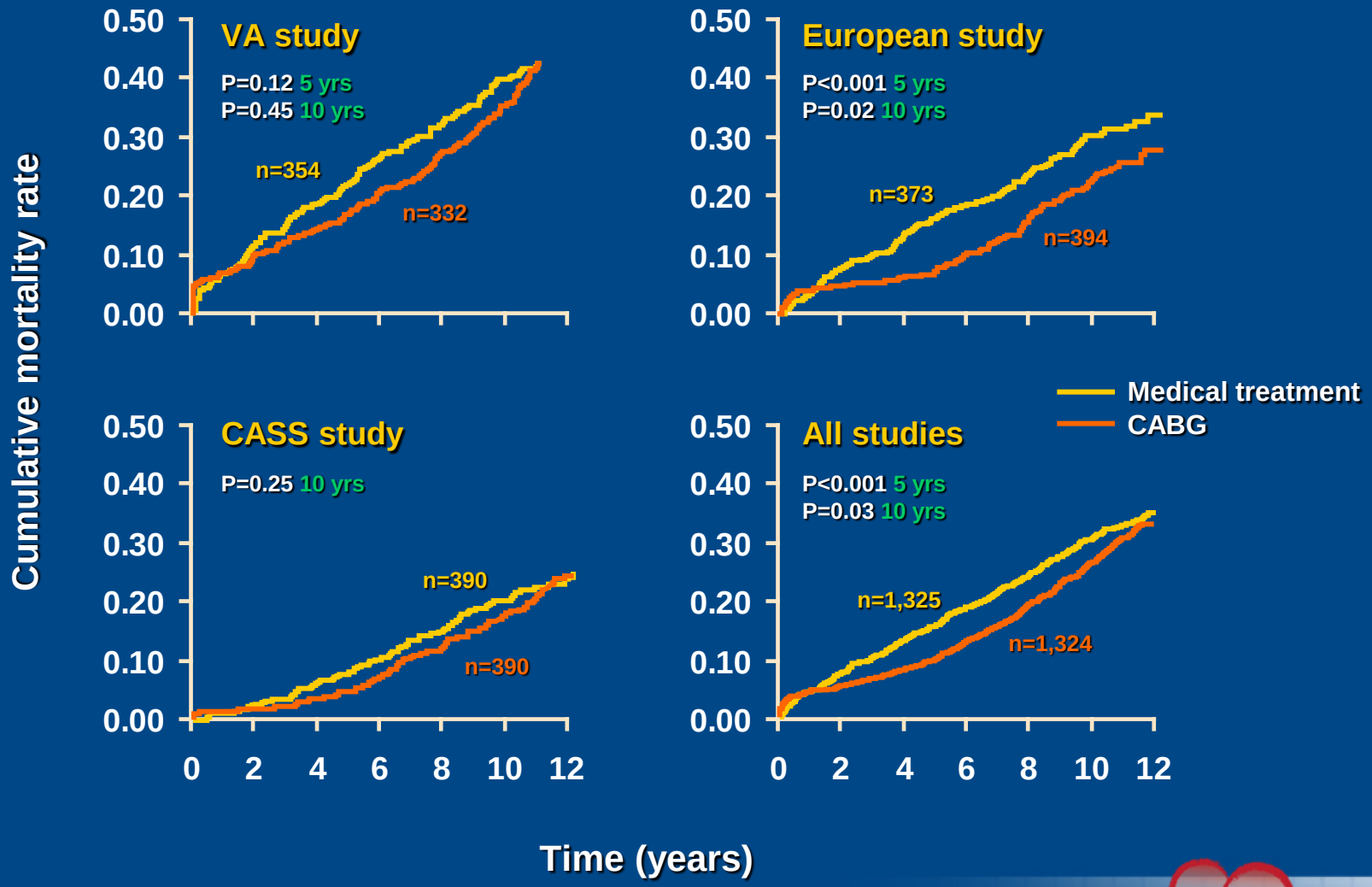
Impact of Revascularization on Outcomes in SIHD: Review of Evidence

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



Yusuf et al. Lancet 1994;344:563-570.

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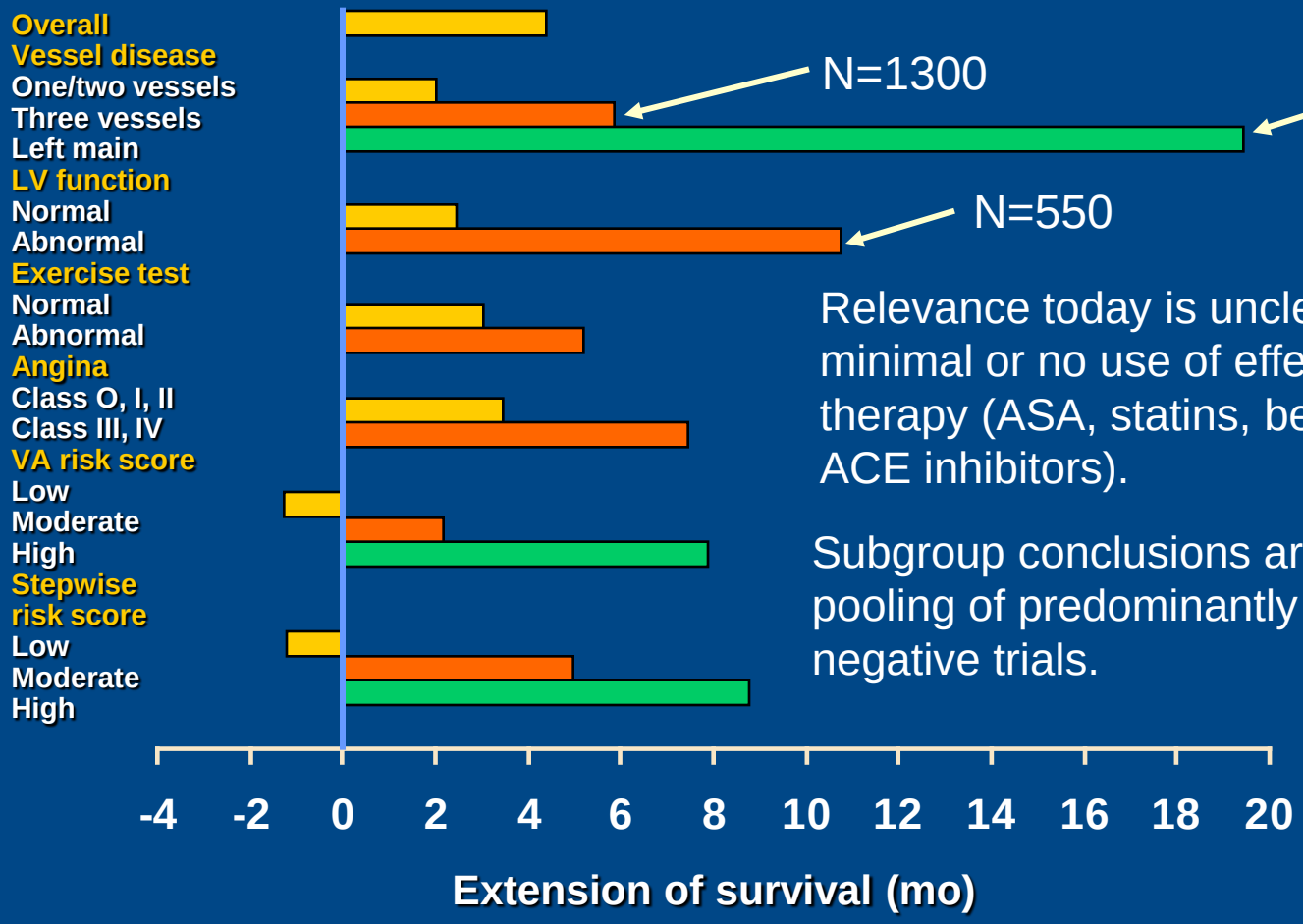
Extension of Survival (in months) at 10 Years After CABG in Various Subgroups



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.

Yusuf et al. Lancet 1994;344:563-570.

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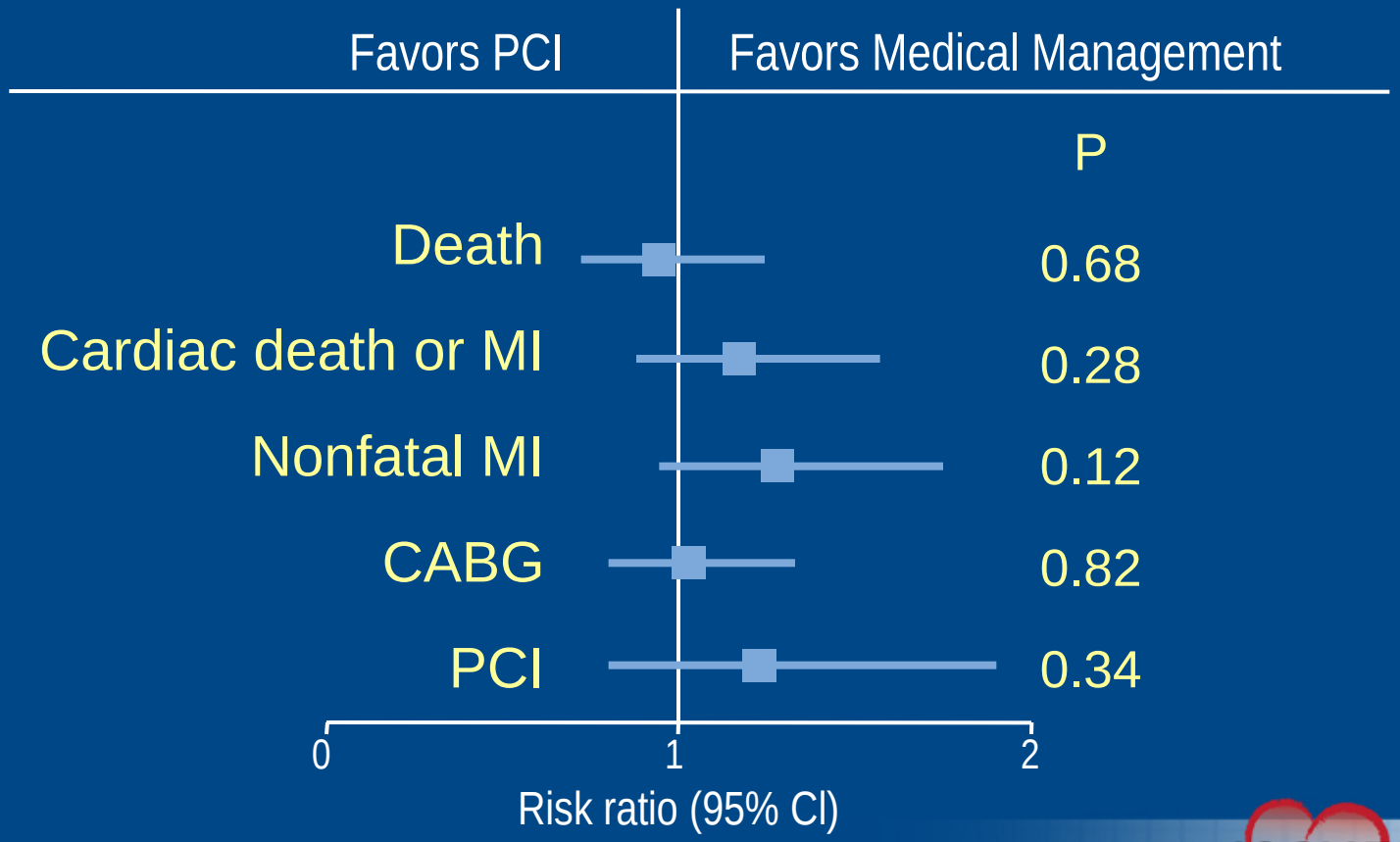
SIHD: PCI vs. Medicine Pre-COURAGE

Meta-analysis of 11 randomized trials; N = 2950



Katritsis DG et al. *Circulation.* 2005;111:2906-12.

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Trials of Optimal Medical Therapy With or Without Revascularization

- COURAGE
- BARI 2D
- FAME 2

COURAGE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 12, 2007 VOL. 356 NO. 15

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., Merril 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

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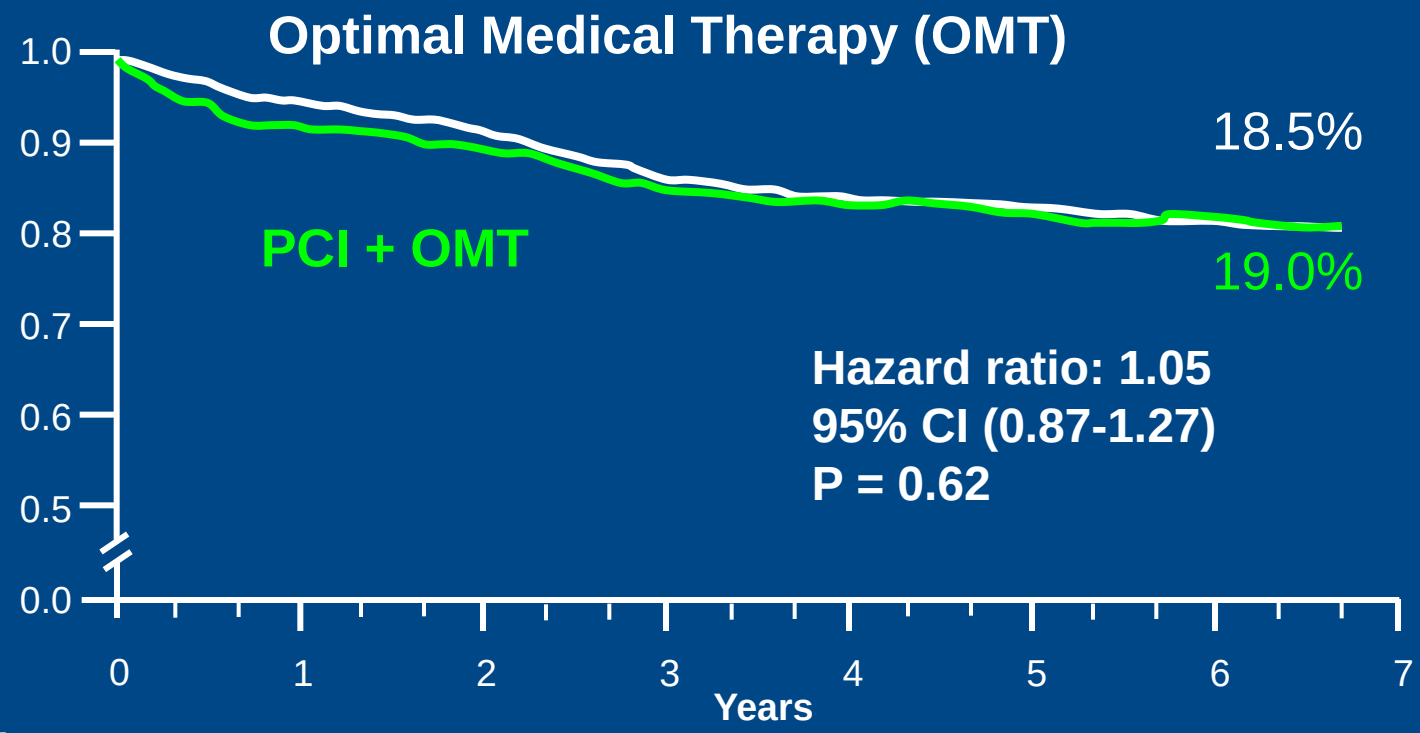
PCI Did Not Reduce Death or MI in SIHD Patients



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

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BARI 2D

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2009 VOL. 360 NO. 24

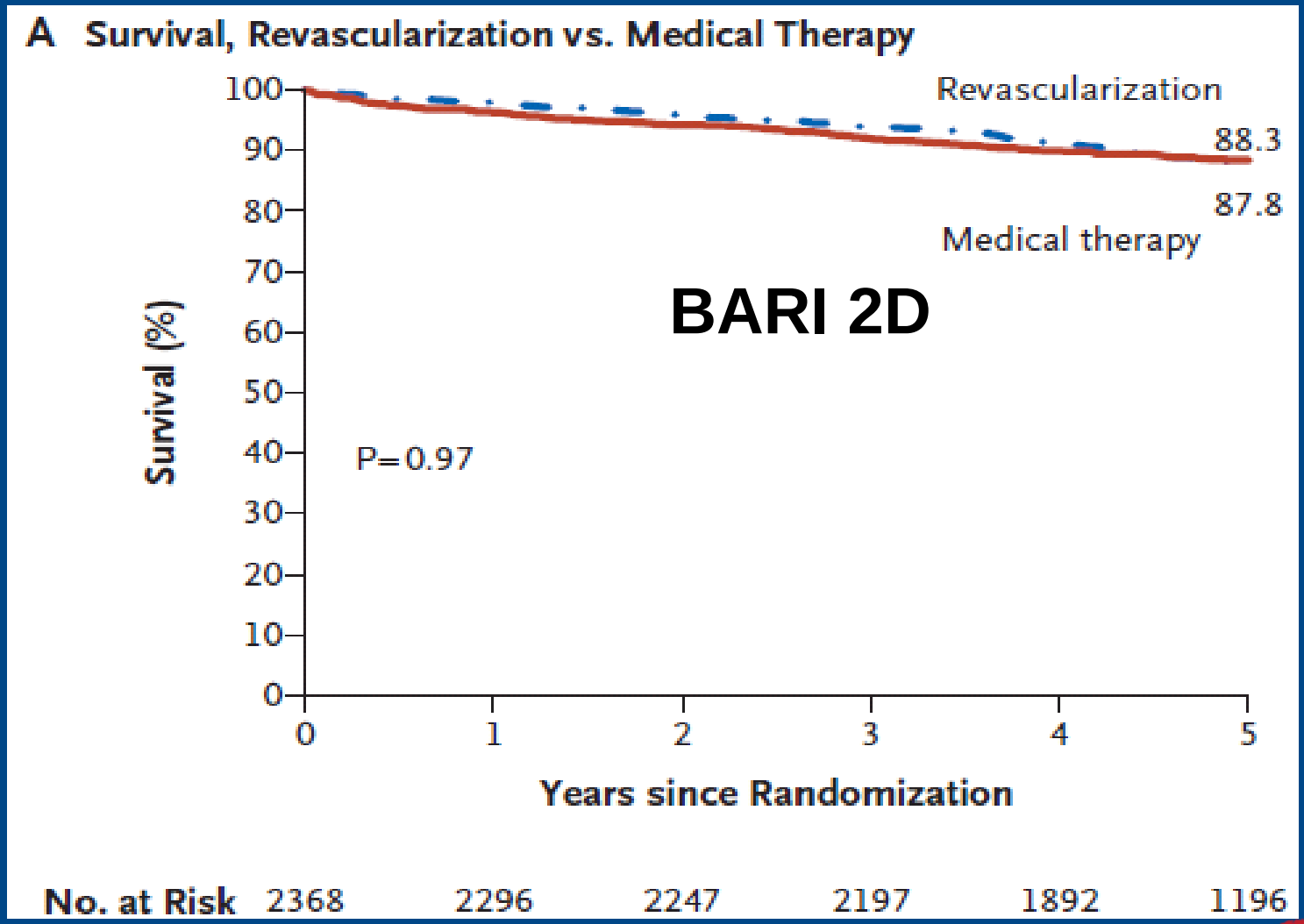
A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease

The BARI 2D Study Group*

- 2368 patients with type 2 diabetes and SIHD randomized to prompt revascularization + OMT or OMT alone
- Primary endpoint: all-cause death

BARI 2D Study Group. *N Engl J Med* 2009;360:2503-2515.

Revascularization Did Not Improve Survival in SIHD Patients with Diabetes



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

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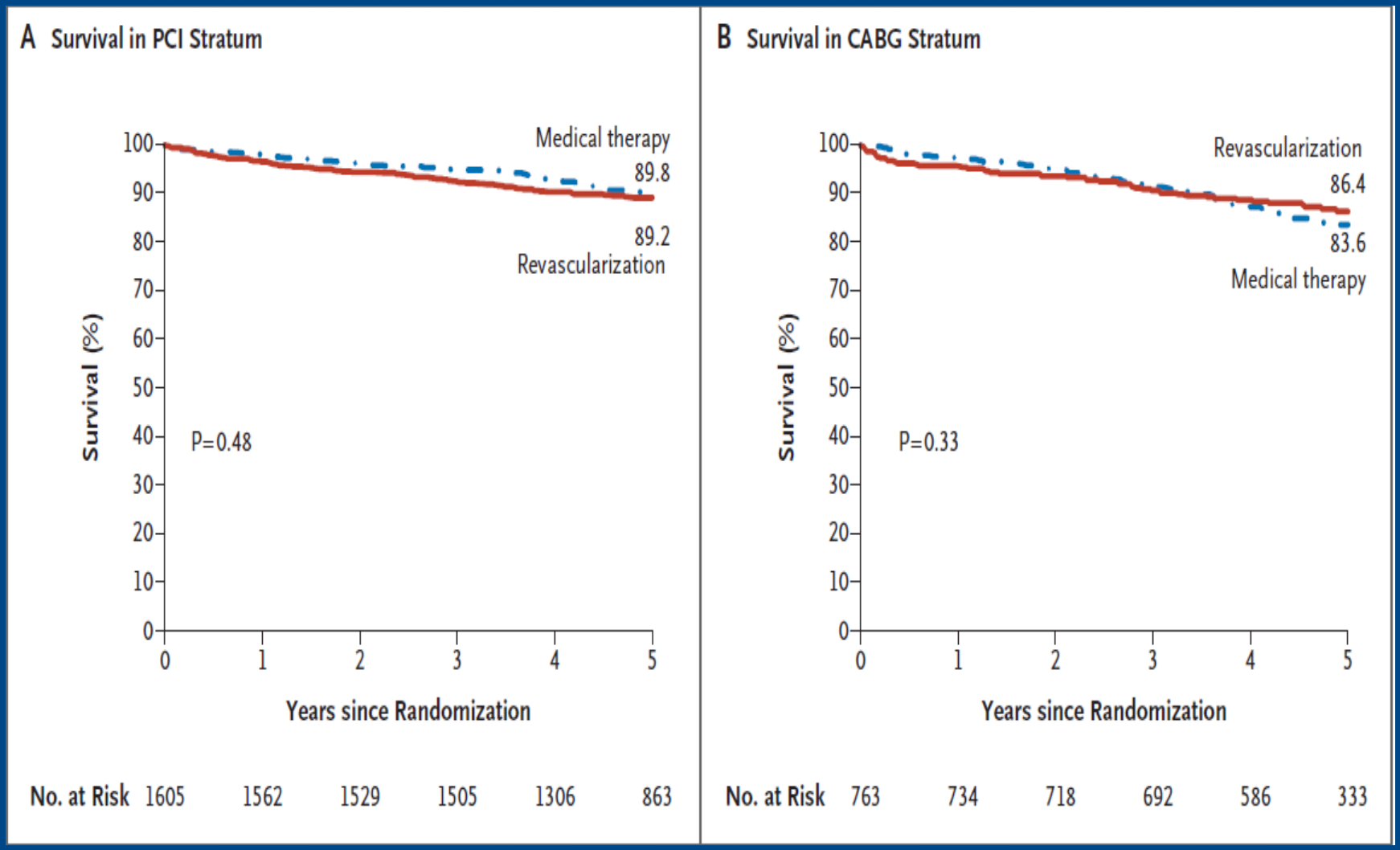
BARI 2D Survival by Revascularization Mode

PCI vs. CABG Selected by Treating Physicians



35% DES (after April 2003, 61% DES)

84% IMA grafts

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

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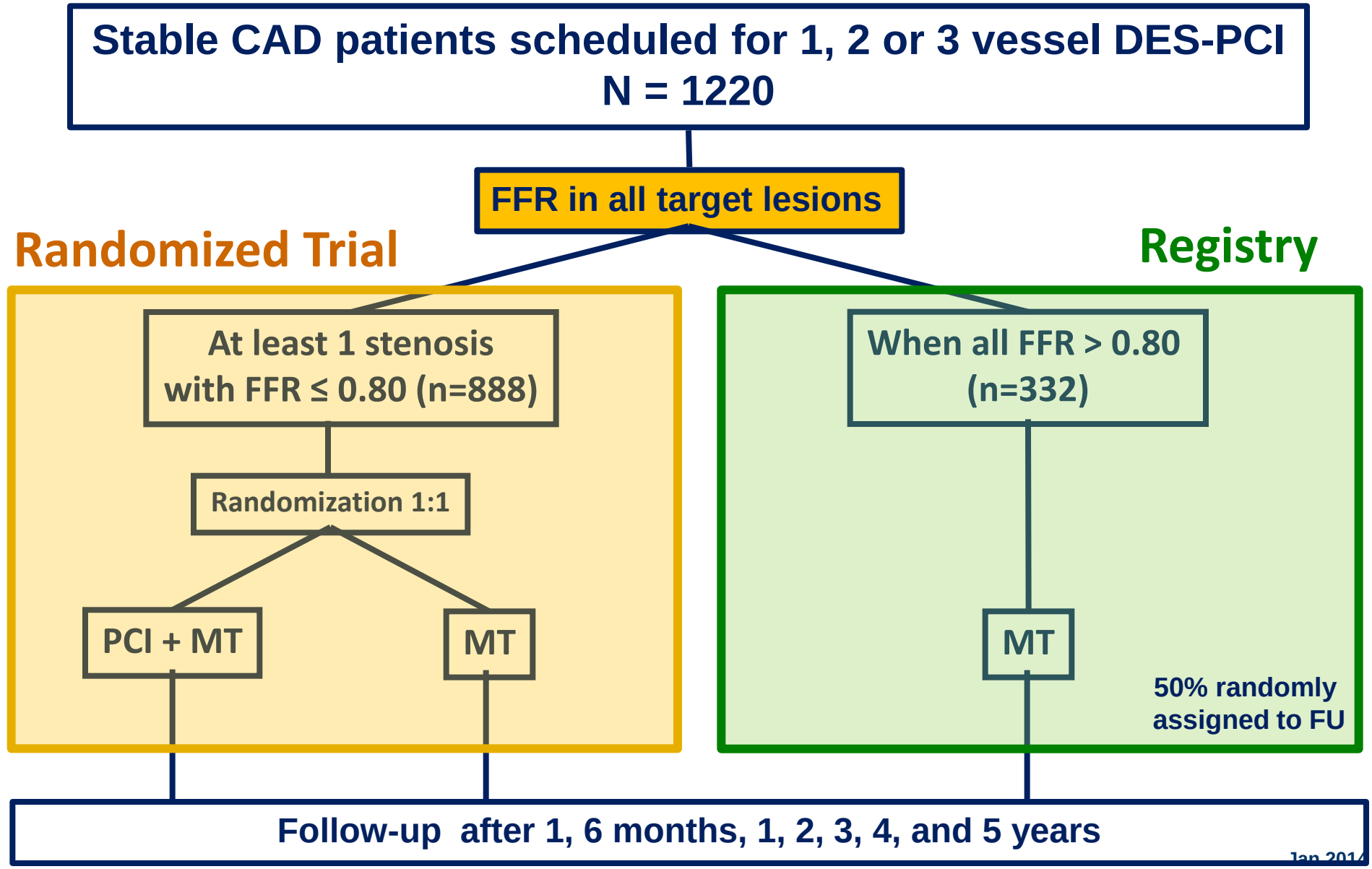
FAME 2

NEJM 2012;367:991-1001.



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

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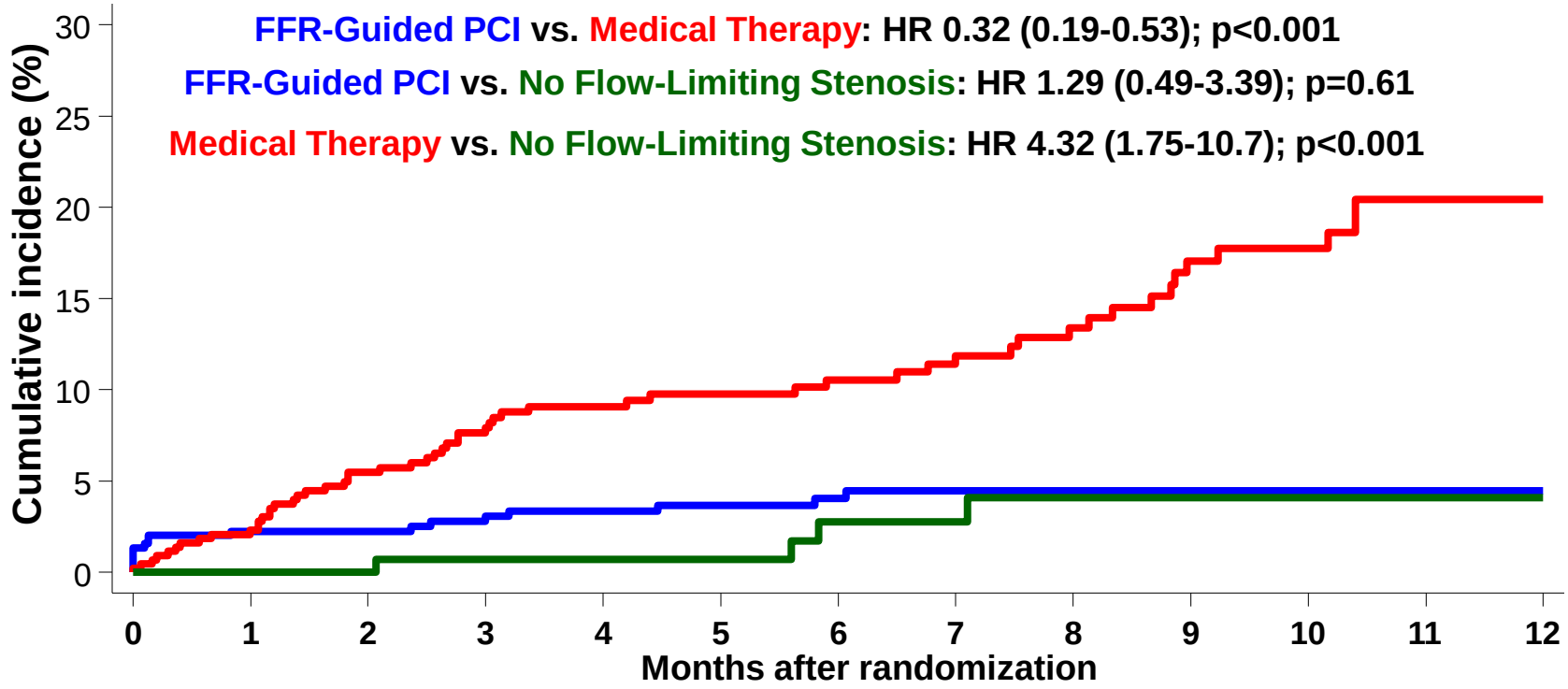
FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD

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.

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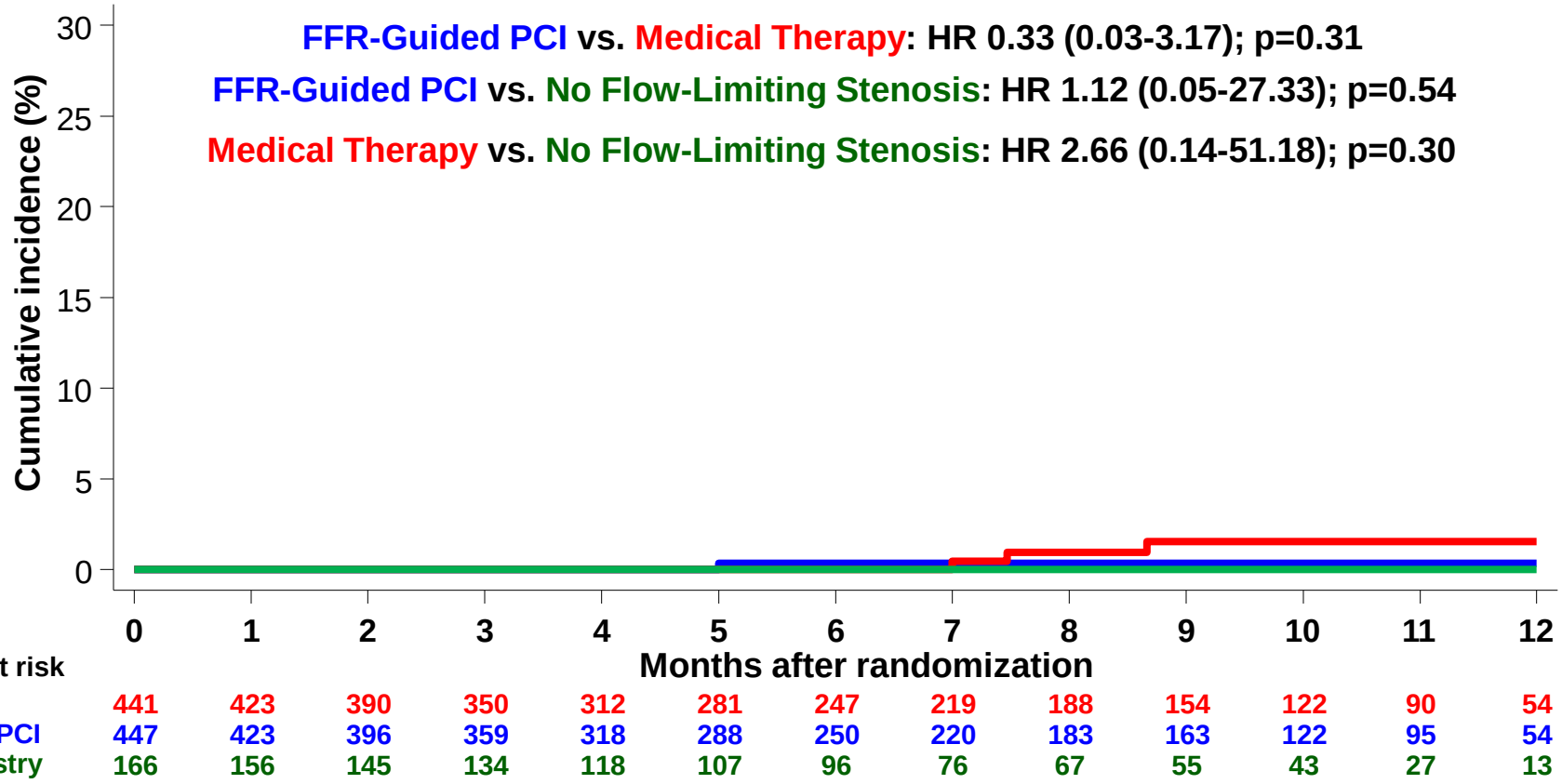
FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD

No Difference in All-Cause Mortality



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

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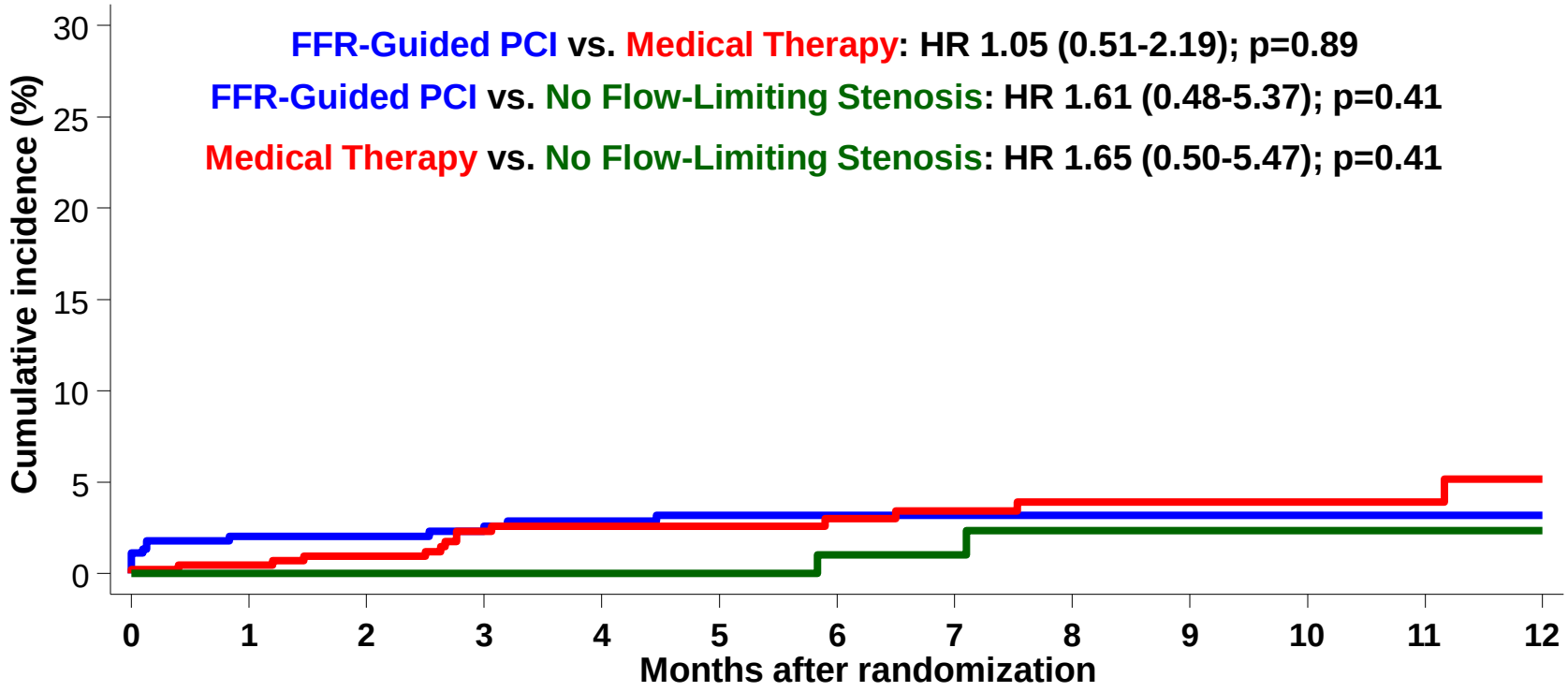
FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD

No Difference in Myocardial Infarction



No. at risk

MED	441	421	386	341	304	273	239	212	182	148	117	85	48
FFR-PCI	447	414	388	352	309	278	244	214	177	157	119	94	54
Registry	166	156	145	134	118	107	95	75	65	53	42	26	13

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

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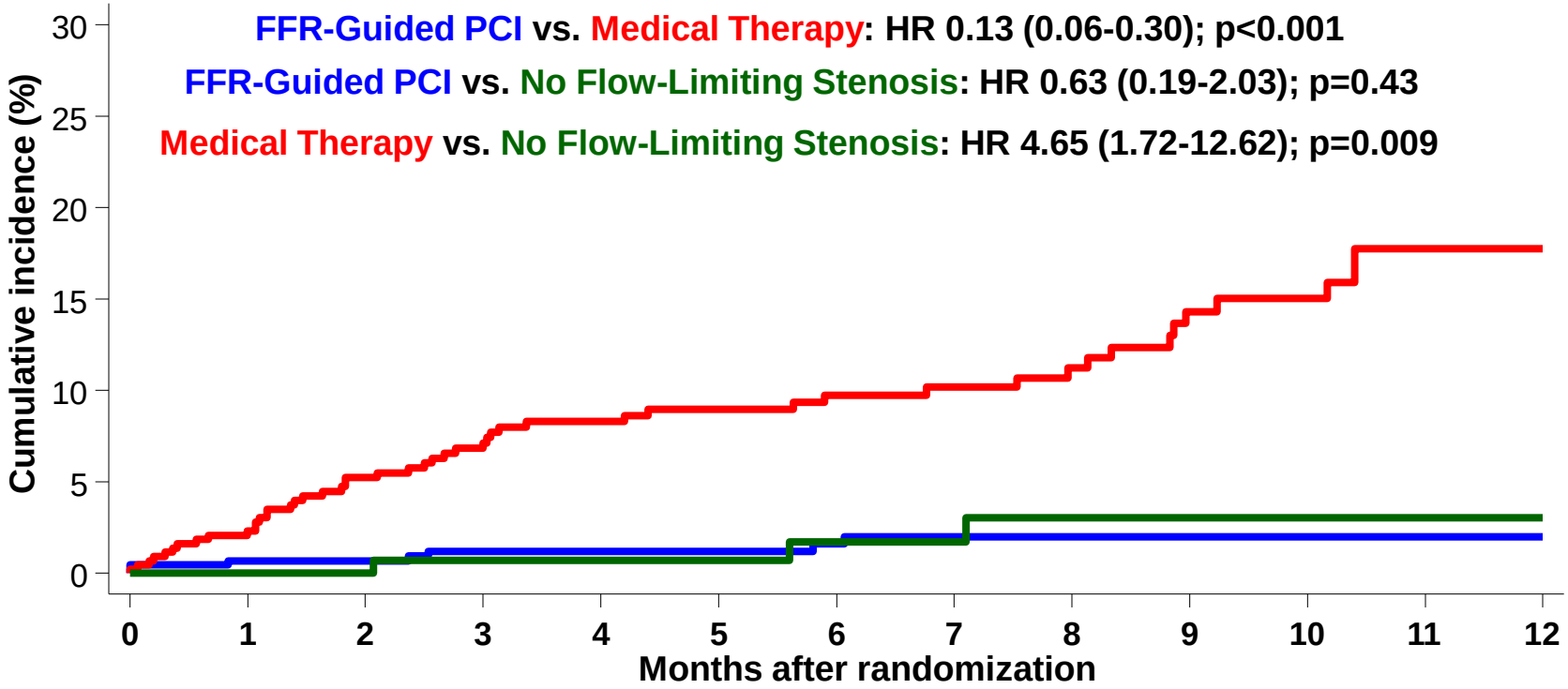
FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD

Primary Endpoint Driven by Urgent Revasc



No. at risk													
MED	441	414	371	325	286	256	223	195	164	129	101	71	38
FFR-PCI	447	421	395	356	315	285	248	217	180	160	119	93	53
Registry	166	156	145	133	117	106	94	75	65	53	42	26	13

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

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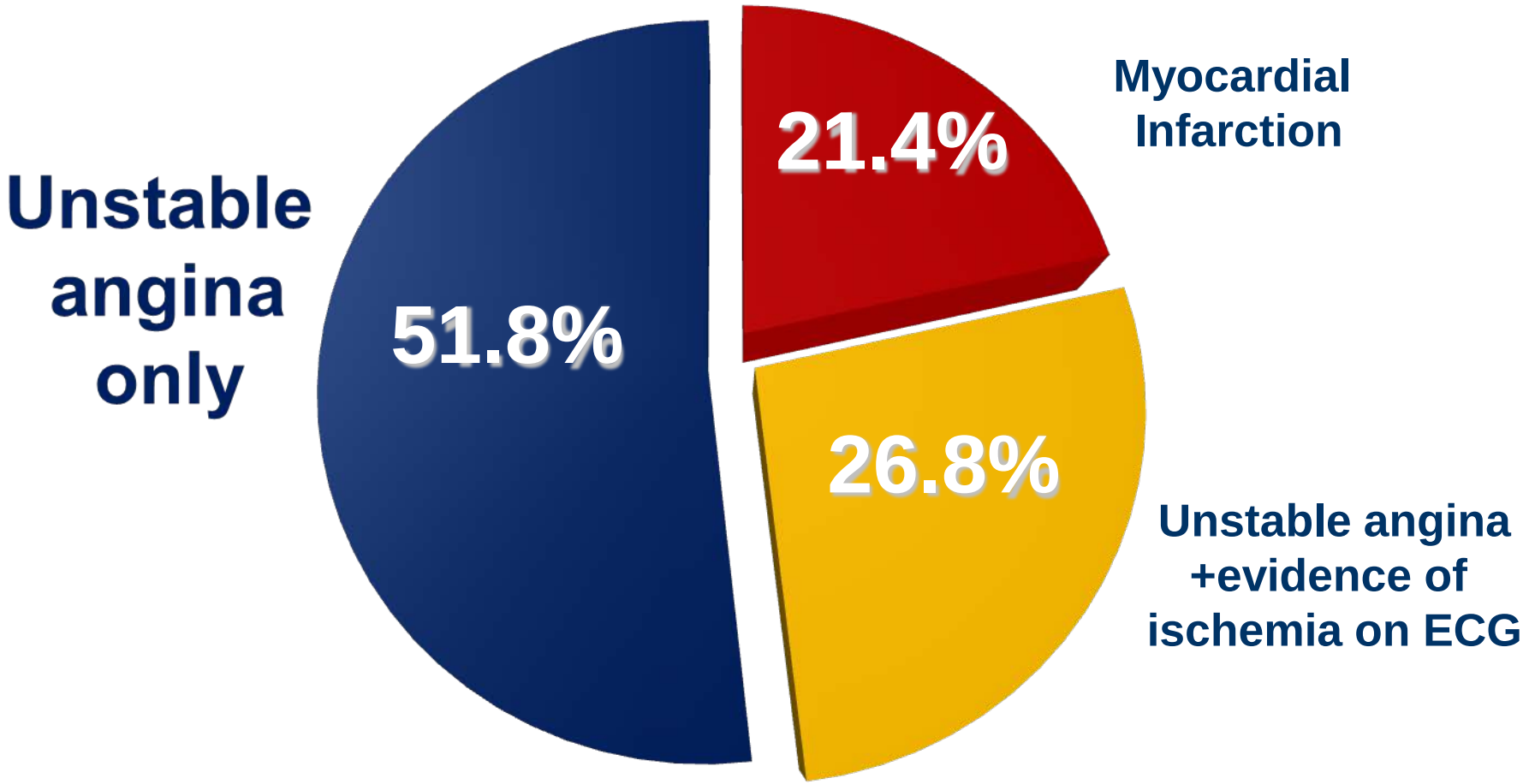
FAME 2: FFR-Guided PCI vs. Medical Therapy in Stable CAD

Reasons for Urgent Revascularization



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

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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

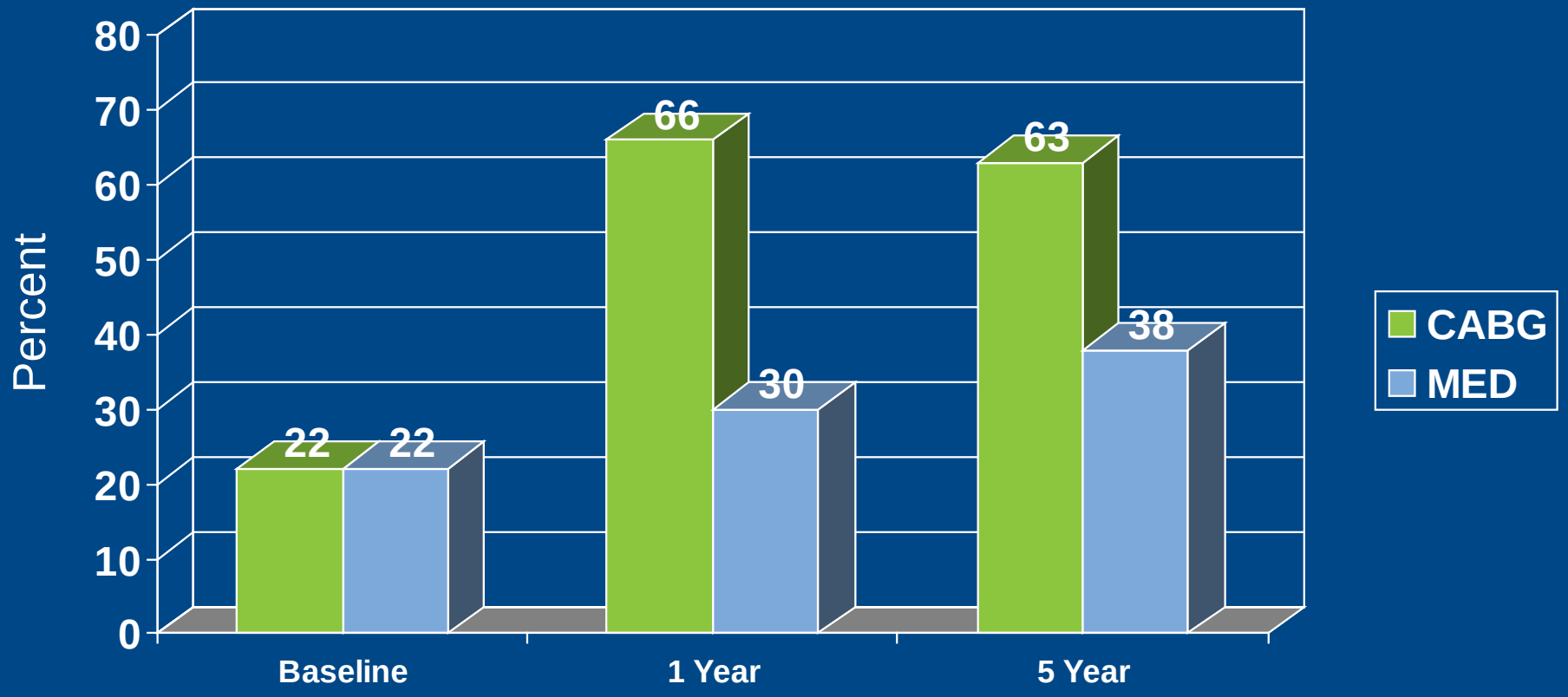
Revascularization to Improve Survival Compared With Medical Therapy

3-vessel disease with or without proximal LAD artery disease*		
CABG	I	B
	IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX score >22) who are good candidates for CABG.	B
PCI	IIb—Of uncertain benefit	B
2-vessel disease with proximal LAD artery disease*		
CABG	I	B
PCI	IIb—Of uncertain benefit	B
2-vessel disease without proximal LAD artery disease*		
CABG	IIa—With extensive ischemia	B
	IIb—Of uncertain benefit without extensive ischemia	C
PCI	IIb—Of uncertain benefit	B
1-vessel proximal LAD artery disease		
CABG	IIa—With LIMA for long-term benefit	B
PCI	IIb—Of uncertain benefit	B
1-vessel disease without proximal LAD artery involvement		
CABG	III: Harm	B
PCI	III: Harm	B
LV dysfunction		
CABG	IIa—EF 35% to 50%	B
CABG	IIb—EF <35% without significant left main CAD	B
PCI	Insufficient data	
Survivors of sudden cardiac death with presumed ischemia-mediated VT		
CABG	I	B
PCI	I	C
No anatomic or physiologic criteria for revascularization		
CABG	III: Harm	B
PCI	III: Harm	B

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)



Rogers et al. *Circulation* 1990;82:1647-1658.

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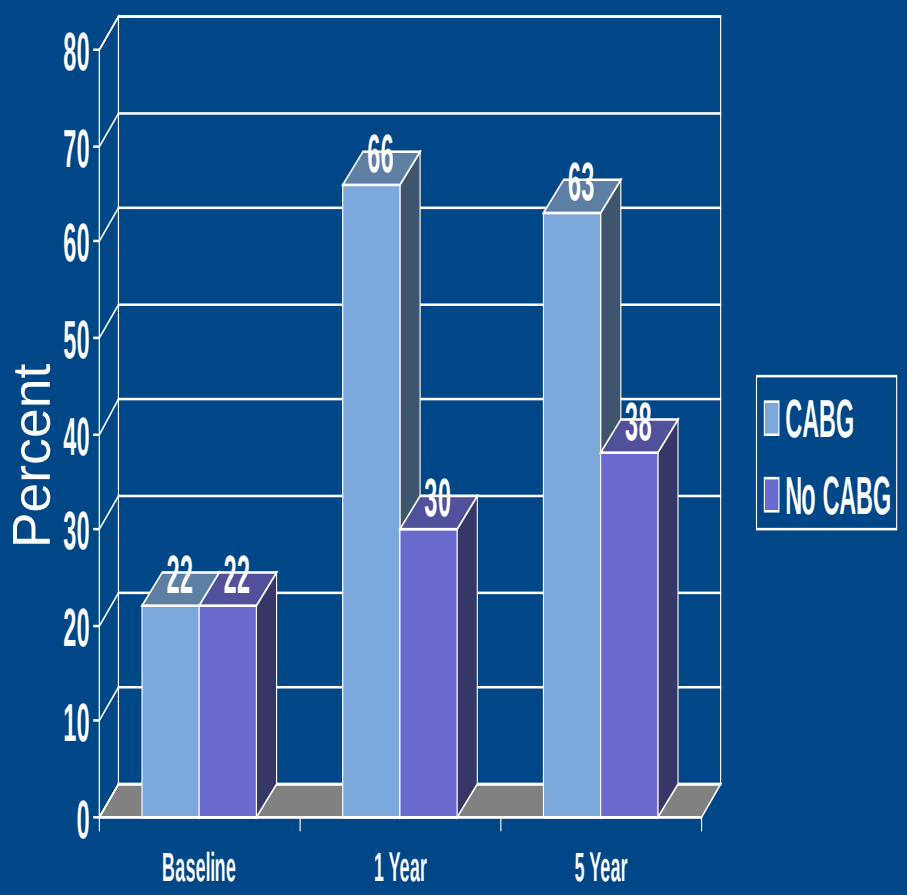
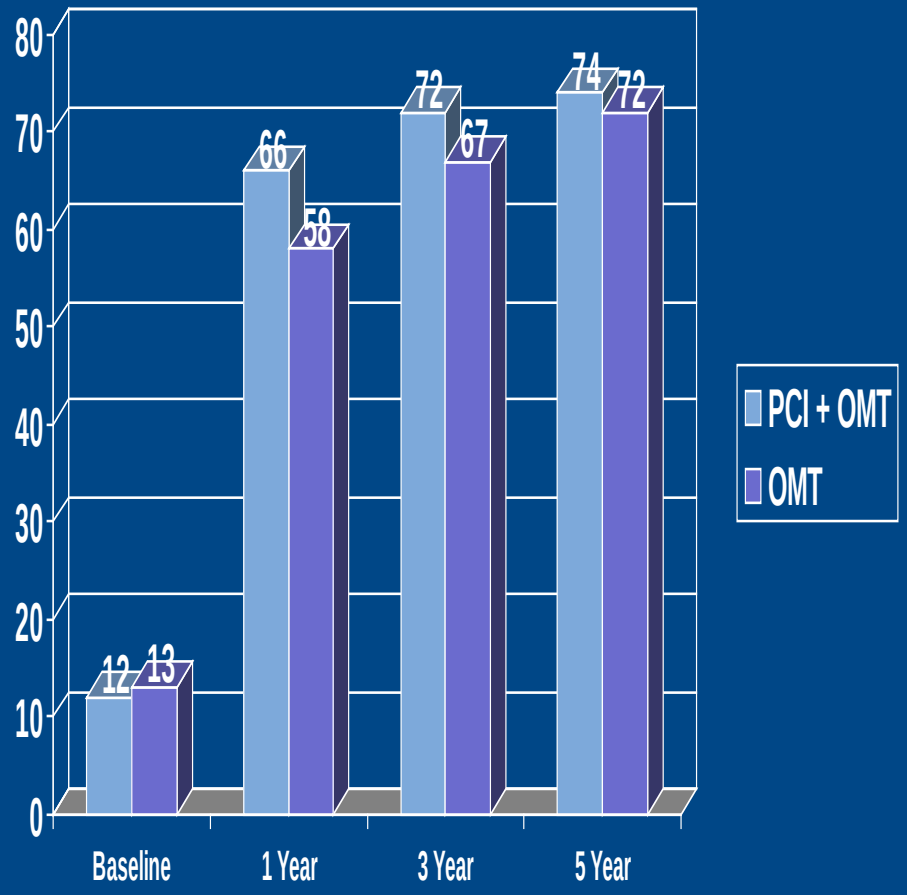
Freedom from Angina: CASS vs. COURAGE

Freedom from angina rates have markedly increased with "optimal" medical therapy





Rogers et al. *Circulation* 1990;82:1647-1658.
Boden et al. *N Engl J Med* 2007; 356: 1503-1516

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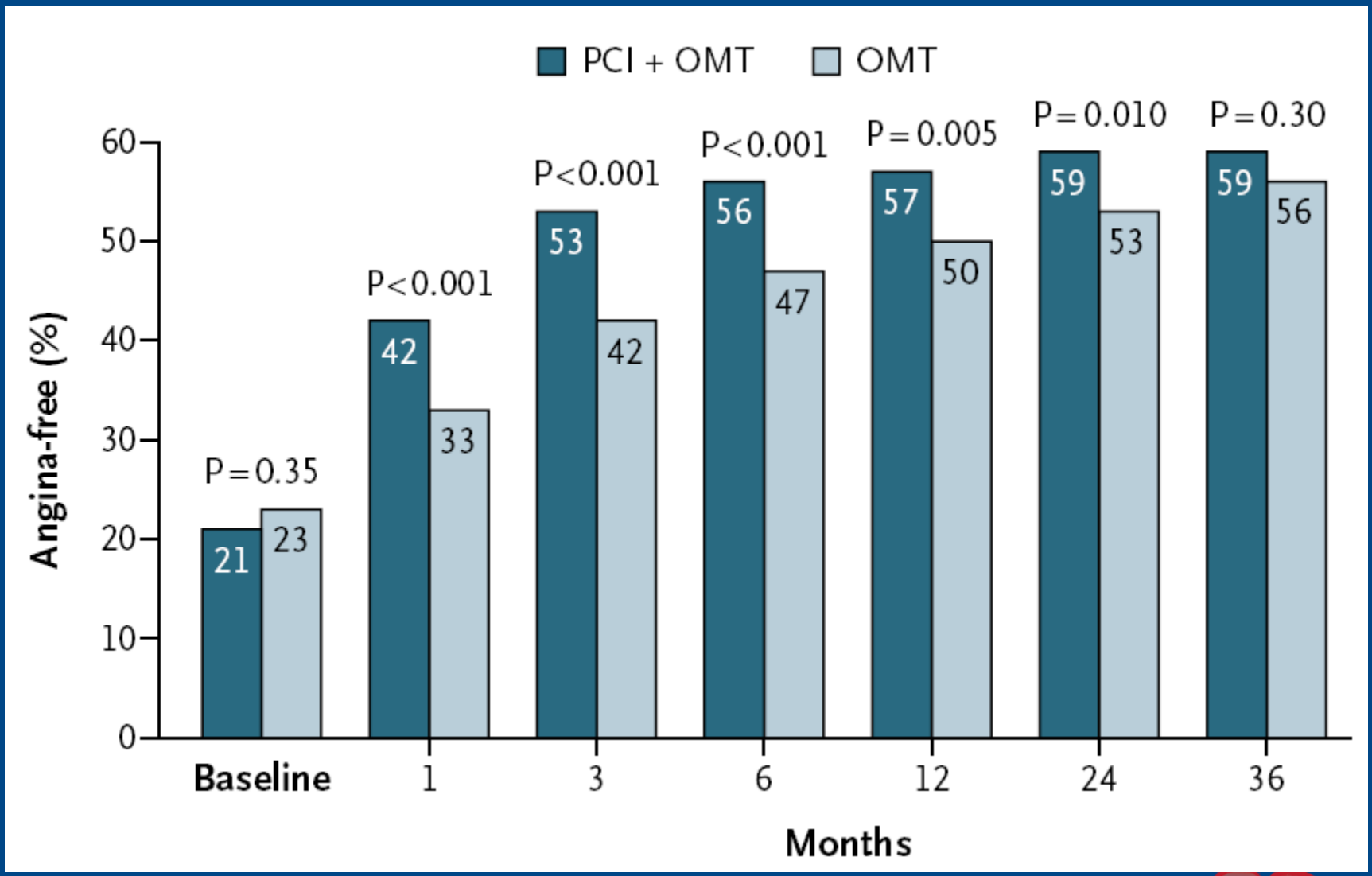
Freedom from Angina During COURAGE*



*by SAQ Angina Frequency Score

Weintraub et al. NEJM 2008;359:677- 87.

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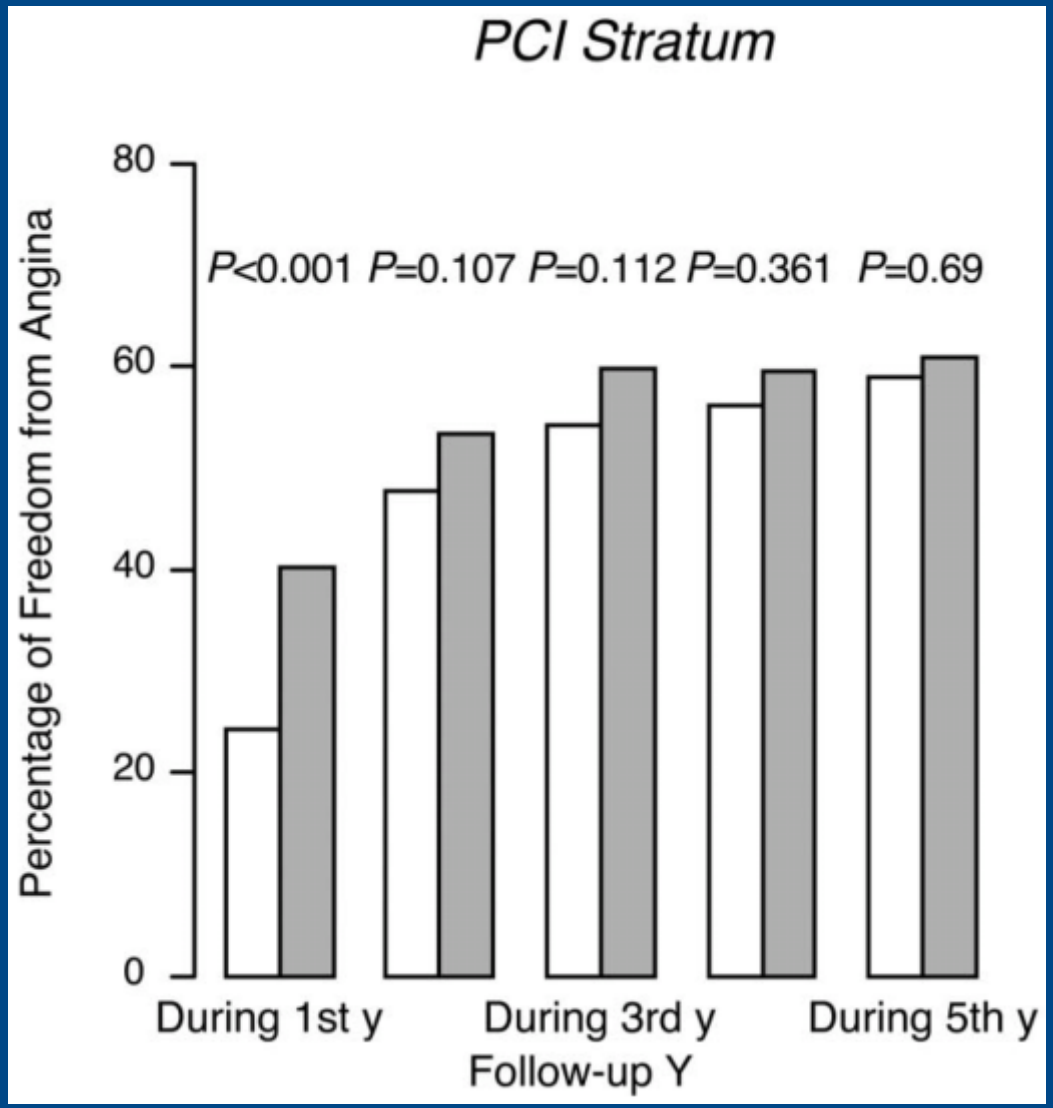
Freedom from Angina in BARI 2D: PCI



Dagenais et al. Circulation 2011;123:1492-1500

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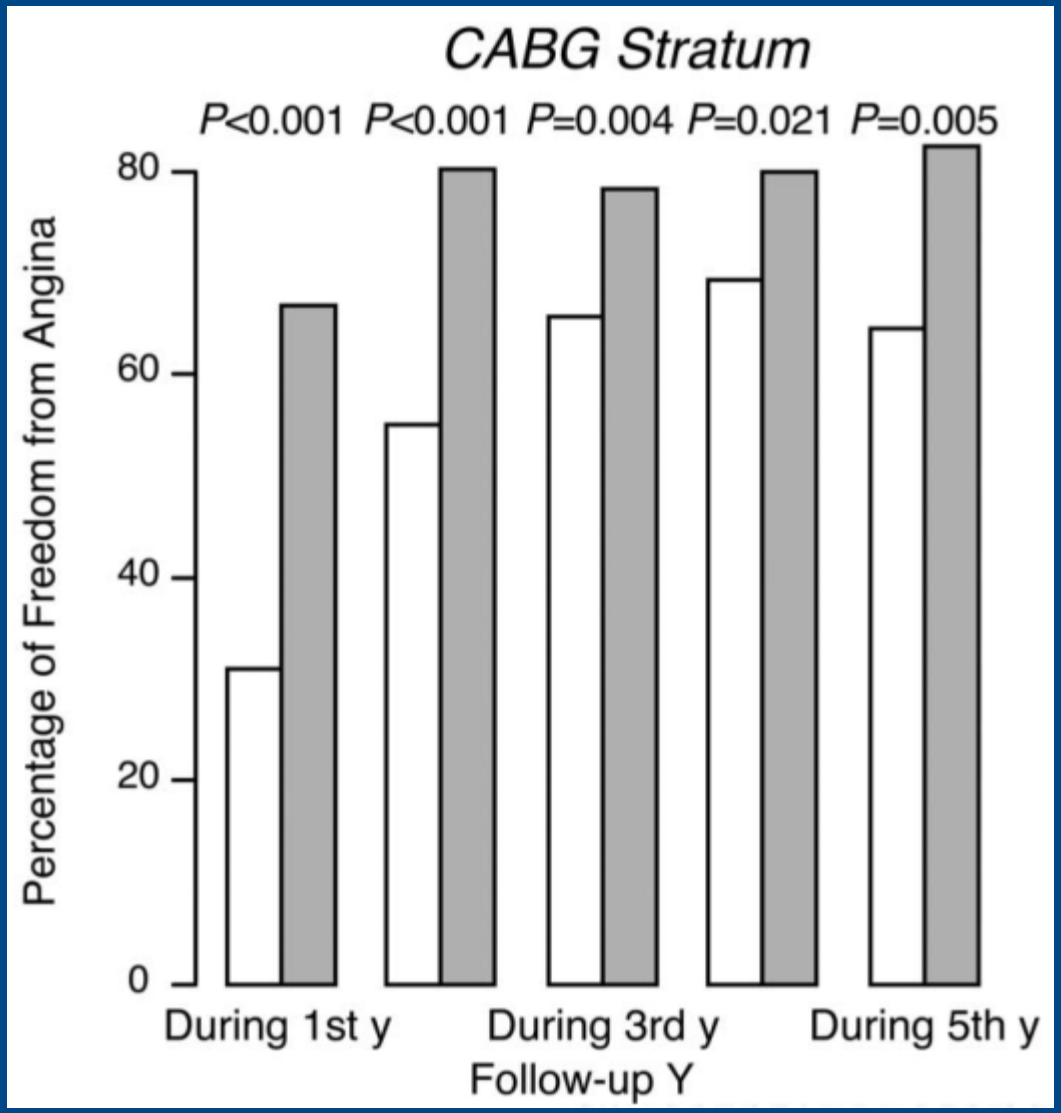
Freedom from Angina in BARI 2D: CABG



Dagenais et al. Circulation 2011;123:1492-1500

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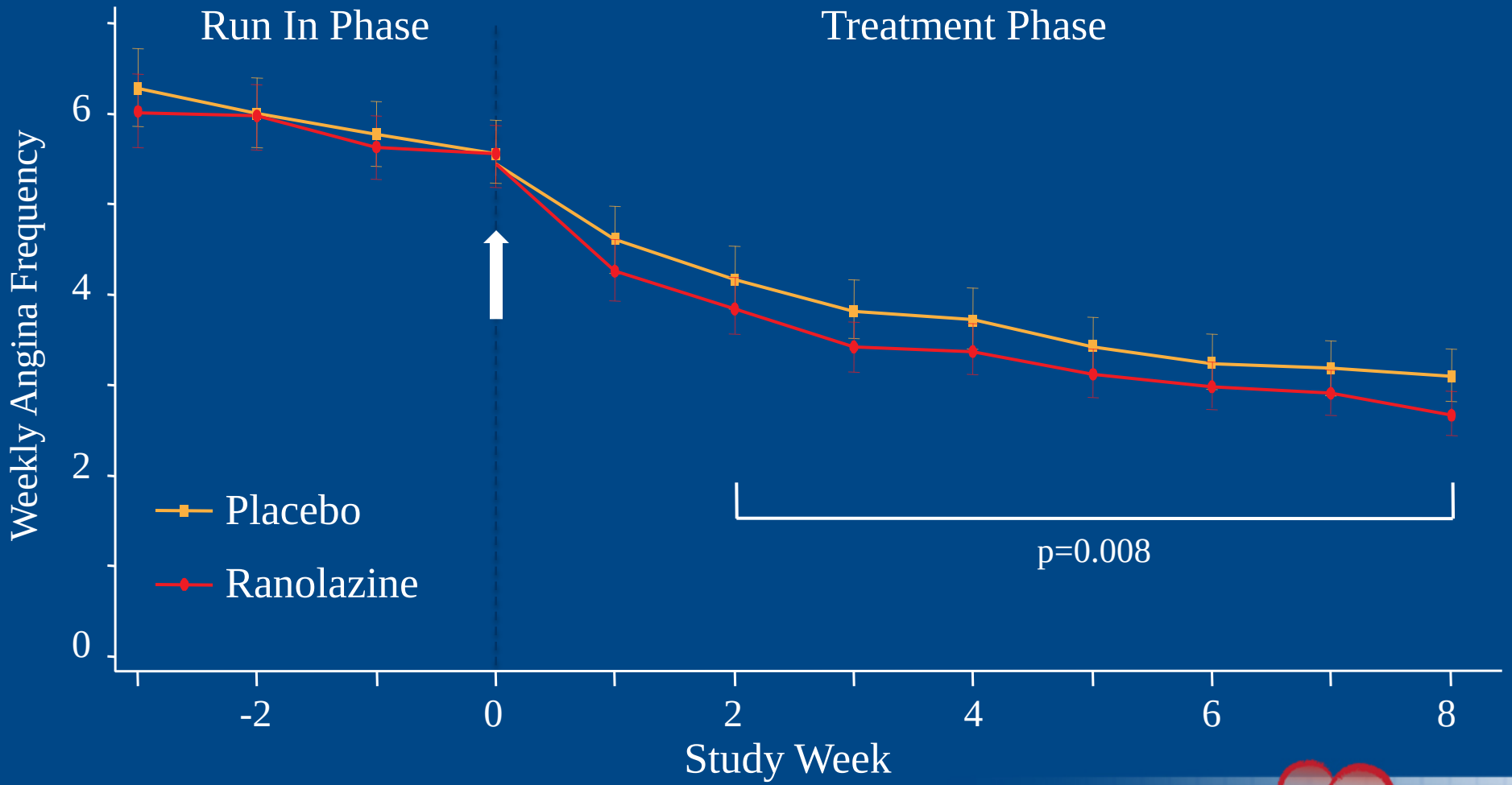
The Challenge with Angina Frequency as an Endpoint: Placebo Effect

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



Kosiborod et al. JACC2013

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Revascularization to Improve Symptoms

- ≥1 significant stenosis amenable to revascularization and unacceptable angina despite guideline-directed medical therapy

2011 ACCF/AHA/SCAI PCI Guidelines

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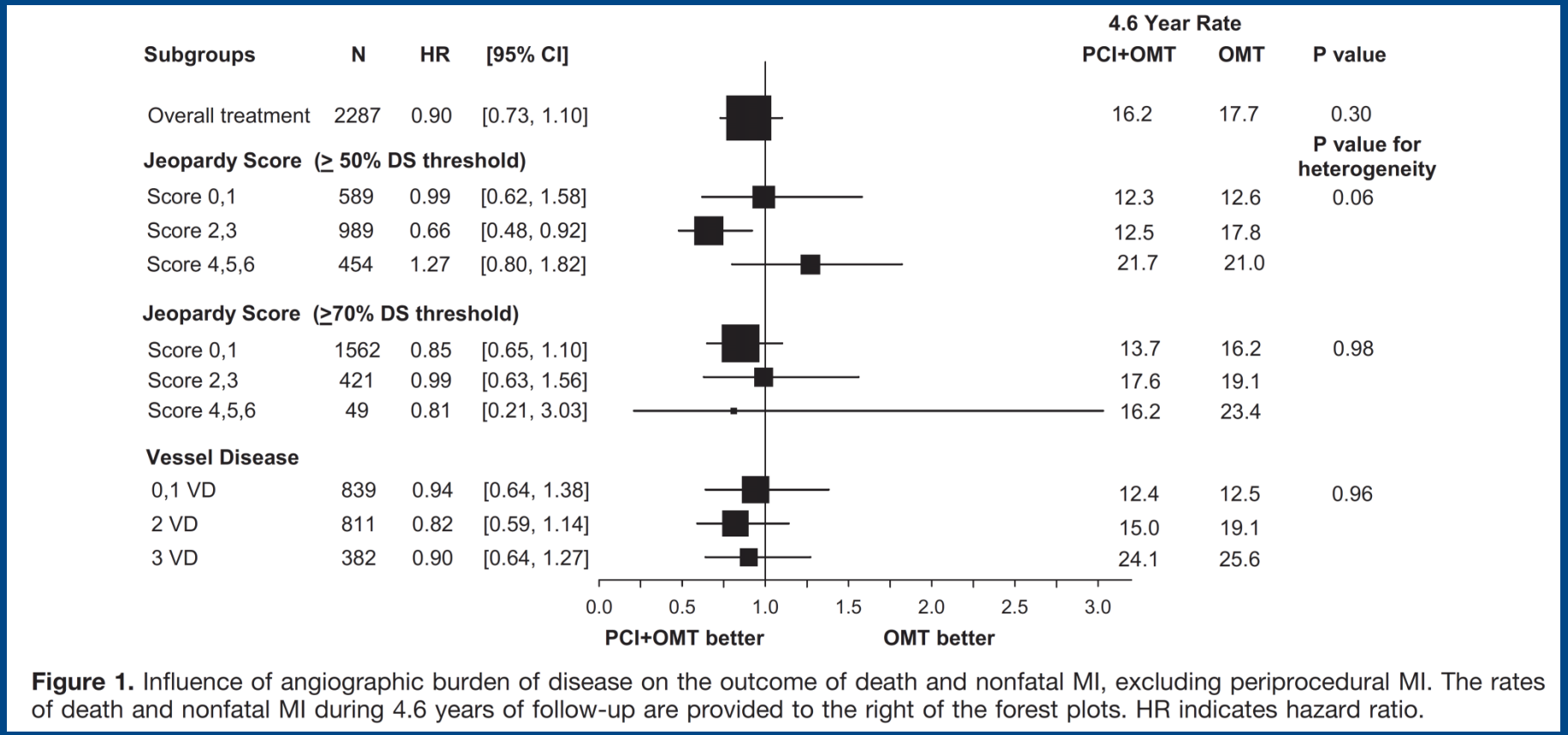
Design Limitations of Prior Strategy Trials

- 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



Subgroups	N	HR	[95% CI]	4.6 Year Rate PCI+OMT	4.6 Year Rate OMT	P value
Overall treatment	2287	0.90	[0.73, 1.10]	16.2	17.7	0.30
Jeopardy Score (≥ 50% DS threshold)						**P value for heterogeneity**
Score 0,1	589	0.99	[0.62, 1.58]	12.3	12.6	0.06
Score 2,3	989	0.66	[0.48, 0.92]	12.5	17.8	
Score 4,5,6	454	1.27	[0.80, 1.82]	21.7	21.0	
Jeopardy Score (≥70% DS threshold)						
Score 0,1	1562	0.85	[0.65, 1.10]	13.7	16.2	0.98
Score 2,3	421	0.99	[0.63, 1.56]	17.6	19.1	
Score 4,5,6	49	0.81	[0.21, 3.03]	16.2	23.4	
Vessel Disease						
0,1 VD	839	0.94	[0.64, 1.38]	12.4	12.5	0.96
2 VD	811	0.82	[0.59, 1.14]	15.0	19.1	
3 VD	382	0.90	[0.64, 1.27]	24.1	25.6	

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.

Mancini et al. *Circ Cardiovasc Qual Outcomes* 2009;2;320-327.

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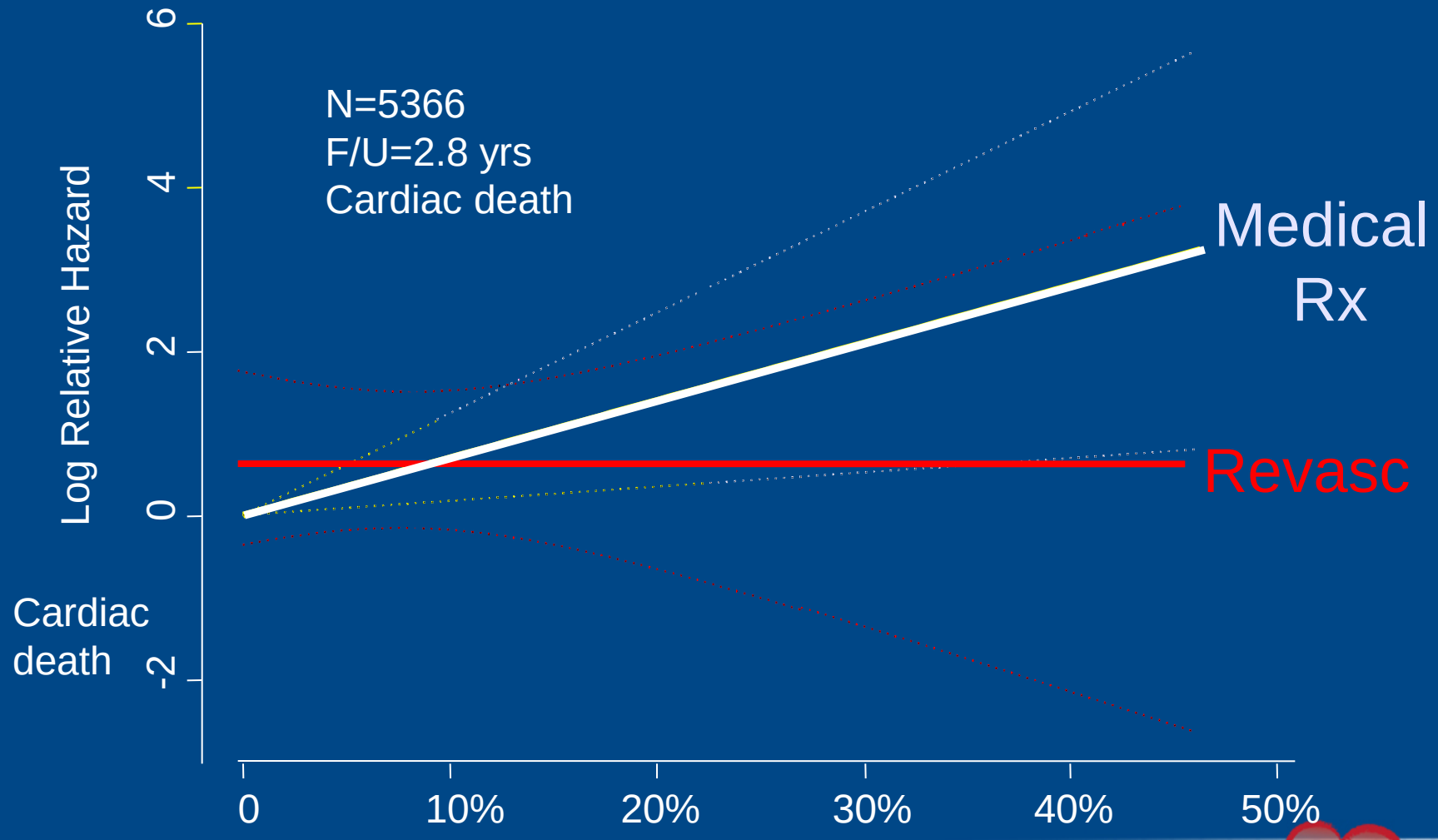
Proximal LAD and Risk of Death or MI

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 a. *Circulation.* 2010; 122: A10145

Observational study: Revascularization was associated with lower risk of cardiac death only in those with >10% ischemia on perfusion imaging



Hachamovitch et al. JNC 2006;13:768-78.

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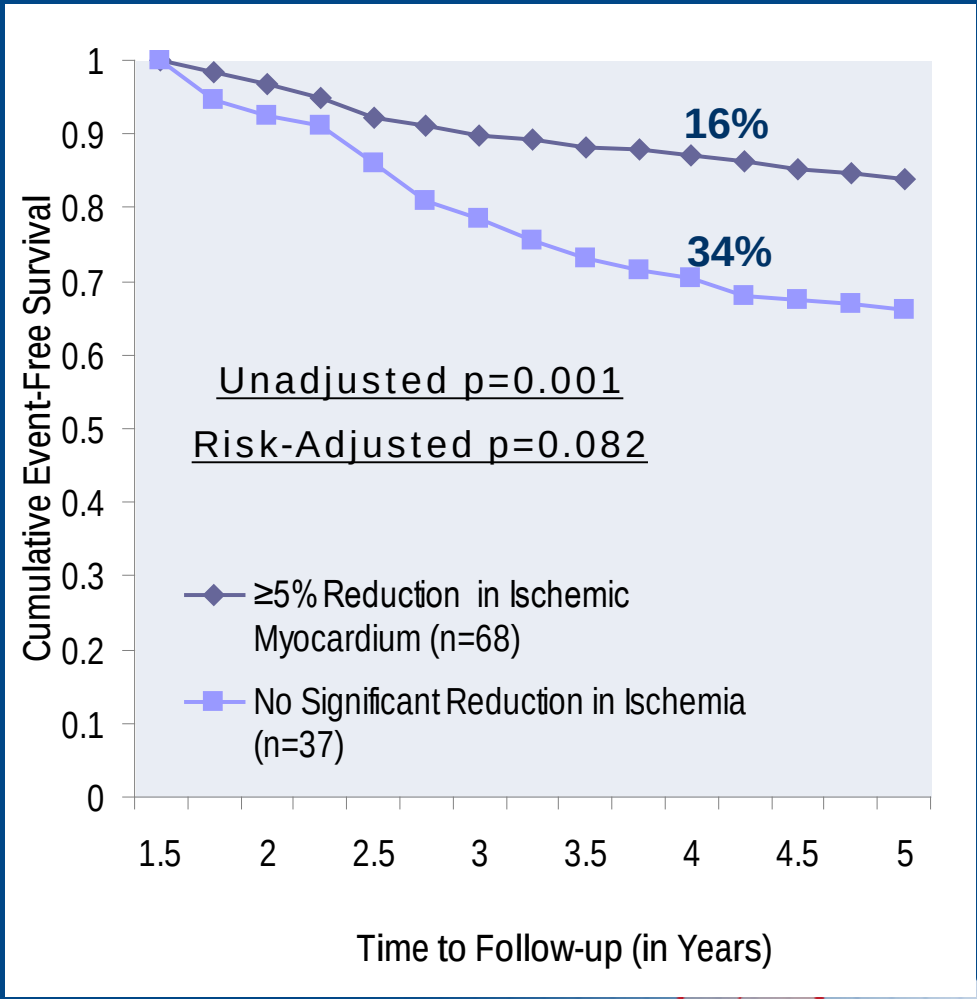
COURAGE Serial Nuclear Substudy: Outcomes in 105 Patients with Moderate-to-Severe Baseline Ischemia Who Returned for 2nd Study @ 6-18 months

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?



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

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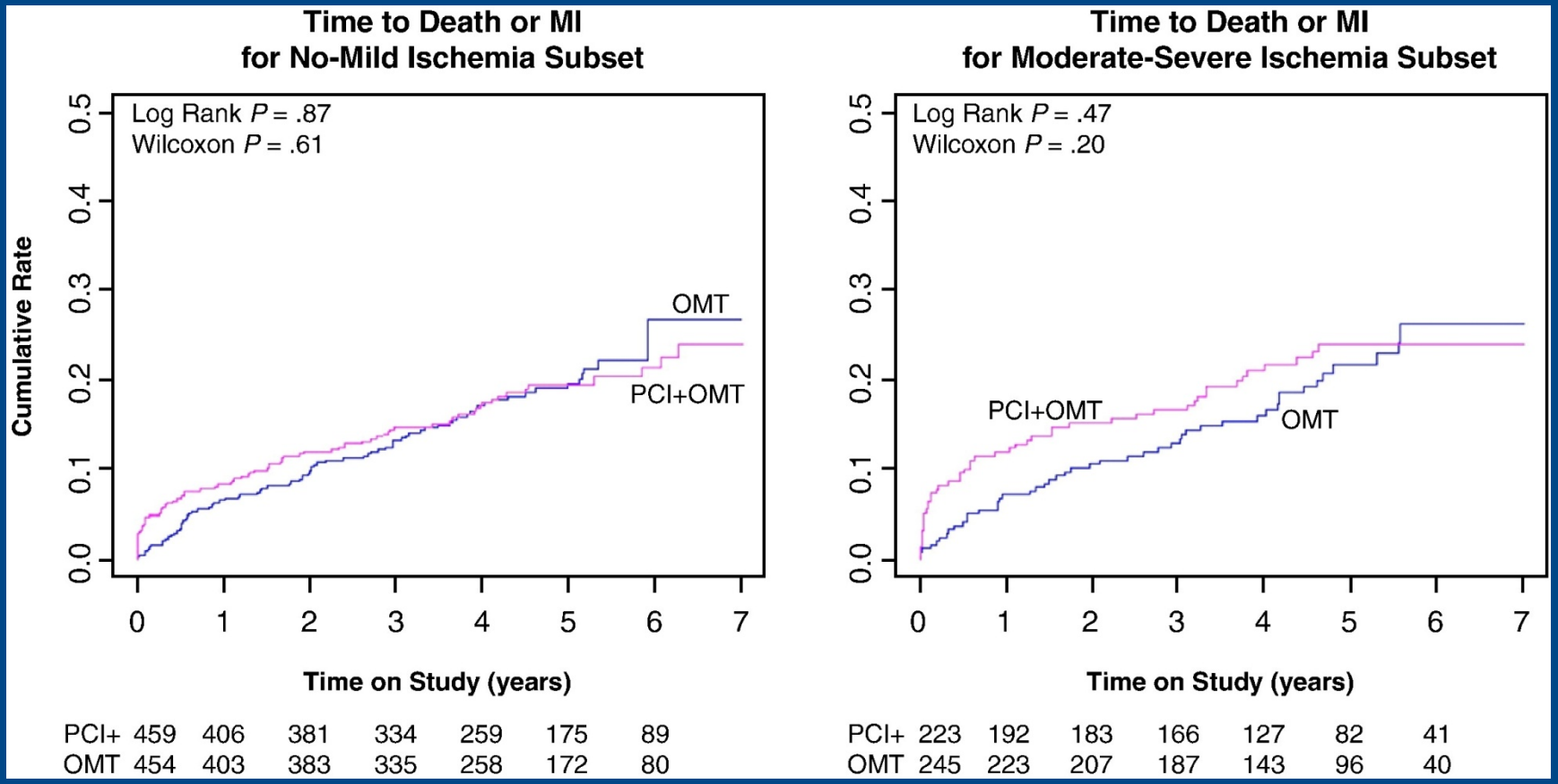
PCI did not Reduce Events

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

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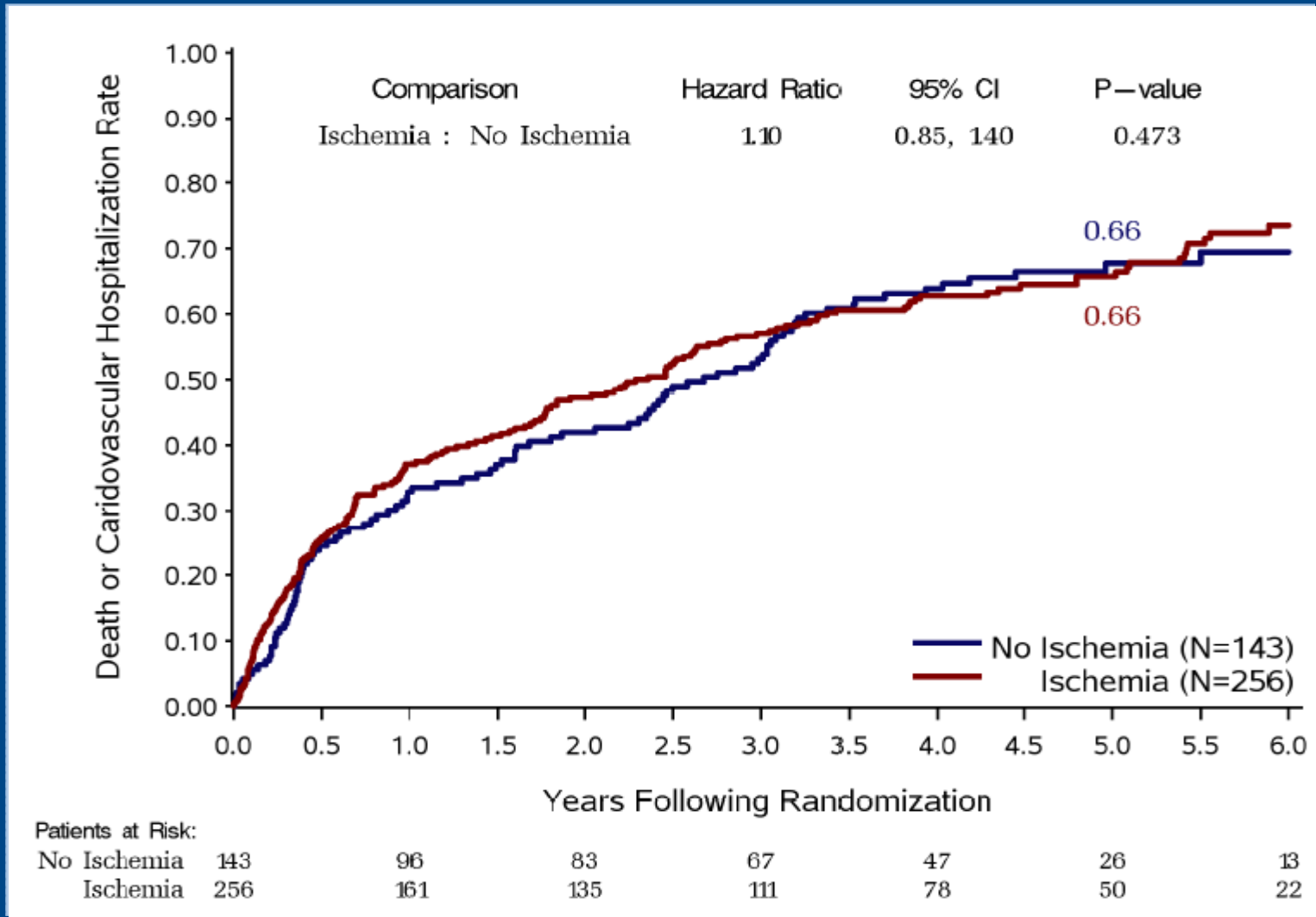
Survival in Ischemic vs. Non-Ischemic Patients in STICH

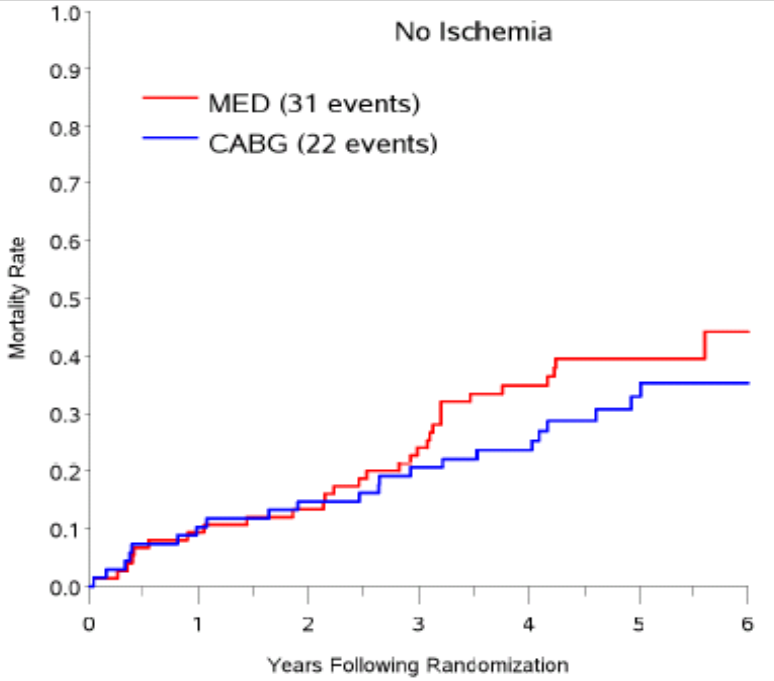
There was no difference between patients with vs. those without ischemia in all-cause mortality or other endpoints

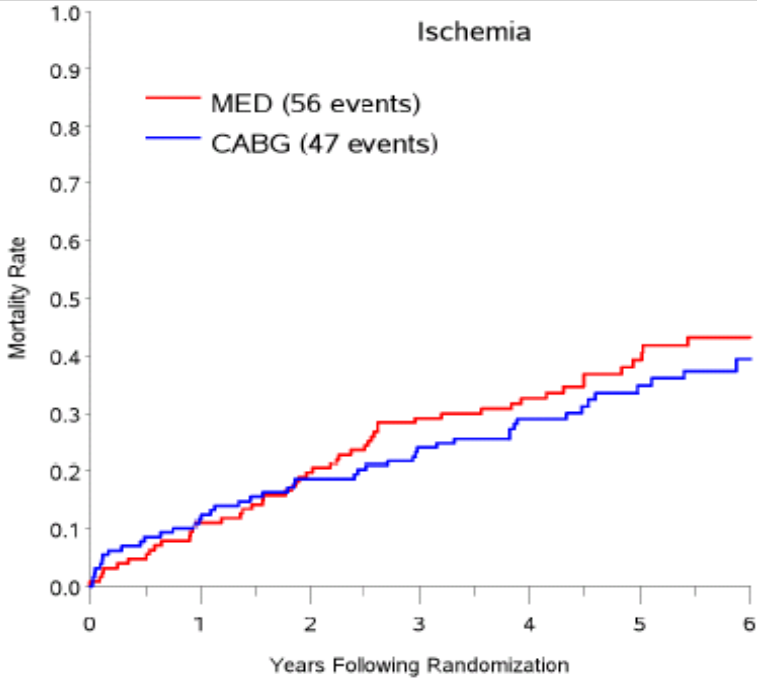


Panza et al. *JACC* 2013

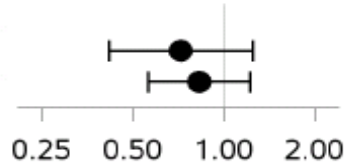
STICH: Survival by Presence of Ischemia and Treatment Group

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





Sub-group	N	Events	Hazard Ratio	95% CI	5 Year Rates MED Group	5 Year Rates CABG Group
No Ischemia	143	53	0.72	0.42, 1.25	39.4 %	32.9 %
Ischemia	256	103	0.83	0.56, 1.23	39.2 %	34.8 %



Interaction with Treatment
P-value = 0.643

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

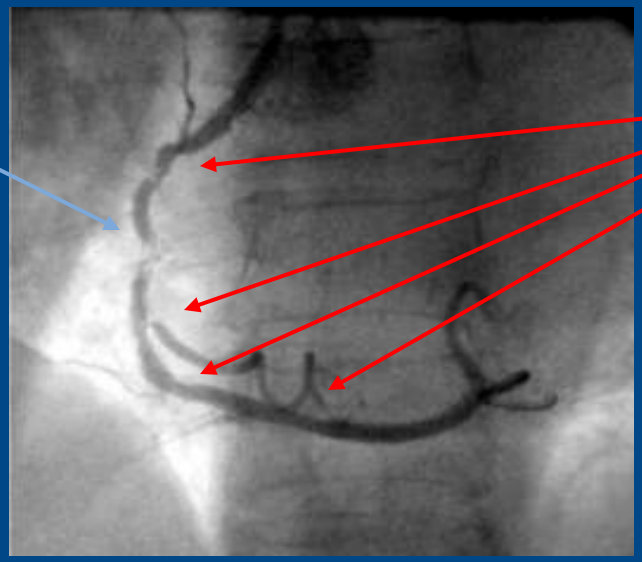
- Dissociation between the angiographic (or physiologic) severity of a stenosis and underlying atheroma and propensity to become a culprit lesion
- Atherosclerosis is a systemic disease, with diffuse coronary artery involvement
- Medical therapy has changed the underlying biology and natural history of atherothrombotic disease

Severe Obstruction (angina, no rupture) vs Mild Obstruction (no angina, likely to rupture)

Severe fibrotic plaque
- **Severe obstruction**
- **No lipid**
- **Fibrosis, Ca^{2+}**

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.

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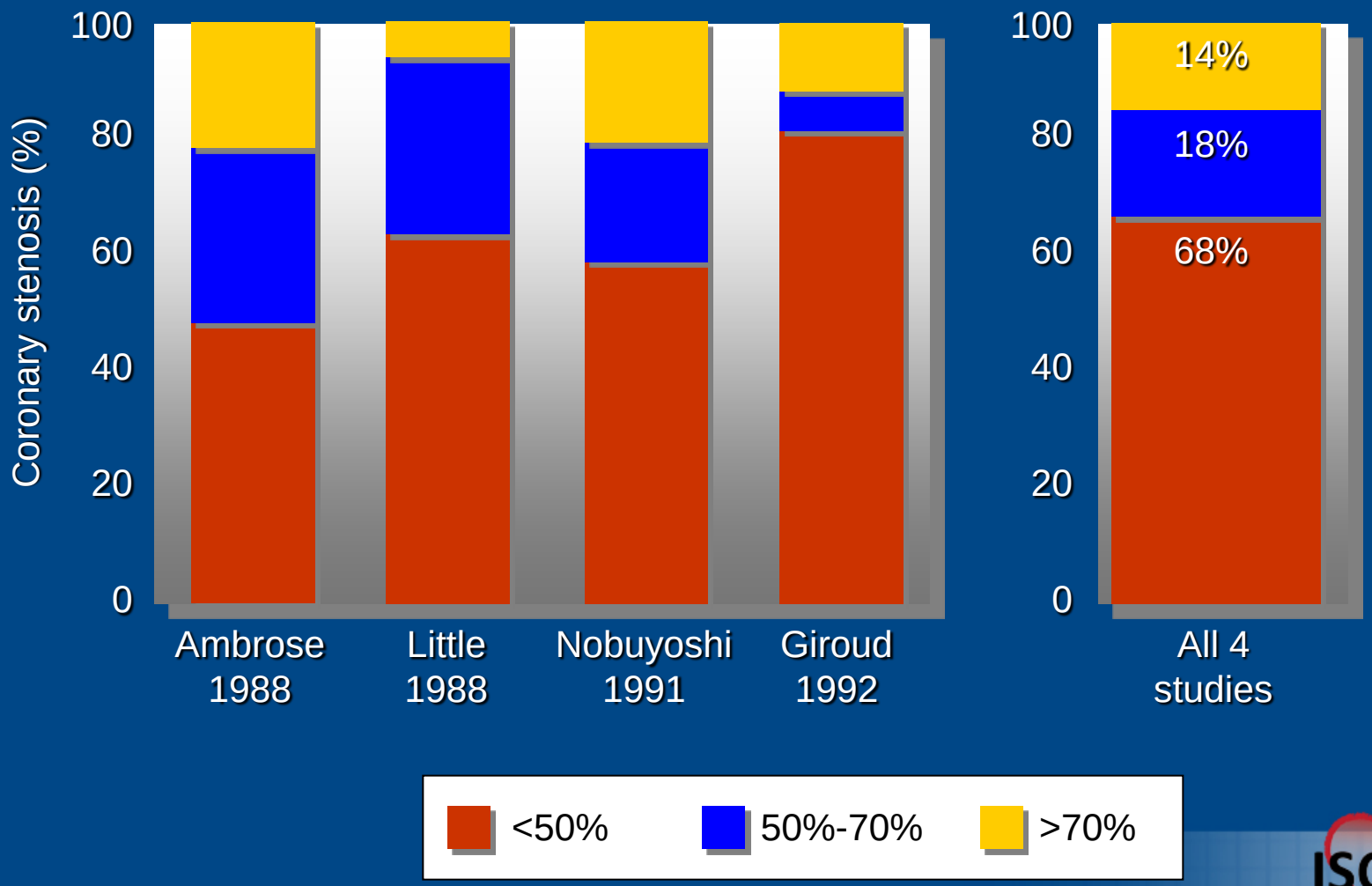
Coronary Stenosis Severity Prior to MI



Falk et al. *Circulation*. 1995;92:657-671.

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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

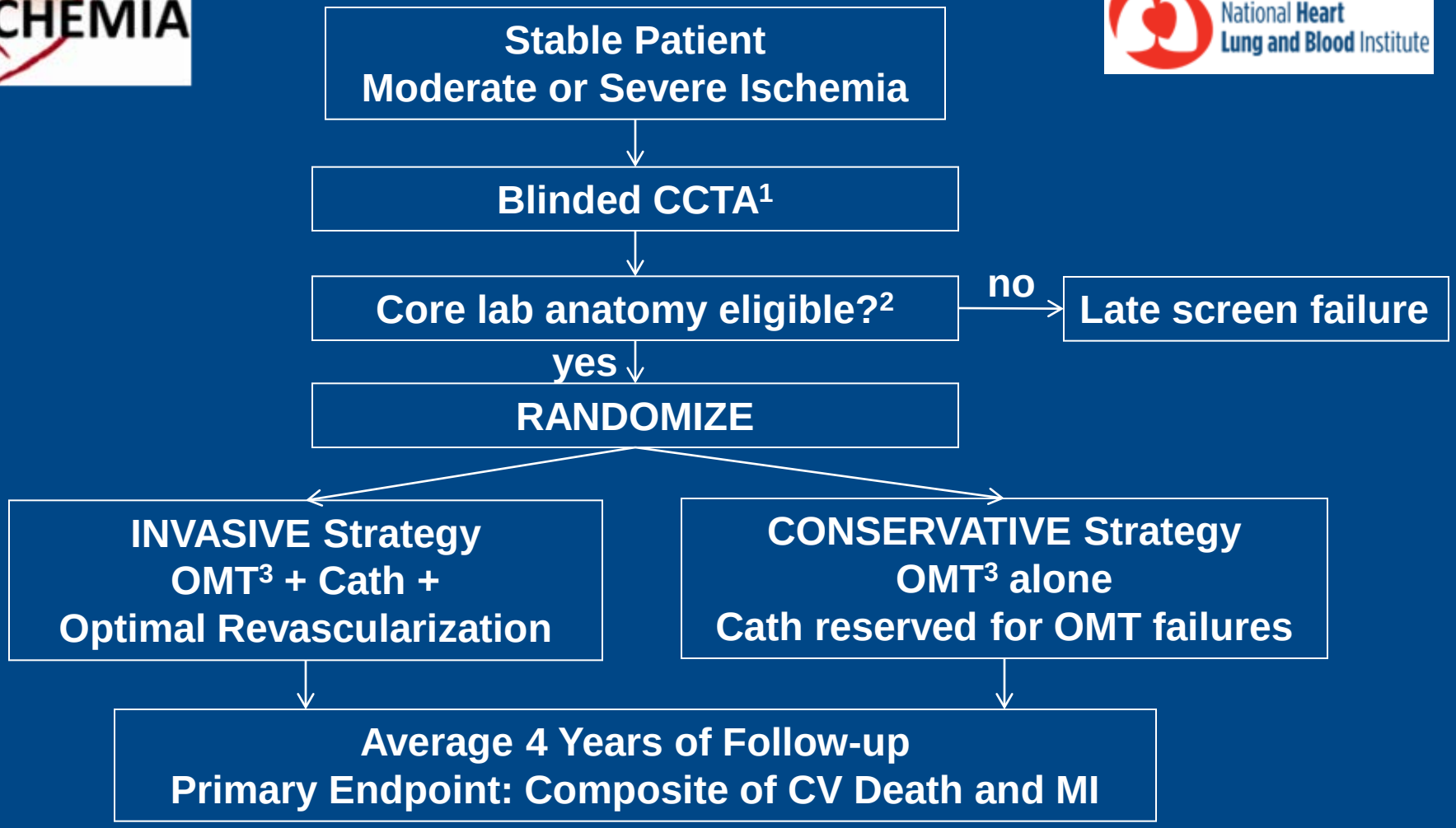
- Patients: stable, at least moderate ischemia (core lab)
- Primary Aim: to determine whether an initial invasive strategy of cath and revascularization (PCI or CABG) + OMT is superior to a conservative strategy of OMT alone, with cath reserved for OMT failure
- Composite Primary Endpoint: CV death or MI
- Major Secondary Endpoint: angina-related QOL
- Sample Size: 8,000
- Follow-up: average ~ 4 years

Ischemia Eligibility Criteria

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

Nuclear Perfusion	Echo/CMR Wall Motion	CMR Perfusion
≥10% myocardium	≥3/16 segments with stress-induced severe hypokinesis or akinesis	≥12.5% myocardium

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



[1]CCTA will be performed in all patients with eGFR ≥60 mL/min
[2]Exclude patients with LM disease or no obstructive disease
[3]OMT=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 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

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

Selected Trial Exclusion Criteria

- Unacceptable level of angina despite maximal medical therapy
- Very dissatisfied with medical management of angina
- LM on CCTA
- ACS within the previous 2 months
- PCI or CABG within the previous 12 months
- eGFR < 30 ml/min

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Exclusion Criteria

- LVEF < 35%
- History of unprotected left main stenosis ≥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
- Prior known coronary anatomy unsuitable for either PCI or CABG
- Unacceptable level of angina despite maximal medical therapy
- Very dissatisfied with medical management of angina
- History of noncompliance with medical therapy
- Acute coronary syndrome within the previous 2 months
- PCI or CABG within the previous 12 months
- Stroke within the previous 6 months or intracranial hemorrhage at any time
- History of ventricular tachycardia requiring therapy for termination, or symptomatic sustained ventricular tachycardia
- NYHA class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months

Exclusion Criteria

- Non-ischemic dilated or hypertrophic cardiomyopathy
- End stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30mL/min
- Severe valvular disease or valvular disease likely to require surgery within 5 years
- 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
- Life expectancy less than 5 years due to non-cardiovascular comorbidity
- Pregnancy (known to be pregnant; to be confirmed before CCTA and/or randomization, if applicable)
- Participants with eGFR 30-59 ml/min who, in the judgment of the participant's physician, are likely to have significant unprotected left main stenosis
- Enrolled in a competing trial that involves a non-approved cardiac drug or device
- Inability to comply with the protocol
- Exceeds the weight or size limit for CCTA or cardiac catheterization at the site

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

Risk Factor	Goal
Smoking	Cessation
Saturated Fat	<7% calories
Physical Activity	≥30 minutes of moderate intensity ≥5 times/week
Medication Adherence	100% adherence
Influenza Vaccination	Recommended to all patients annually

Physiologic Risk Factor Goals

Risk Factor	Goal	
Body Weight by Body Mass Index (kg/m^2)	Initial BMI 25-27.5 >27.5	Weight Loss Goal BMI <25 10% relative weight loss
Blood Pressure	<140/90 mmHg	
LDL-C (primary goal)	<70 mg/dL (1.8 mmol/L)	
Non-HDL-C (secondary goal)	<100 mg/dL (2.6 mmol/L) if TG ≥200 (2.3mmol/L)	
TC:HDL ratio (secondary goal)	<4.0	
Diabetes	<8%.[1] <7% may be appropriate for some.[2]	

[1]For participants with Hx of severe hypoglycemia, extensive comorbidities, and those with long-standing diabetes in whom a goal of <7% is difficult to attain.
[2]For participants with a short duration of diabetes if this can be achieved without significant hypoglycemia or other adverse effects of treatment.

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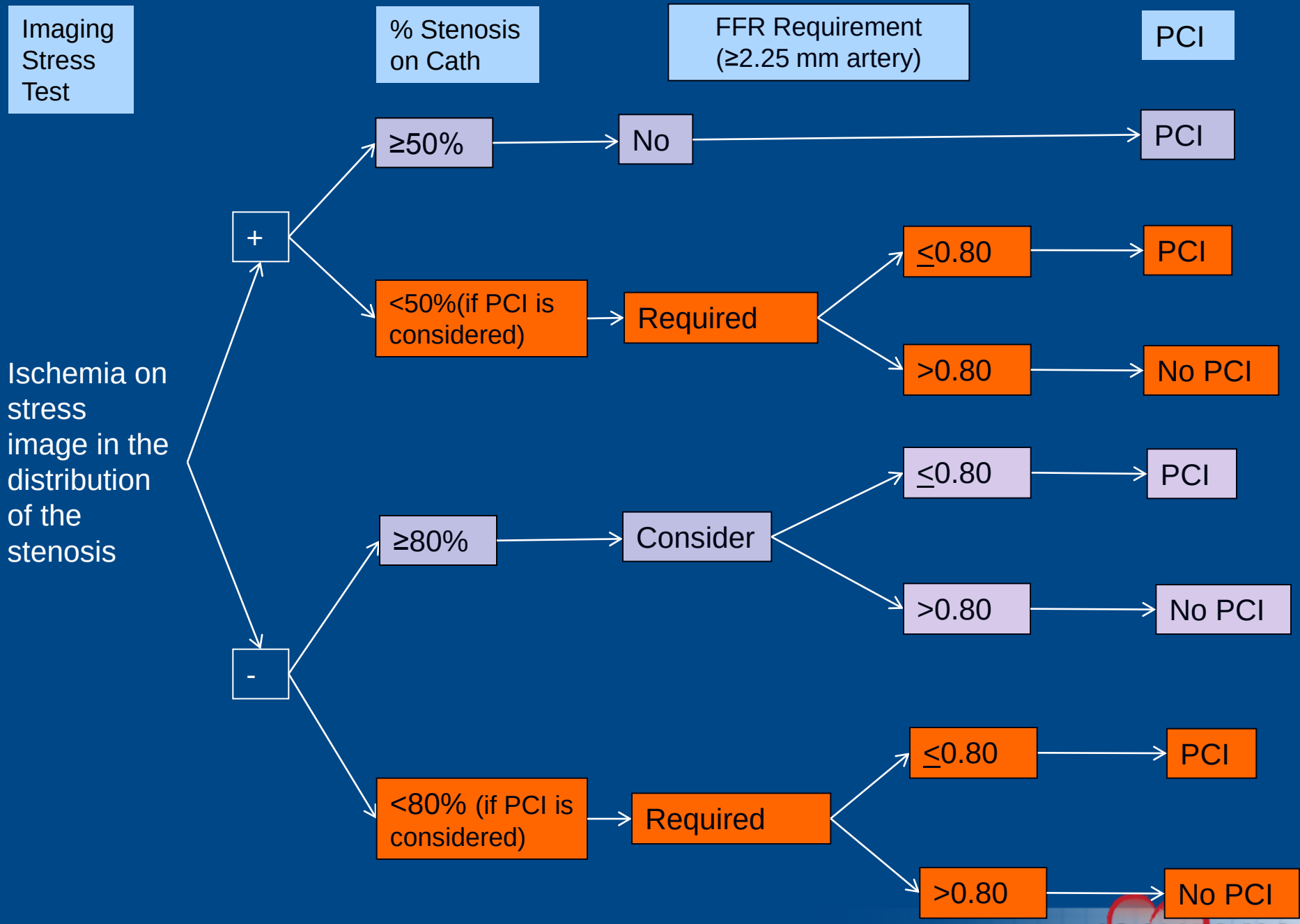
Invasive Strategy

- 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

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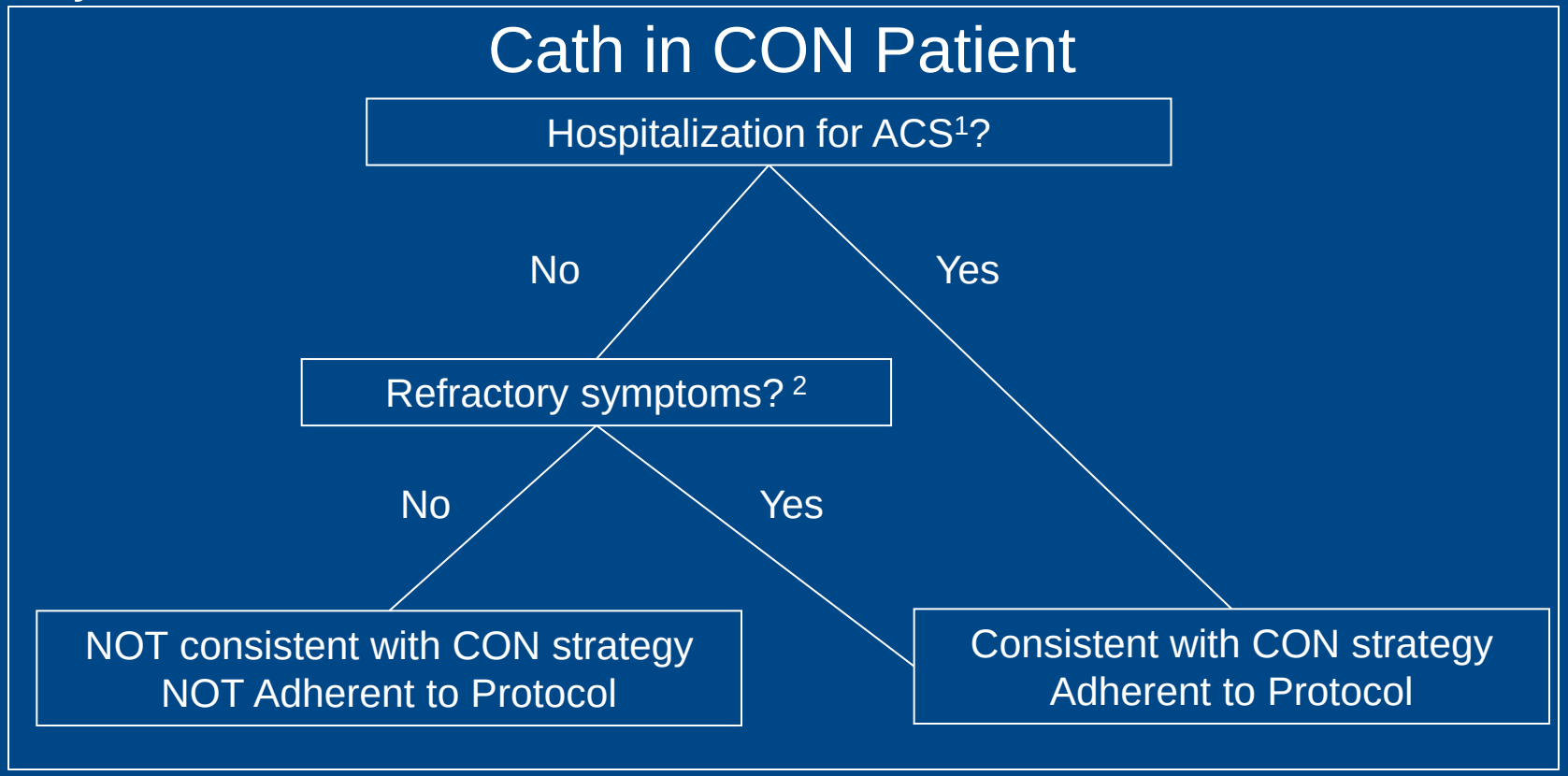
Cath in Patients Randomized to CON Strategy

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



[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

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"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

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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

N = 8000

CON 4-yr	Estimated Power (%)		
Event Rate	**Δ = 13%**	**Δ = 15%**	**Δ = 17%**
15%	67	80	89
20%	82	92	97
25%	92	97	99
30%	97	99	≥99

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

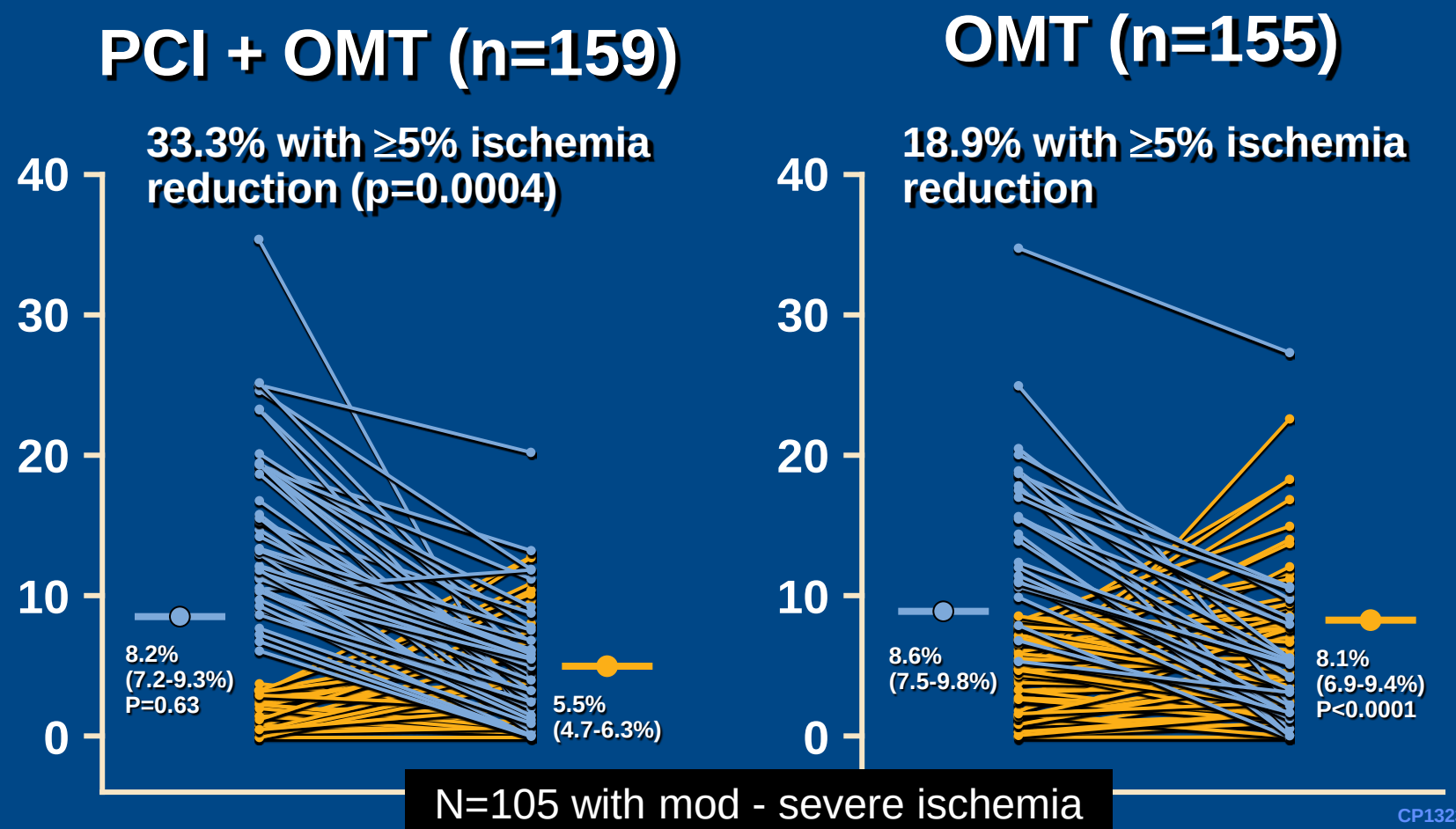
Referral Rates to Cath When Moderate or Severe Ischemia is Detected

- ~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



N=105 with mod - severe ischemia
PCI vs. OMT
78% vs. 52 % reduction in ischemia

CP1323075-17

Circ 2008;117:1283.

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Most Sites Have Multiple Physical Locations

Office with Stress Lab

CCTA/ Revascularization Center

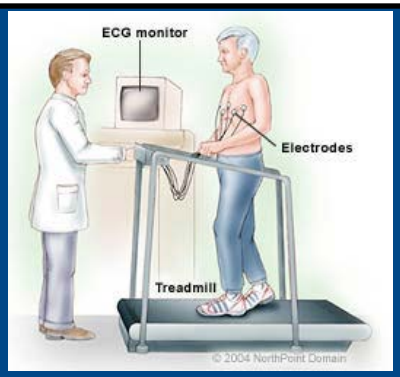
Private Office

Private Office w/ CCTA + Stress Lab

Site B

Office

Stress Lab



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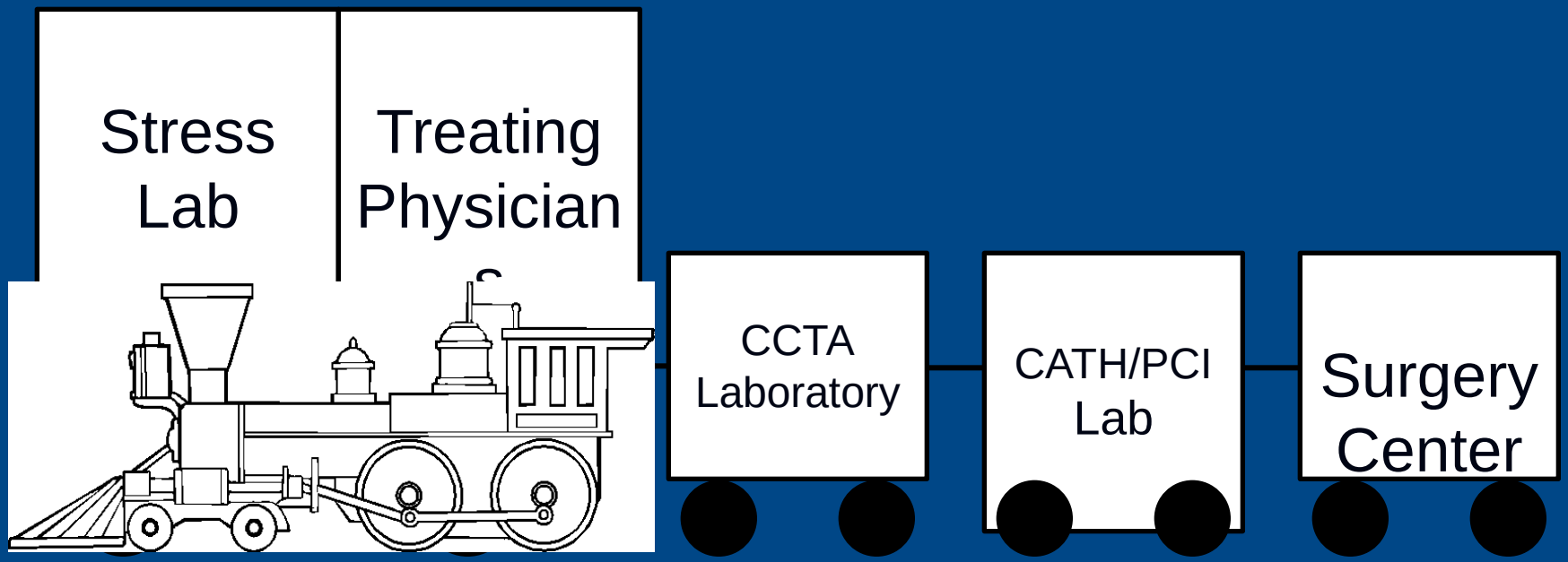
An ISCHEMIA Site Has Many Parts



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

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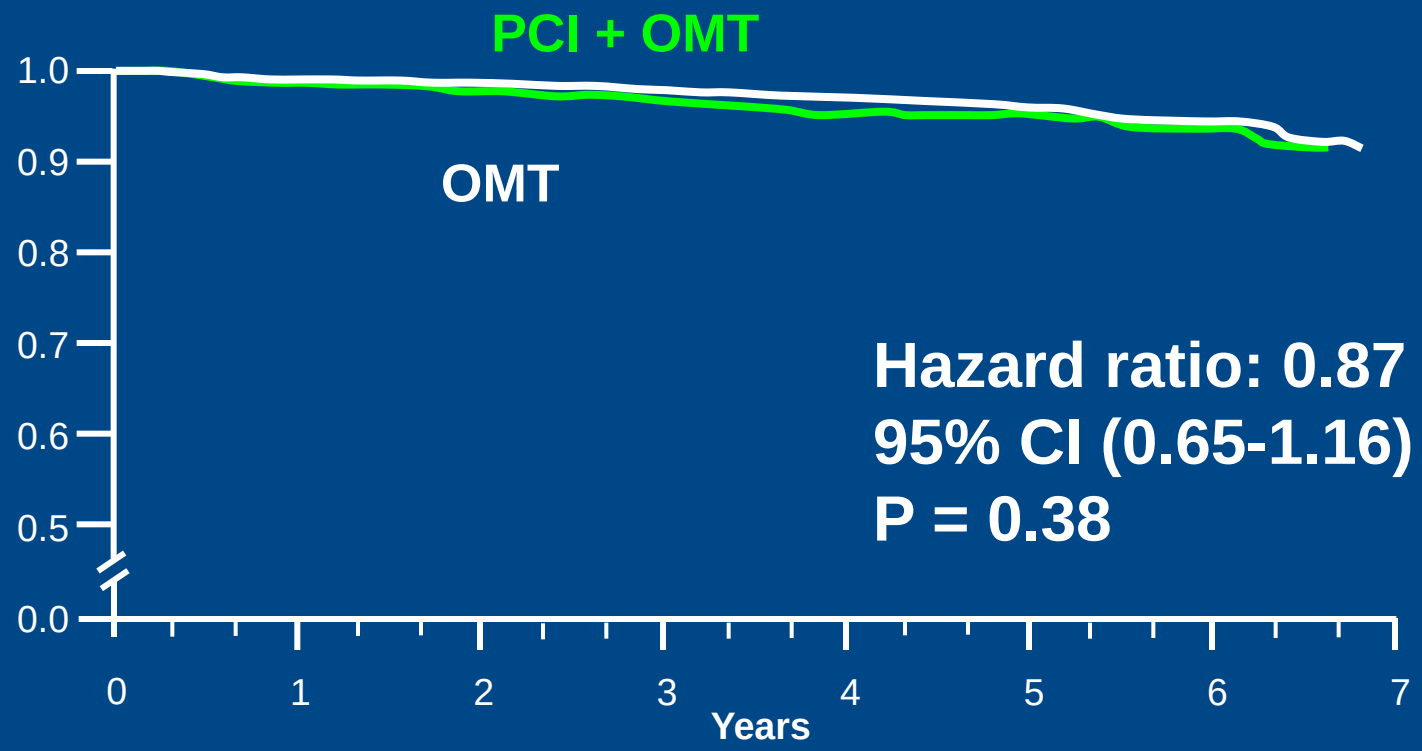
COURAGE: PCI Did Not Improve Survival



Number at Risk

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

Boden WE et al NEJM 2007

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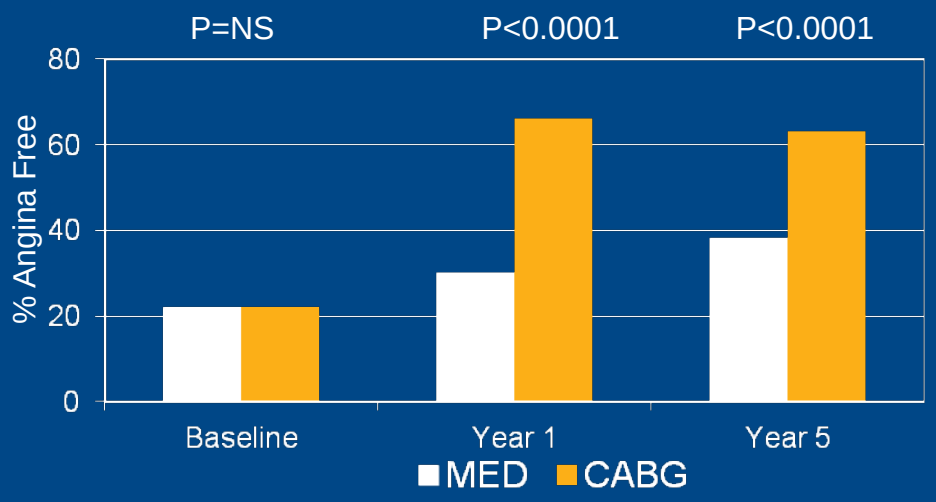
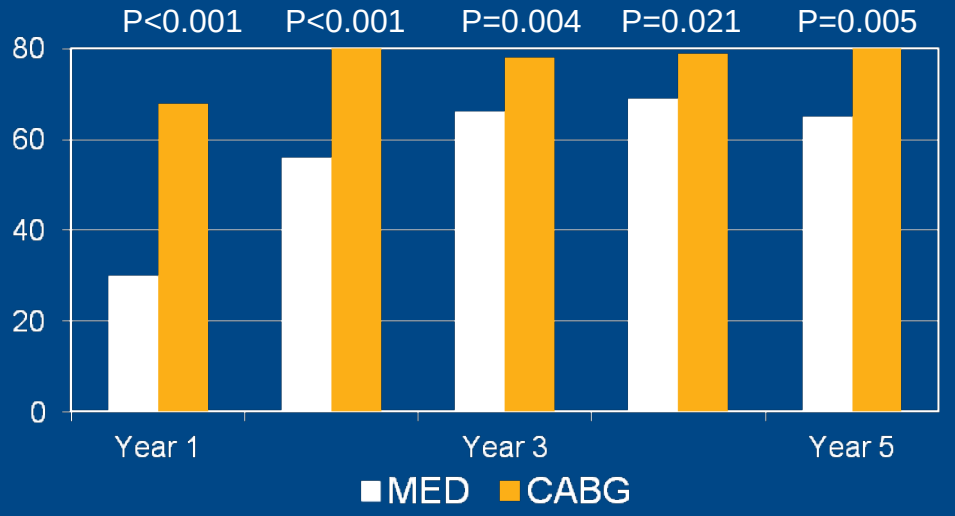
Freedom from Angina: From CASS to BARI 2D

CABG: additional anti-anginal benefit over 5yrs

CASS



BARI 2D - CABG



CABG vs. Medical Rx

(beta blockers + nitrates; no severe angina at baseline)

CABG vs. OMT

(18% angina-free at baseline)

Rogers et al. *Circ* 1990.
Dagenais et al. *Circ* 2011

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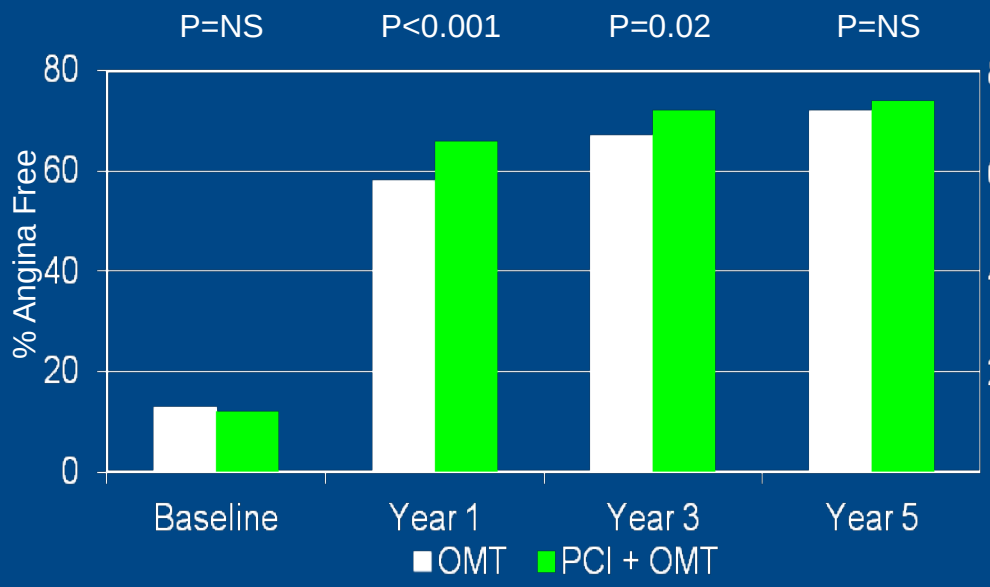
Freedom from Angina: COURAGE and BARI 2D*

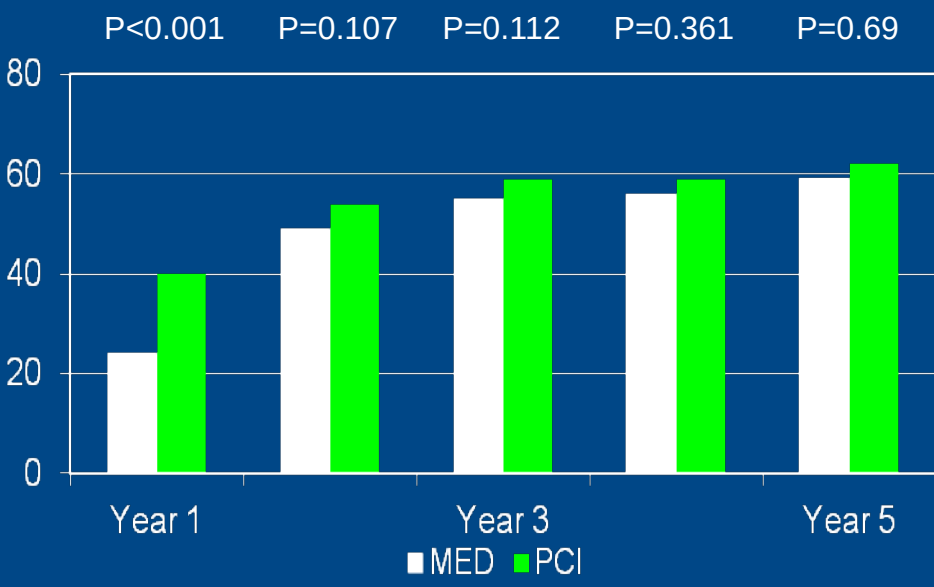
PCI: additional anti-anginal benefit over 1-3yrs

COURAGE



(12% angina-free at baseline)

BARI 2D - PCI



(18% angina-free at baseline)

*CCS Class 0

Boden WE et al. *N Engl J Med* 2007
Dagenais GR et al. Circulation 2011

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