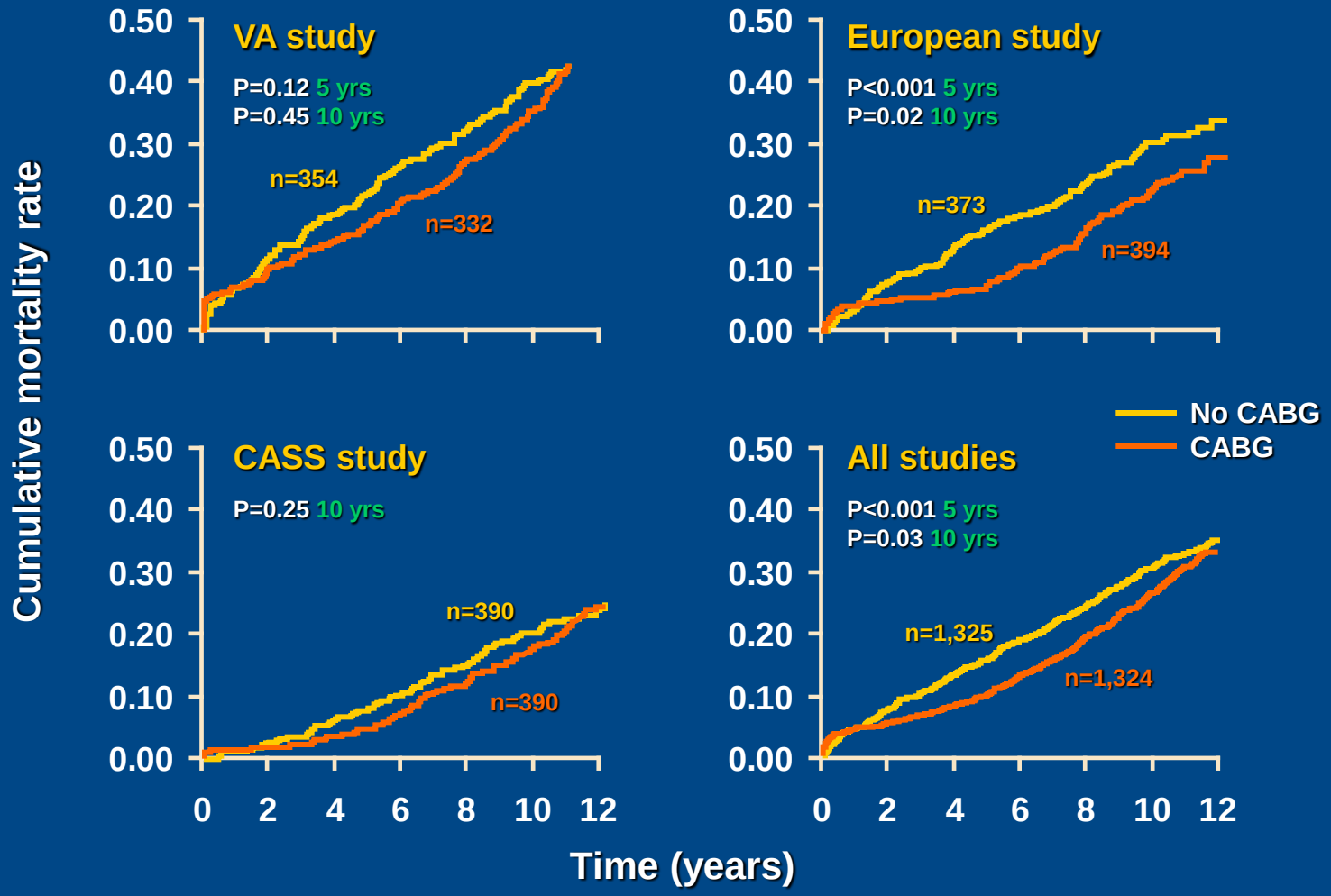
ISCHEMIA Trial

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

CABG vs no CABG

CABG Surgery Trialists Collaboration; 10-year outcome



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

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

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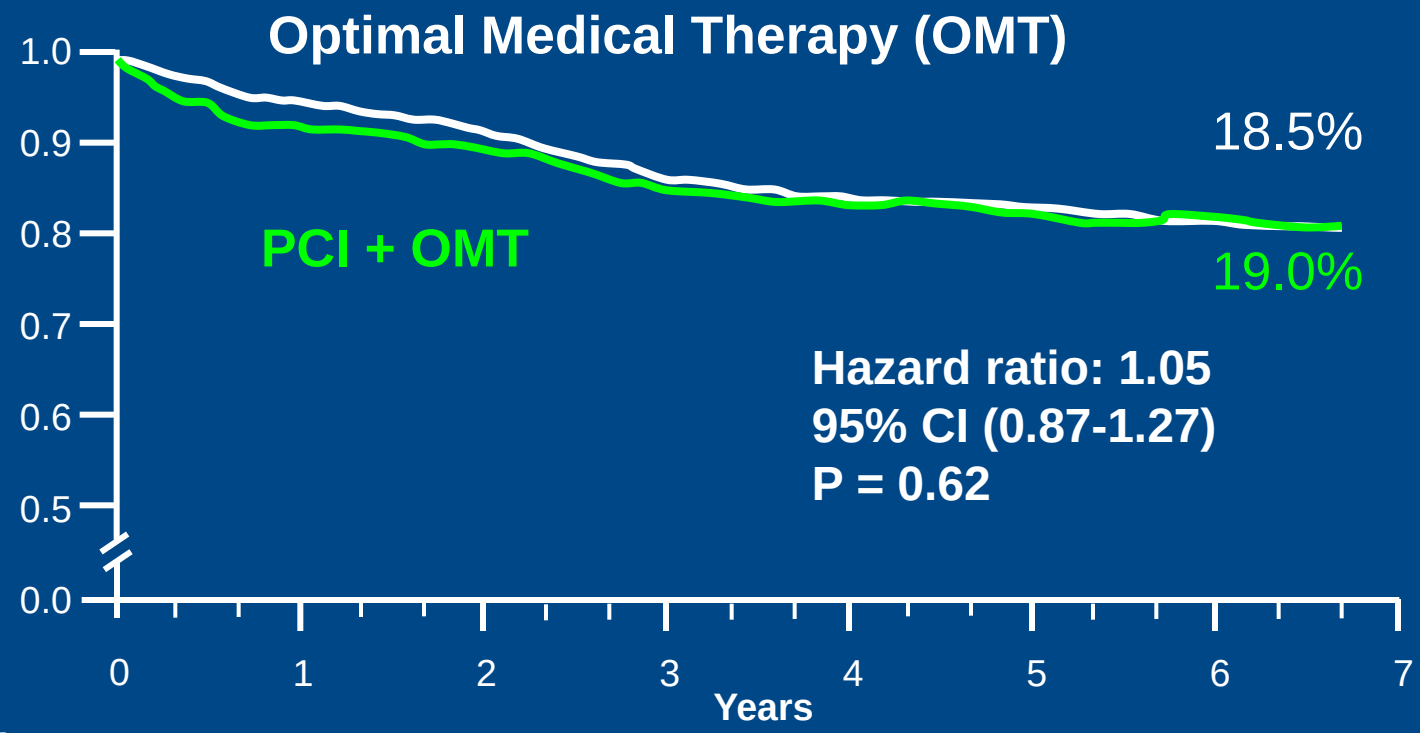
A Strategy of Routine PCI Did Not Reduce Death or MI in SIHD Patients



Number at Risk

Medical Therapy	1138	1017	959	834	638	408	192	30
PCI	1149	1013	952	833	637	417	200	35

33% PCI rate in OMT; 21% repeat PCI in PCI group

Boden et al NEJM 2007

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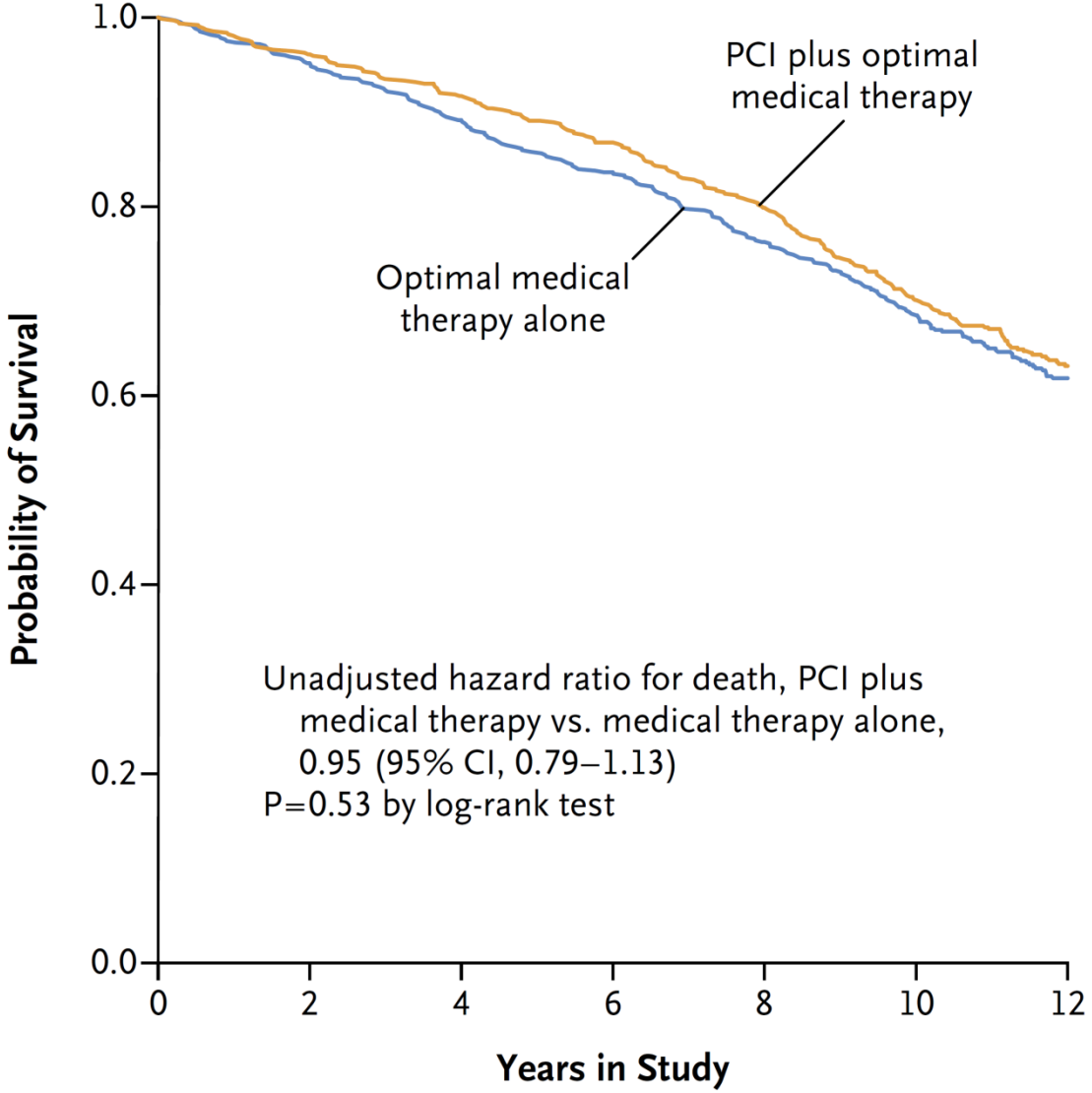
Extended Follow-up Study Cohort



No. at Risk

Optimal medical therapy	598	569	533	500	455	403	280
PCI plus optimal medical therapy	613	589	561	529	486	416	302

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

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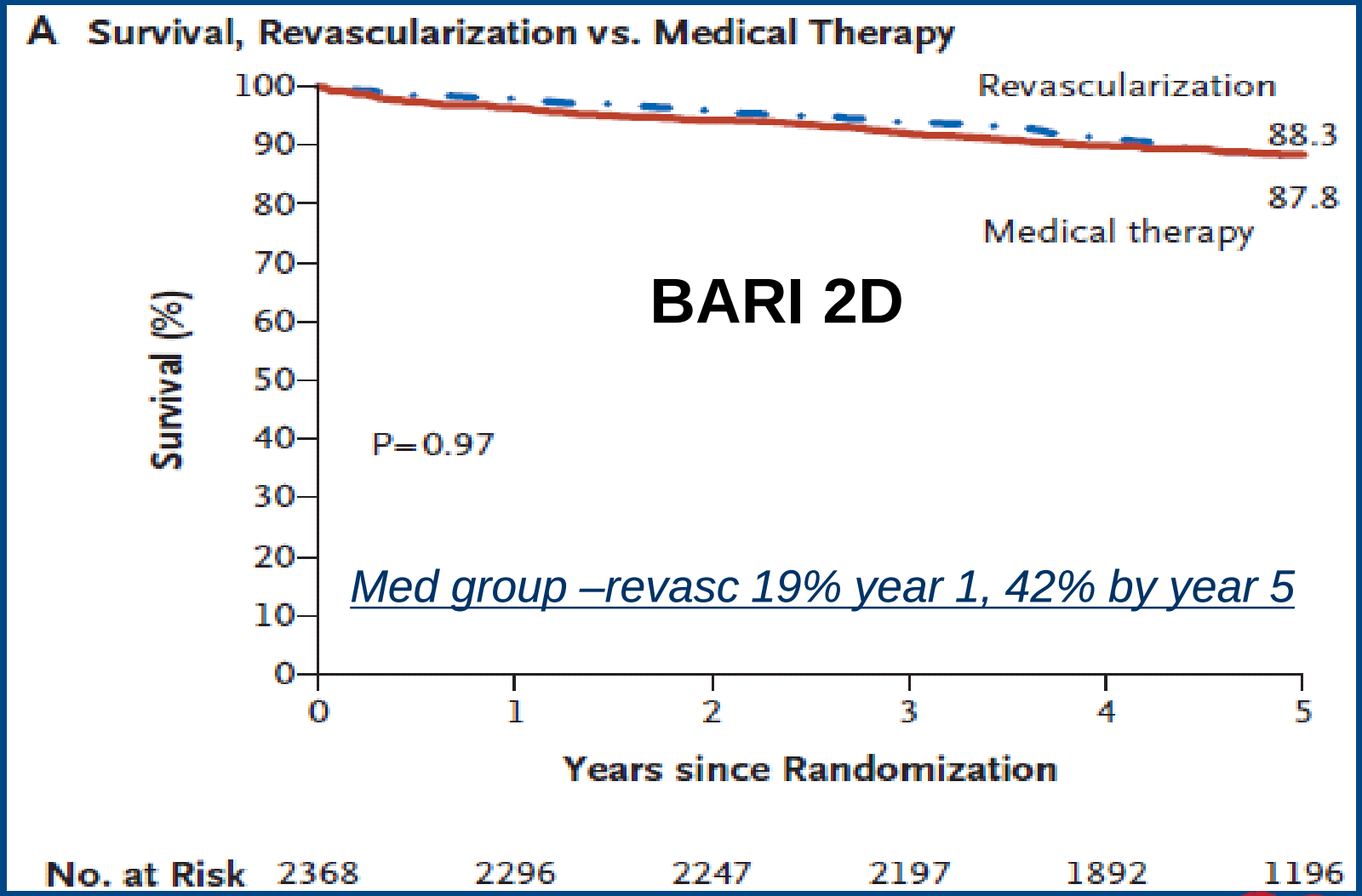
Prompt revascularization did not improve survival in diabetic patients with SIHD



BARI 2D Study Group. N Engl J Med 2009

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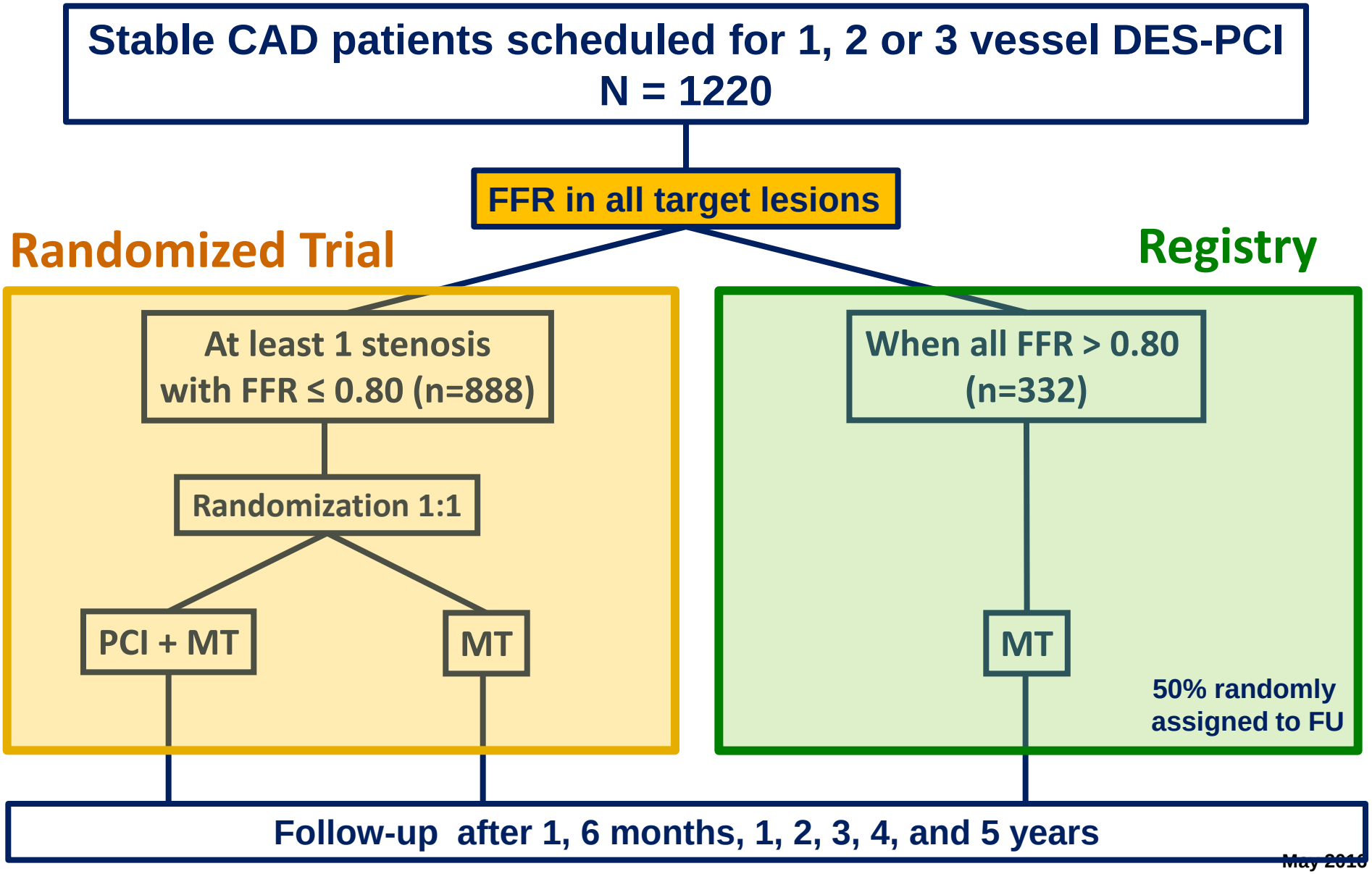
FAME 2

NEJM 2012;367:991-1001.



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

- Stopped early due to reduction in the primary endpoint* in PCI group, due to difference in urgent revascularization rates
- ~1/3 had recent unstable angina
- Recent MI not excluded; only those within 7 days
- ~1/4 had baseline Class III-IV angina
- Peri PCI MI
  - Defined as: 10 X CK-MB OR 5X CKMB AND new Q's

*Death, MI, urgent revascularization

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

FAME 2 Two Year Clinical Events and Revascularization

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

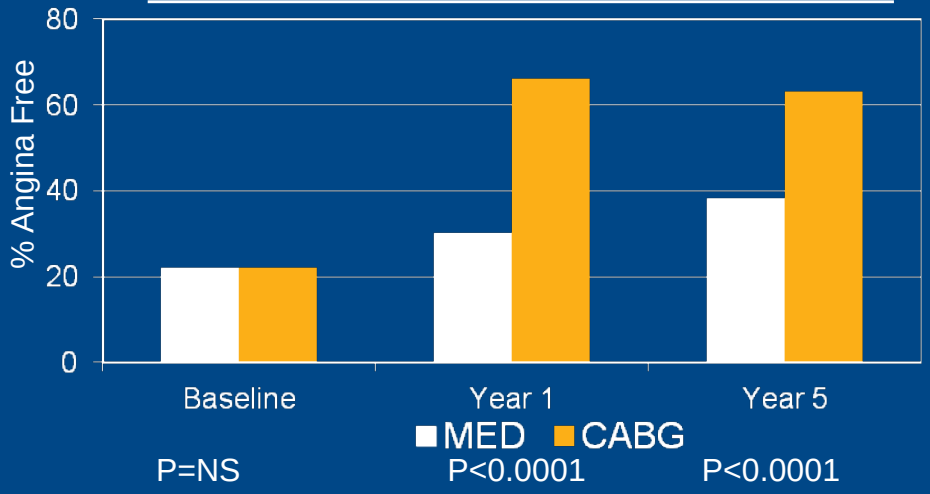
De Bruyne et al NEJM 2014

Design Limitations of Prior Trials

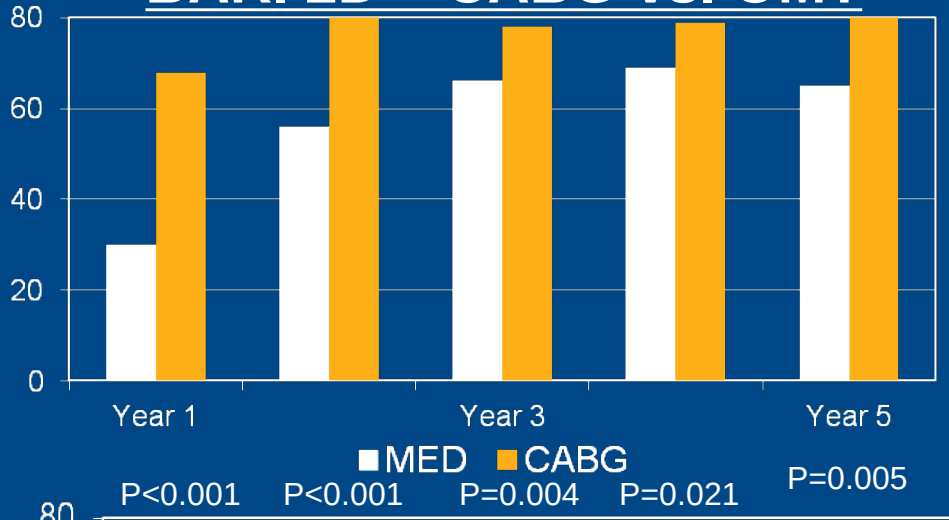
- Low risk patients included
- Revascularization procedures not optimal in COURAGE and BARI 2D (little DES, no FFR)
- Referral bias by randomizing after cath
- Small sample size (FAME 2)

Majority of patients angina-free with current medical therapy

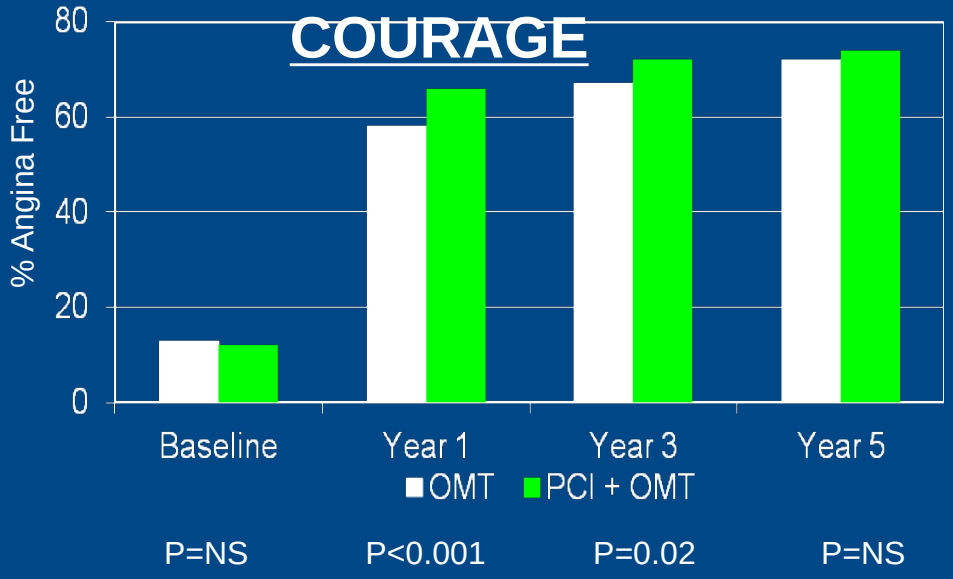
CASS: CABG vs. no CABG



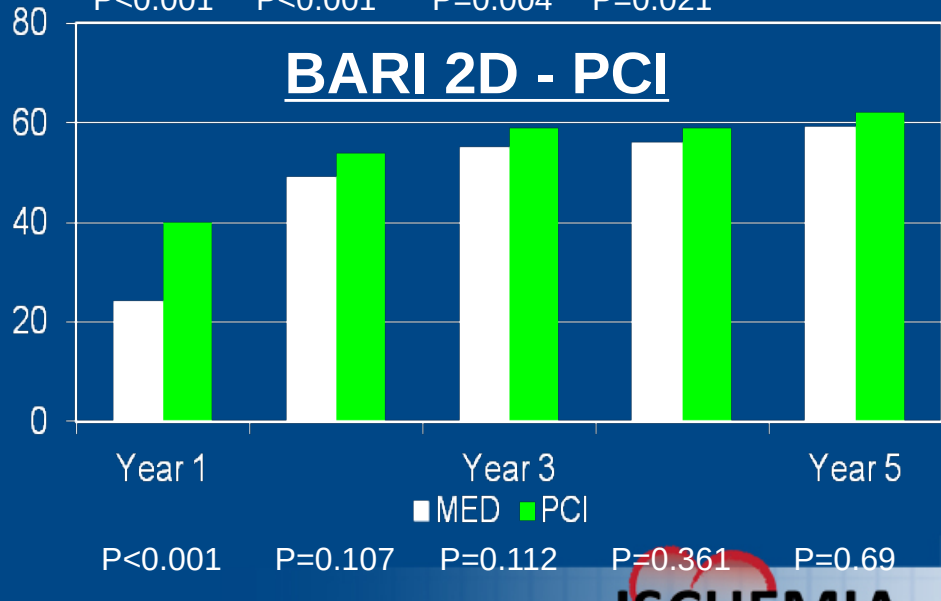
BARI 2D – CABG vs. OMT



COURAGE

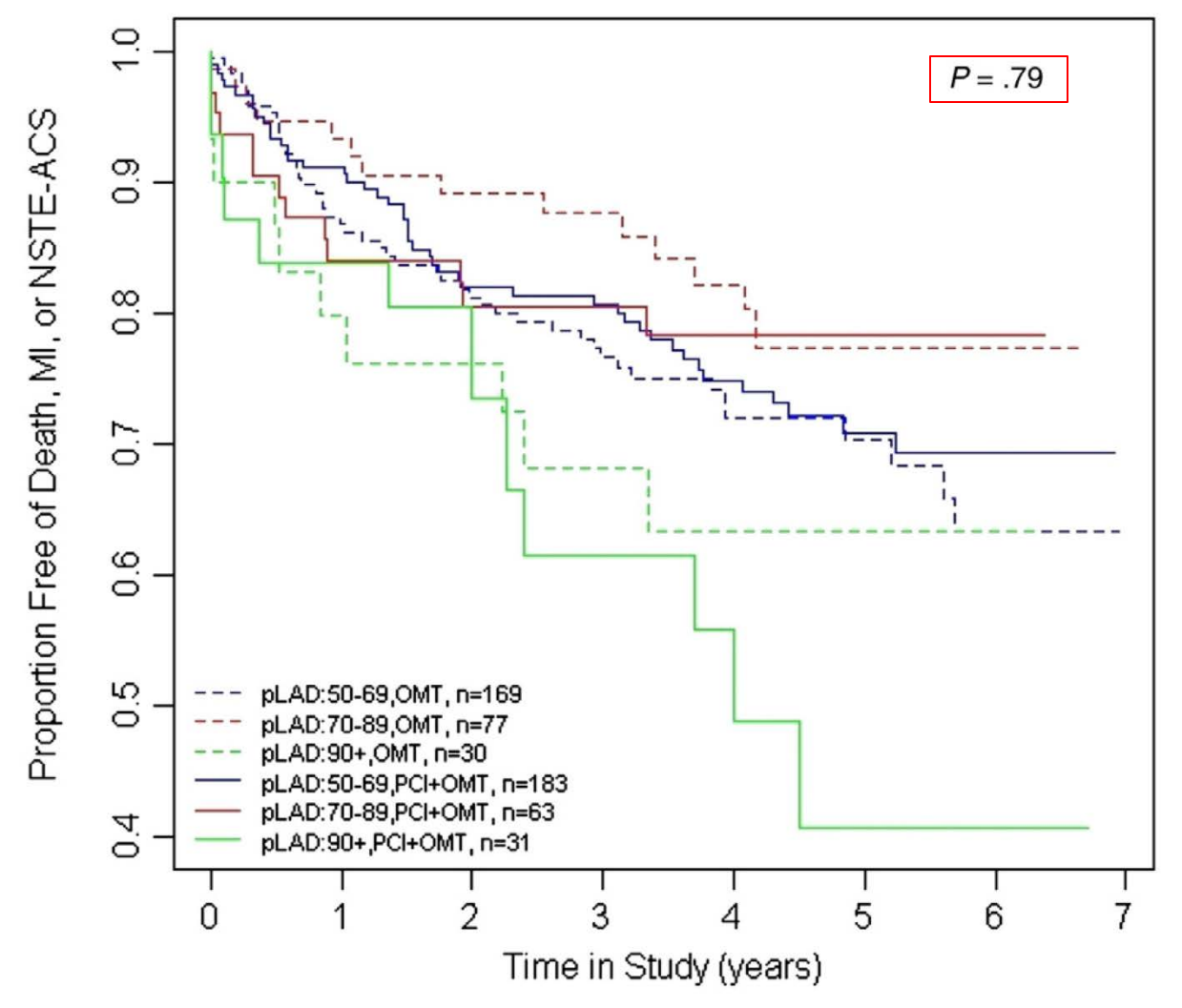


BARI 2D - PCI



Rogers et al. *Circ* 1990, Boden WE et al. *N Engl J Med* 2007, Dagenais et al. *Circ* 2011

COURAGE: Proximal LAD & Prognosis



50-69%

70-89%

90+%

Mancini et al. Am Heart J 2013;166:481-7.

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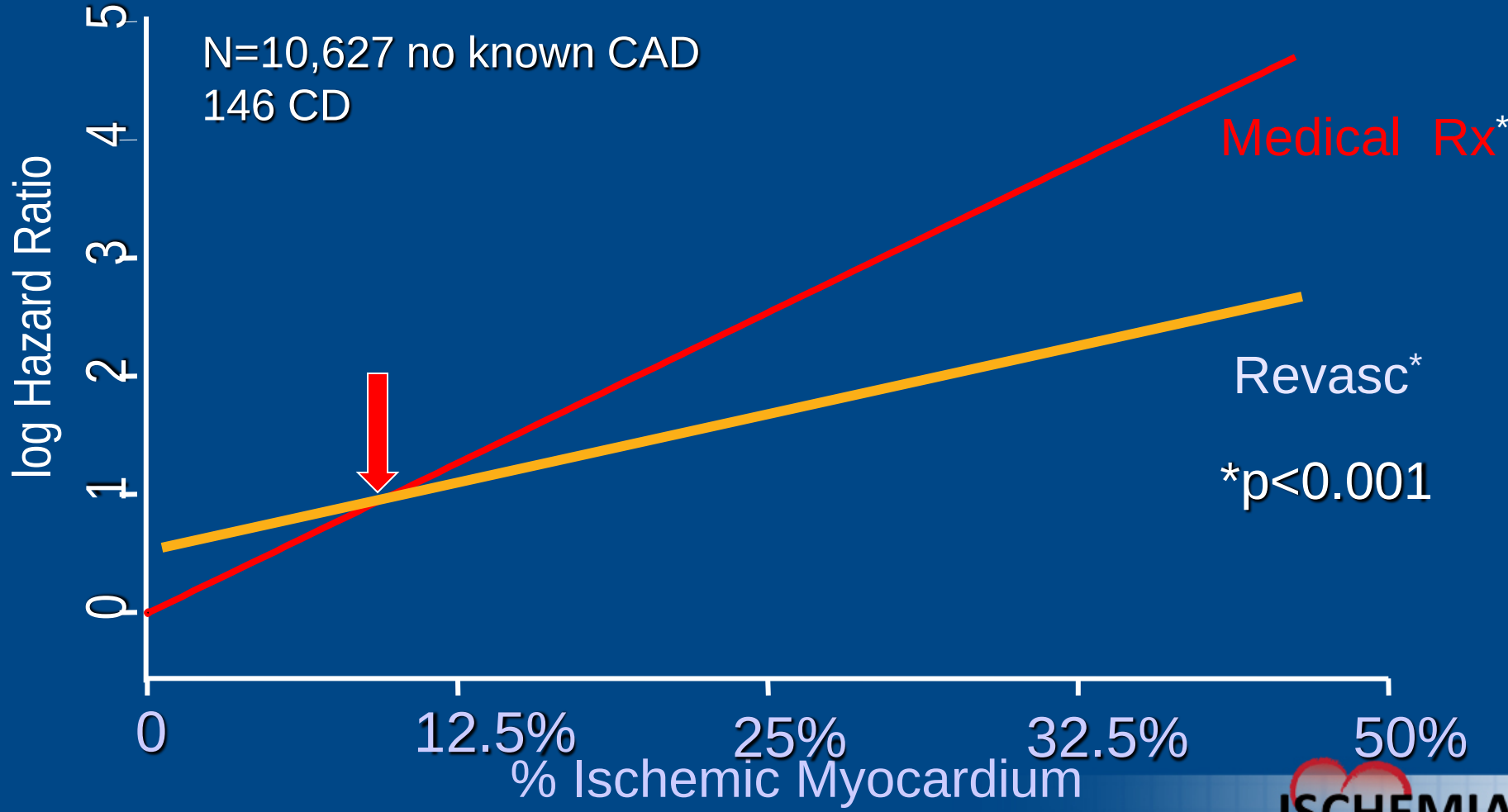
Observational study: Revascularization was associated with lower risk of cardiac death only in those with >10% ischemia on perfusion imaging



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

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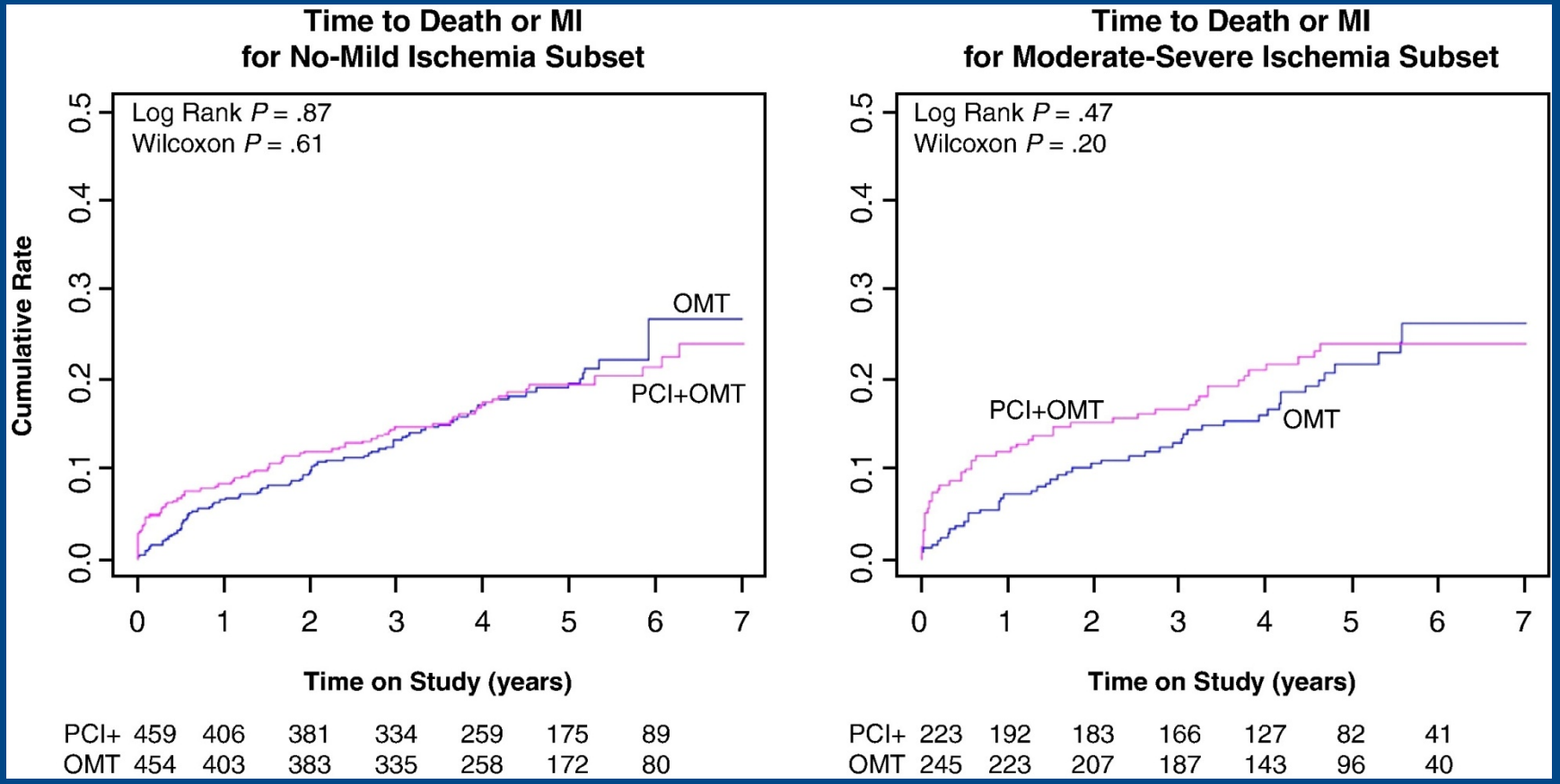
PCI did not Reduce Events: COURAGE nuclear substudy

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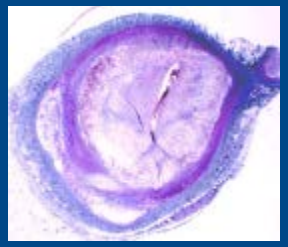
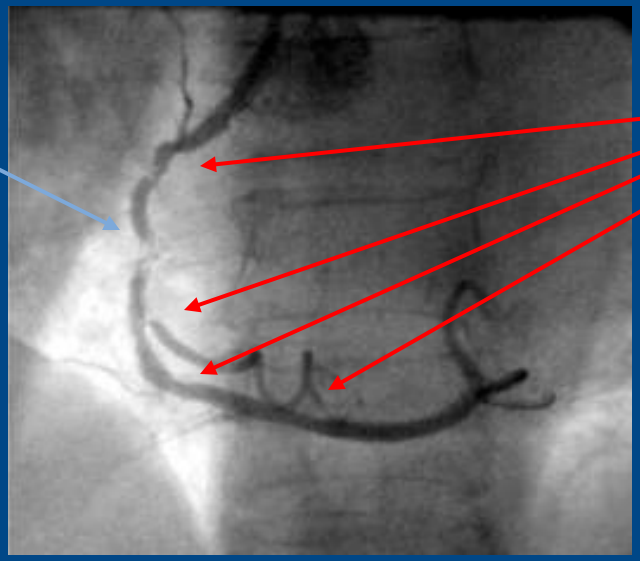
Severe Obstruction (angina, no rupture) vs Mild Obstruction (no angina, likely to rupture)

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





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

Exertional angina
- **(+) ETT**

Revascularization
Anti-anginal Rx

Plaque rupture
- **Acute MI**
- **Unstable angina**
- **Sudden death**

Pharmacologic stabilization
Early identification of high-risk?

Courtesy of PH Stone, MD.

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Stable Patient
At Least Moderate Ischemia*
(determined by site; read by core lab)

Blinded CCTA[1]

Core lab anatomy eligible?[2] — no → **Late screen failure**

yes

RANDOMIZE

INVASIVE Strategy	**CONSERVATIVE Strategy**
OMT[3] + Cath +	**OMT[3] alone**
Optimal Revascularization	**Cath reserved for OMT failures**

Average 3 Years of Follow-up
Primary Endpoint: Composite of CV Death and MI

*** Patients with eGFR <30 or on dialysis will be enrolled in the ISCHEMIA CKD ancillary trial**

[1]CCTA may not be performed in participants with eGFR <60 mL/min
[2]Exclude participants with LM disease or no obstructive disease
[3]OMT=optimal medical therapy

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Major Exclusion Criteria

- LVEF < 35%
- Coronary anatomy unsuitable for either PCI or CABG
- Unacceptable level of angina despite maximal medical therapy or 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
- Prior CABG, unless cath already done to show anatomy amenable to revascularization
- ACS within 2 months
- PCI within 12 months
- Stroke within 6 months
- NYHA Class III-IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months

Optimal Medical Therapy

- Applied equally to CON and INV, based on guidelines
- Study team at each site is responsible for implementation of OMT, working with participant's personal MD
- Local circumstances will dictate how study team collaborates with personal physician
- Cath done in conservative strategy for acute ischemic events or refractory symptoms

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

End