



COURAGE





Presenter Conflict Disclosure

Name: **William E. Boden, MD, FACC**

Within the past 12 months, the presenter or their spouse/partner have had the financial interest/arrangement or affiliation with the organization listed below.

Company Name:

- Merck
- Pfizer
- Kos/Abbott Laboratories
- Sanofi-Aventis
- CV Therapeutics
- Novartis
- PDL BioPharma

Relationship:

- Research grant support
- Research grant support; Speaker's Bureau
- Research grant support/Consultant/Speaker
- Research Grant Support; Speaker's Bureau
- Speaker's Bureau
- Speaker's Bureau
- Speaker's Bureau; Consultant



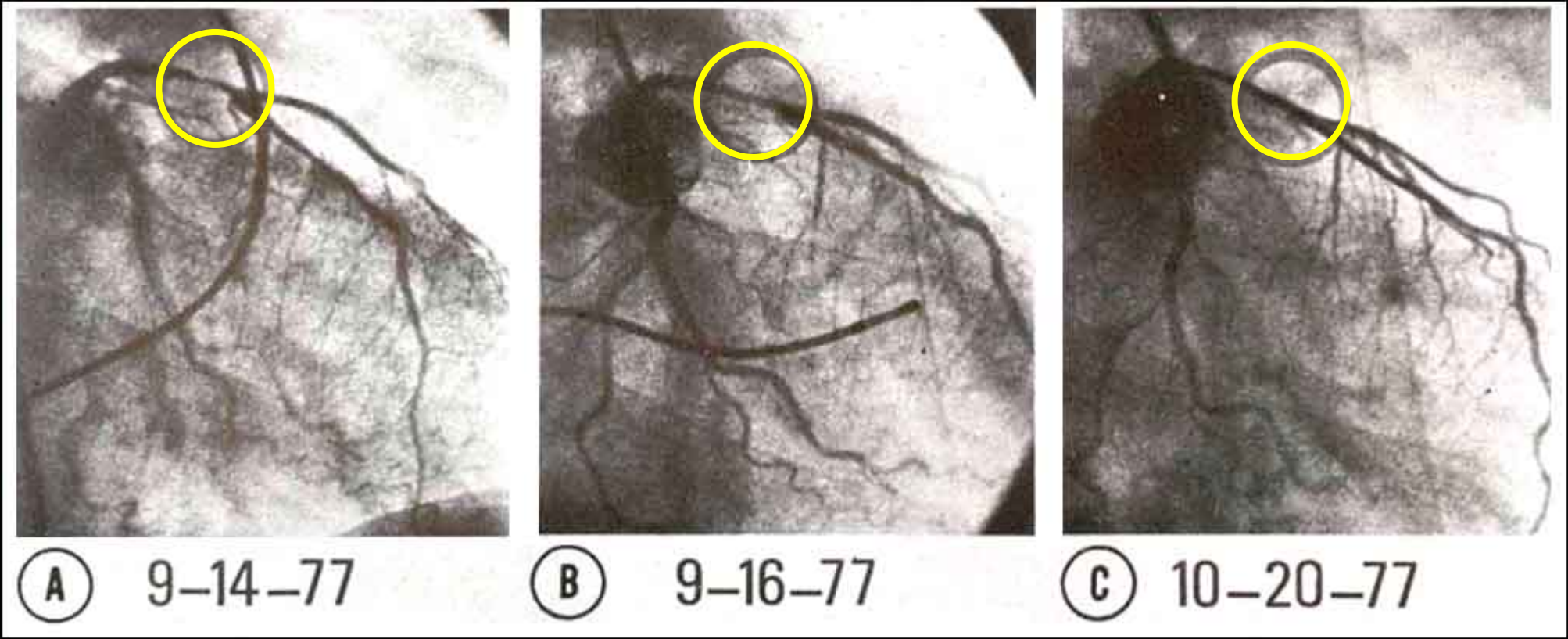


COURAGE

Clinical Outcomes Utilizing
Revascularization and
Aggressive Guideline-Driven
Drug Evaluation



The First Coronary Angioplasty for Stable CAD; 1977



First coronary angioplasty lesion (circles) two days before (A), immediately after (B), and one month after (C) balloon dilation



Conventional Wisdom

Treatment Assumptions in CAD Management:

- Patients with symptomatic CAD and chronic angina who have significant coronary stenoses “need” revascularization
- Revascularization is required to improve prognosis
- PCI is less invasive than CABG surgery (i.e., is safer) and, therefore, should be selected



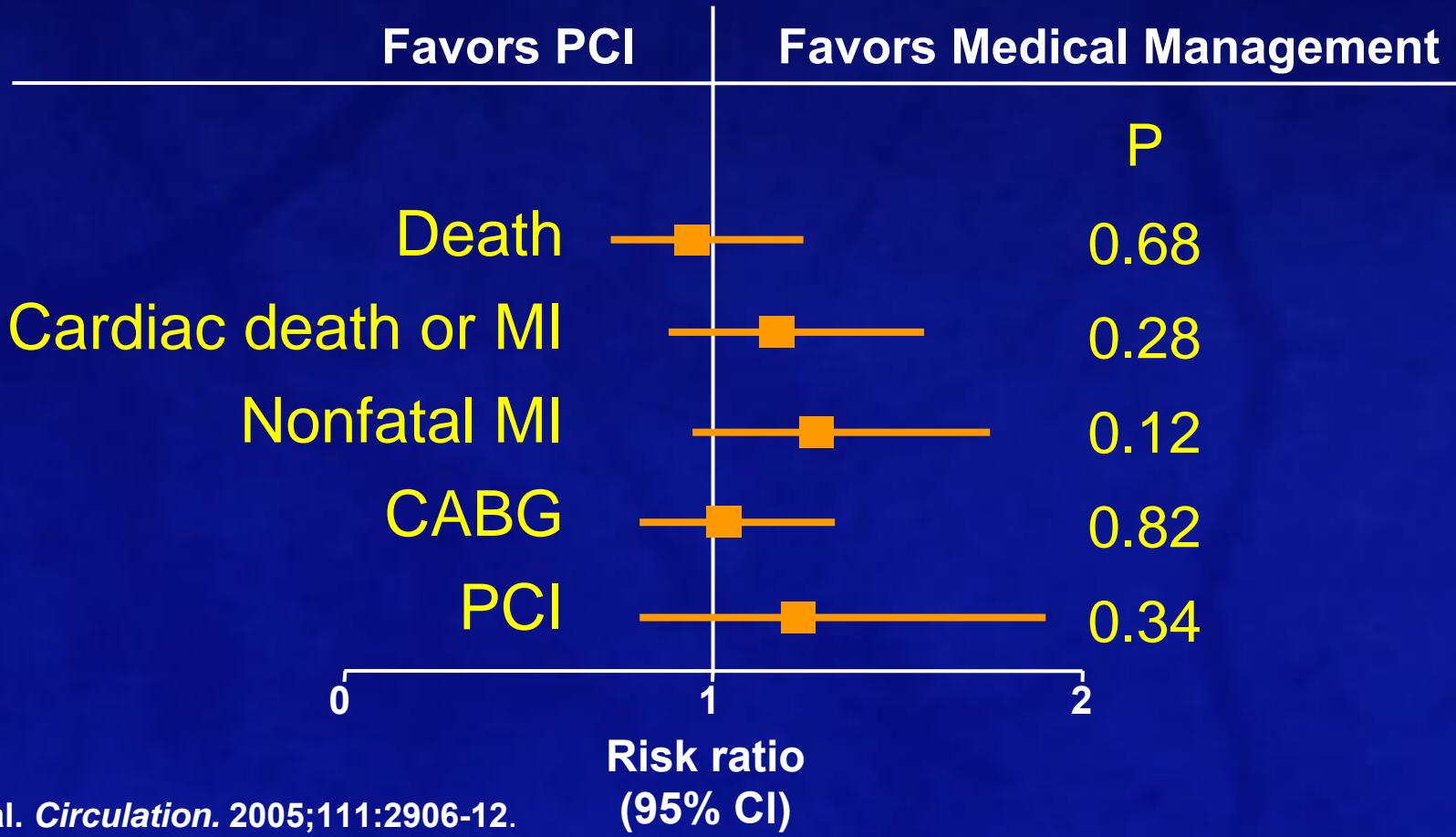
Background

- **More than 1 million PCI procedures are performed in the U.S. annually, the great majority of which are undertaken electively in patients with stable CAD**
- **Although successful PCI of flow-limiting stenoses might be expected to reduce the rate of death, MI or hospitalization for ACS, prior studies have shown only that PCI decreases the frequency of angina and improves short-term exercise performance**



Stable CAD: PCI vs Conservative Medical Management

Meta-analysis of 11 randomized trials; N = 2,950





A North American Trial



19 US Non-VA Hospitals



15 VA Hospitals



16 Canadian Hospitals

50 Hospitals

**2,287 patients
enrolled between
6/99-1/04**



Funding

- Cooperative Studies Program of the U.S. Department of Veterans Affairs Office of Research and Development
- Canadian Institutes of Health Research
- Merck, Pfizer, Bristol-Myers Squibb, and Fujisawa; others



Hypothesis

PCI + Optimal Medical Therapy

will be Superior to

Optimal Medical Therapy Alone



Primary Outcome

Death or Nonfatal MI



Secondary Outcomes

- **Death, MI, or Stroke**
- **Hospitalization for Biomarker (-) ACS**
- **Cost, Resource Utilization**
- **Quality of Life, including Angina**
- **Cost-Effectiveness**



Design

- Randomization to PCI + Optimal Medical Therapy vs Optimal Medical Therapy alone
- Intensive, guideline-driven medical therapy and lifestyle intervention in both groups
- 2.5 to 7 year (mean 4.6 year) follow-up



Definition of MI

- In patients with a clinical presentation c/w an acute ischemic syndrome and who have 1 of the following:
 - New Q Waves ≥ 0.03 sec in ≥ 2 contiguous leads as assessed by ECG Core Laboratory reading
 - For Spontaneous MI: CK/CK-MB ≥ 1.5 X UNL or (+) Troponin ≥ 2.0 X UNL
 - For Peri-PCI MI: CK/CK-MB ≥ 3.0 X UNL or (+) Troponin ≥ 5.0 X UNL (only if CK not available)
 - For Post-CABG MI: CK-MB ≥ 10.0 X UNL or (+) Troponin ≥ 10.0 xUNL (only if CK not available)



Inclusion Criteria

- Men and Women
- 1, 2, or 3 vessel disease
($> 70\%$ visual stenosis of proximal coronary segment)
- Anatomy suitable for PCI
- CCS Class I-III angina
- Objective evidence of ischemia at baseline
- ACC/AHA Class I or II indication for PCI



Exclusion Criteria

- Uncontrolled unstable angina
- Complicated post-MI course
- Revascularization within 6 months
- Ejection fraction <30%
- Cardiogenic shock/severe heart failure
- History of sustained or symptomatic VT/VF



Objective Evidence of Ischemia

- Spontaneous ST-T changes on ECG
- ≥ 1 mm ST deviation on treadmill test
- Ischemic imaging defect



Coronary Intervention

- Best practice
- May use all FDA or Health Canada approved devices
- Completeness of revascularization as clinically appropriate



Risk Factor Goals

Variable	Goal						
Smoking	Cessation						
Total Dietary Fat / Saturated Fat	<30% calories / <7% calories						
Dietary Cholesterol	<200 mg/day						
LDL cholesterol (primary goal)	60-85 mg/dL						
HDL cholesterol (secondary goal)	>40 mg/dL						
Triglyceride (secondary goal)	<150 mg/dL						
Physical Activity	30-45 min. moderate intensity 5X/week						
Body Weight by Body Mass index	<table border="0"> <tr> <td><u>Initial BMI</u></td> <td><u>Weight Loss Goal</u></td> </tr> <tr> <td>25-27.5</td> <td>BMI <25</td> </tr> <tr> <td>>27.5</td> <td>10% relative weight loss</td> </tr> </table>	<u>Initial BMI</u>	<u>Weight Loss Goal</u>	25-27.5	BMI <25	>27.5	10% relative weight loss
<u>Initial BMI</u>	<u>Weight Loss Goal</u>						
25-27.5	BMI <25						
>27.5	10% relative weight loss						
Blood Pressure	<130/85 mmHg						
Diabetes	HbA1c <7.0%						



Optimal Medical Therapy

Pharmacologic

- Anti-platelet: aspirin; clopidogrel in accordance with established practice standards
- Statin: simvastatin ± ezetimibe or ER niacin
- ACE Inhibitor or ARB: lisinopril or losartan
- Beta-blocker: long-acting metoprolol
- Calcium channel blocker: amlodipine
- Nitrate: isosorbide 5-mononitrate

Applied to Both Arms by Protocol and Case-Managed



Optimal Medical Therapy

Lifestyle

- Smoking cessation
- Exercise program
- Nutrition counseling
- Weight control

Applied to Both Arms by Protocol and Case-Managed



Statistical Design

- We projected 3-year event rates of 21% in the OMT group and 16.4% in the PCI + OMT group (relative difference = 22%)
- There was 85% power to detect the above difference in the primary outcome at the 5% two-sided level of significance, with a sample size estimate of 2,270 patients

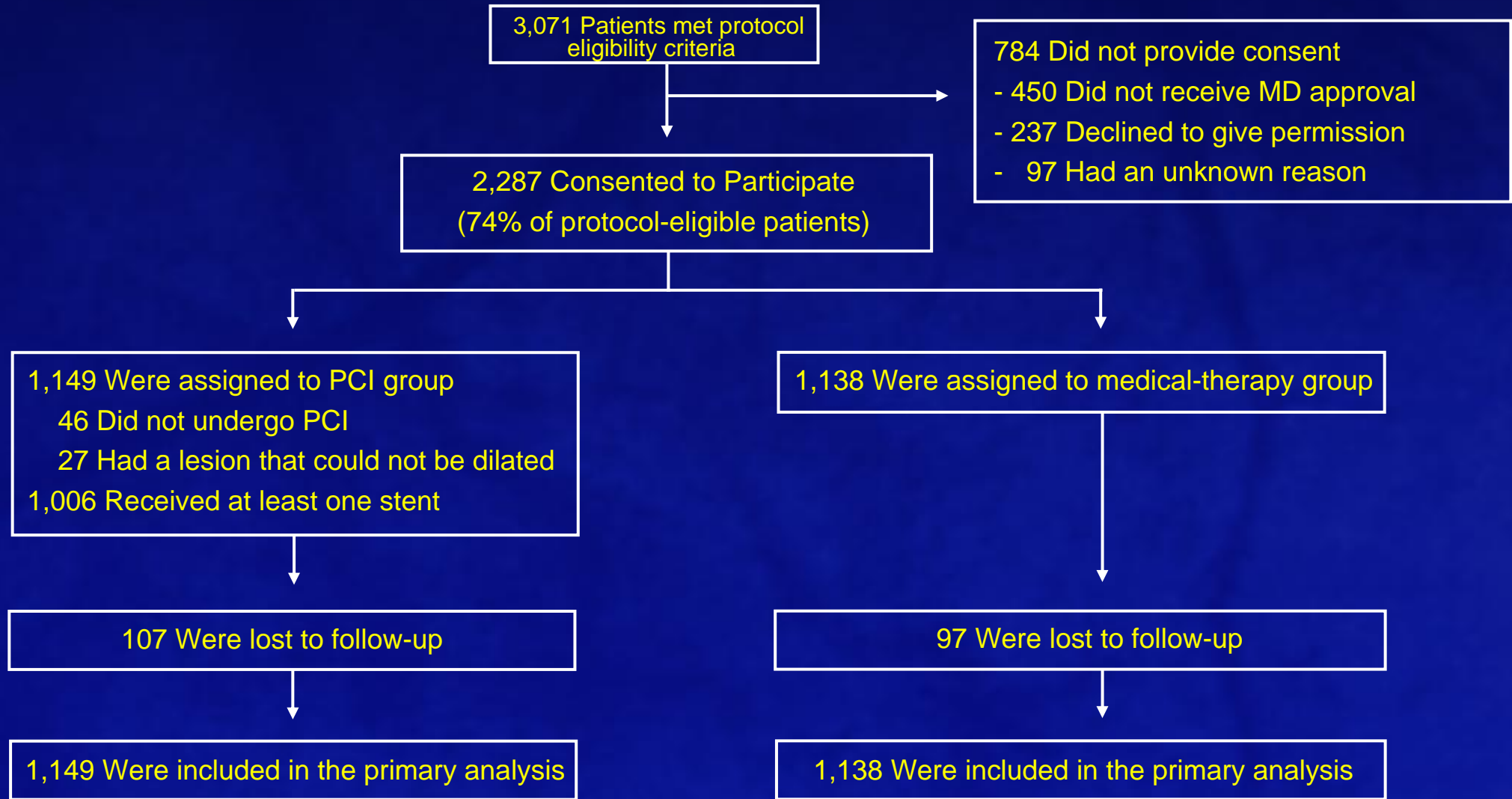


Statistical Methodology

- All analyses were performed according to the intent-to-treat principle
- Cumulative event rates were estimated by the method of Kaplan-Meier and treatment effects were assessed using Cox proportional hazards models
- Comparison of categorical variables used chi-square test or the Wilcoxon rank sum test, while the Student t-test was used for continuous variables



Enrollment and Outcomes





Baseline Clinical and Angiographic Characteristics

Characteristic	PCI + OMT (N=1149)	OMT (N=1138)	P Value
Age – yr.	62 ± 10.1	62 ± 9.7	0.54
Sex %			0.95
Male	85 %	85 %	
Female	15 %	15 %	
Race or Ethnic group %			0.64
White	86 %	86 %	
Non-white	14 %	14 %	
CLINICAL			
Angina (CCS – class) %			0.24
0 and I	42 %	43 %	
II and III	59 %	56 %	
Median angina duration	5 (1-15) months	5 (1-15) months	
Median angina episodes/week	3 (1-6)	3 (1-6)	



Baseline Clinical and Angiographic Characteristics

Characteristic	PCI + OMT (N=1149)	OMT (N=1138)	P Value
CLINICAL			
History – %			
Diabetes	32 %	35 %	0.12
Hypertension	66 %	67 %	0.53
CHF	5 %	4 %	0.59
Cerebrovascular disease	9 %	9 %	0.83
Myocardial infarction	38 %	39 %	0.80
Previous PCI	15 %	16 %	0.49
CABG	11 %	11 %	0.94



Baseline Clinical and Angiographic Characteristics

Characteristic	PCI + OMT (N=1149)	OMT (N=1138)	P Value
CLINICAL			
Stress test			0.84
Total patients - %	85 %	86 %	
Treadmill test	57 %	57 %	0.84
Pharmacologic stress	43 %	43 %	
Nuclear imaging - %	70 %	72 %	0.59
Single reversible defect	22 %	23 %	0.09
Multiple reversible defects	65 %	68 %	0.09
ANGIOGRAPHIC			
Vessels with disease – %			0.72
1, 2, 3	31, 39, 30 %	30, 39, 31 %	
Disease in graft	62 %	69 %	0.36
Proximal LAD disease	31 %	37 %	0.01
Ejection fraction	60.8 ± 11.2	60.9 ± 10.3	0.86





Long-Term Improvement in Treatment Targets (Group Median \pm SE Data)

Treatment Targets	Baseline		60 Months	
	PCI +OMT	OMT	PCI +OMT	OMT
SBP	131 \pm 0.77	130 \pm 0.66	124 \pm 0.81	122 \pm 0.92
DBP	74 \pm 0.33	74 \pm 0.33	70 \pm 0.81	70 \pm 0.65
Total Cholesterol mg/dL	172 \pm 1.37	177 \pm 1.41	143 \pm 1.74	140 \pm 1.64
LDL mg/dL	100 \pm 1.17	102 \pm 1.22	71 \pm 1.33	72 \pm 1.21
HDL mg/dL	39 \pm 0.39	39 \pm 0.37	41 \pm 0.67	41 \pm 0.75
TG mg/dL	143 \pm 2.96	149 \pm 3.03	123 \pm 4.13	131 \pm 4.70
BMI Kg/M ²	28.7 \pm 0.18	28.9 \pm 0.17	29.2 \pm 0.34	29.5 \pm 0.31
Moderate Activity (5x/week)	25%	25%	42%	36%



Angiographic Outcomes

- PCI was attempted on 1,688 lesions (in 1,077 patients), of whom 1,006 received at least 1 stent
- 590 patients (59%) received 1 stent and 416 (41%) received 2 or more stents
- Stenosis diameter was reduced from a mean of $83 \pm 14\%$ to **$31 \pm 34\%$** in the 244 non-stented lesions, and from **$82 \pm 12\%$** to **$1.9 \pm 8\%$** in the 1,444 stented lesions
- Angiographic success (<20% residual stenosis by visual assessment) post-PCI was **93%** and clinical success was **89%** post-PCI.

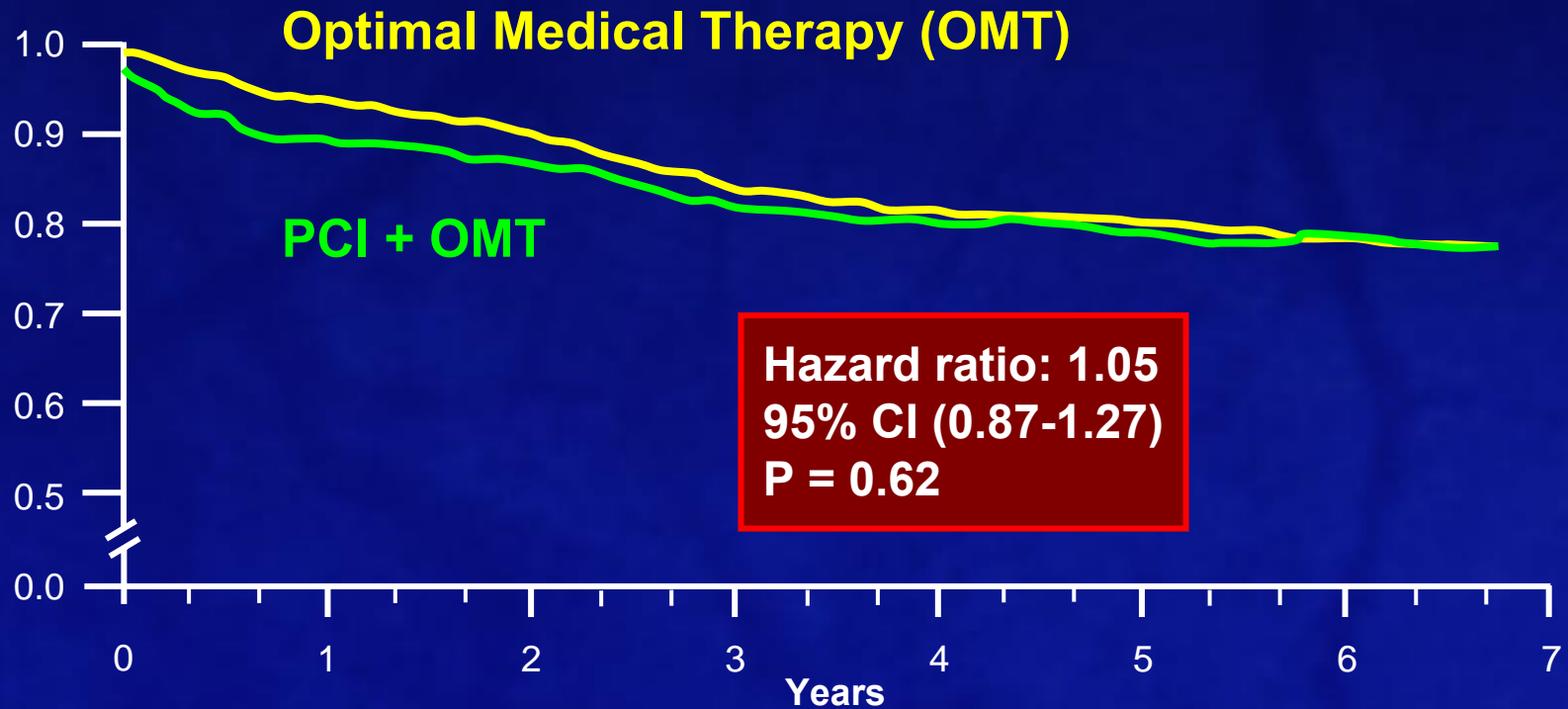


Need for Subsequent Revascularization

- At a median 4.6 year follow-up, **21.1%** of the PCI patients required an additional revascularization, compared to **32.6%** of the OMT group who required a 1st revascularization
- 77 patients in the PCI group and 81 patients in the OMT group required subsequent CABG surgery
- Median time to subsequent revascularization was **10.0** mo in the PCI group and **10.8** mo in the OMT group



Survival Free of Death from Any Cause and Myocardial Infarction

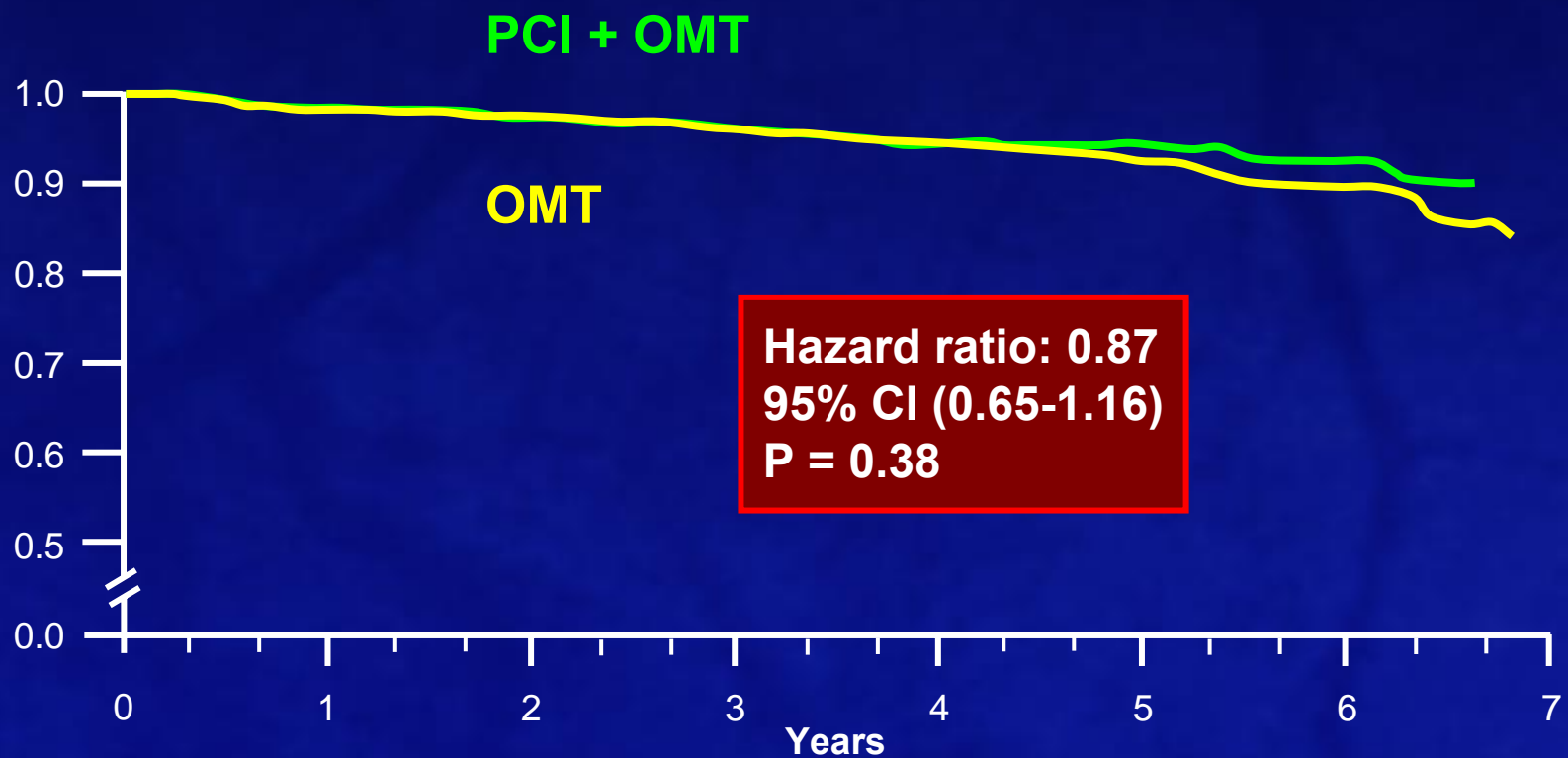


Number at Risk

	0	1	2	3	4	5	6	7
Medical Therapy	1138	1017	959	834	638	408	192	30
PCI	1149	1013	952	833	637	417	200	35



Overall Survival

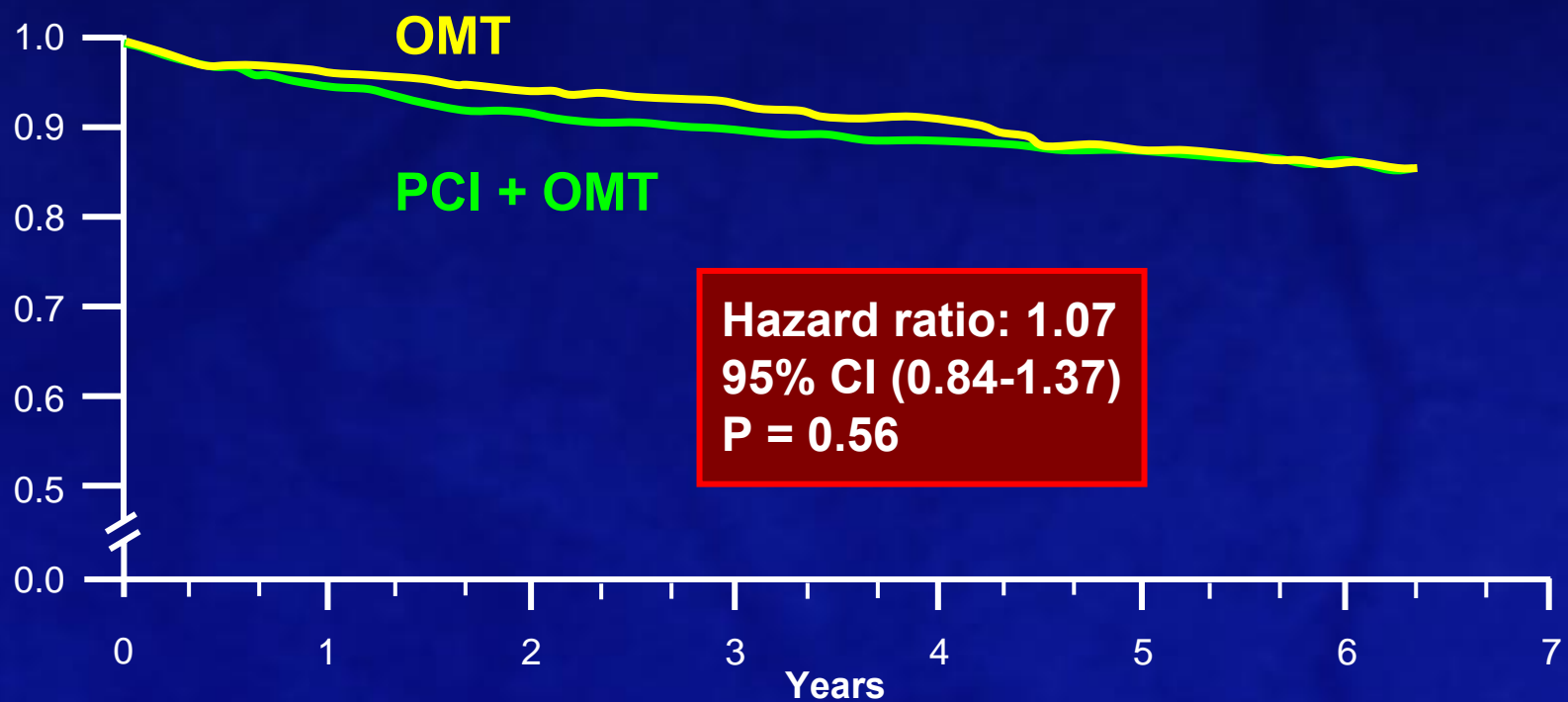


Number at Risk

	0	1	2	3	4	5	6	7
Medical Therapy	1138	1073	1029	917	717	468	302	38
PCI	1149	1094	1051	929	733	488	312	44



Survival Free of Hospitalization for ACS

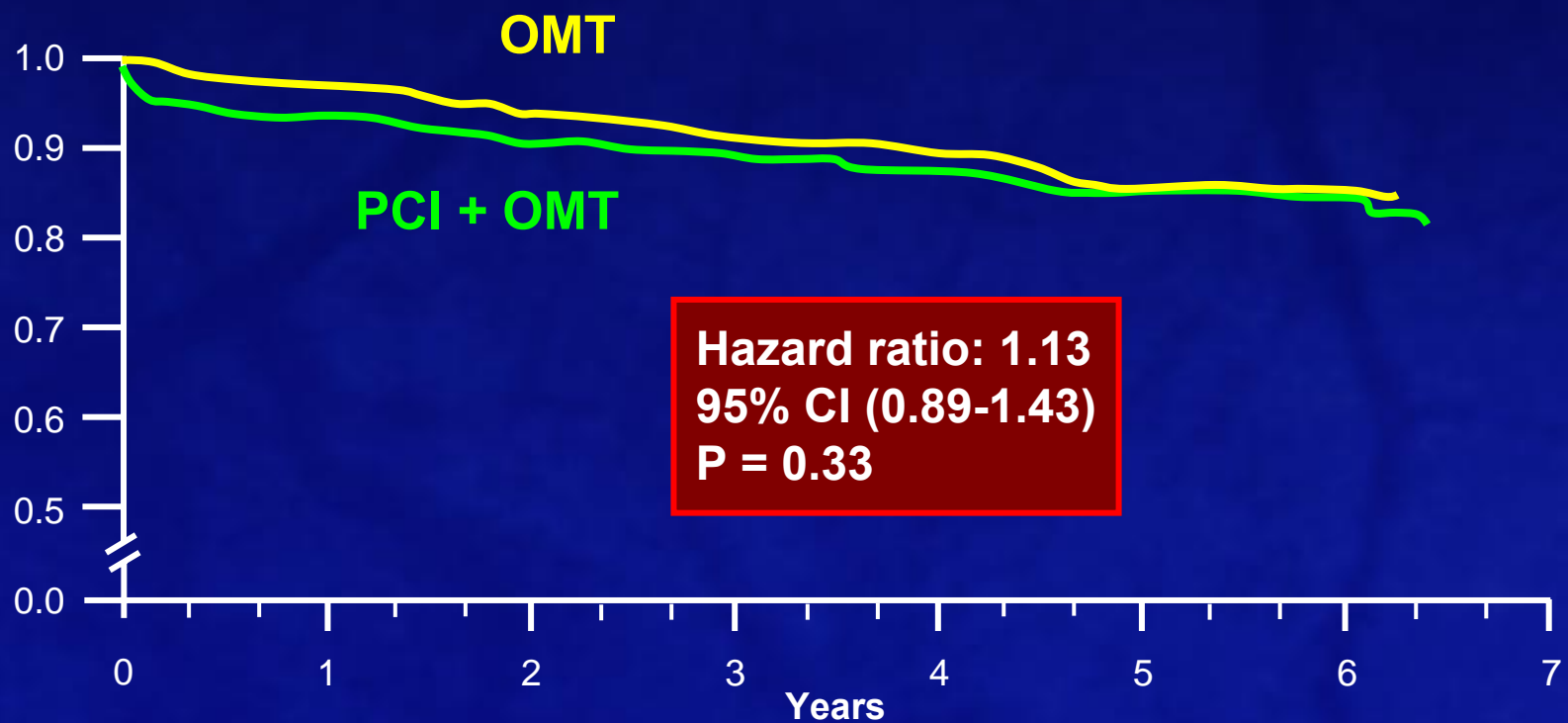


Number at Risk

	0	1	2	3	4	5	6	7
Medical Therapy	1138	1025	956	833	662	418	236	127
PCI	1149	1027	957	835	667	431	246	134



Survival Free of Myocardial Infarction



Number at Risk

	0	1	2	3	4	5	6	7
Medical Therapy	1138	1019	962	834	638	409	192	120
PCI	1149	1015	954	833	637	418	200	134



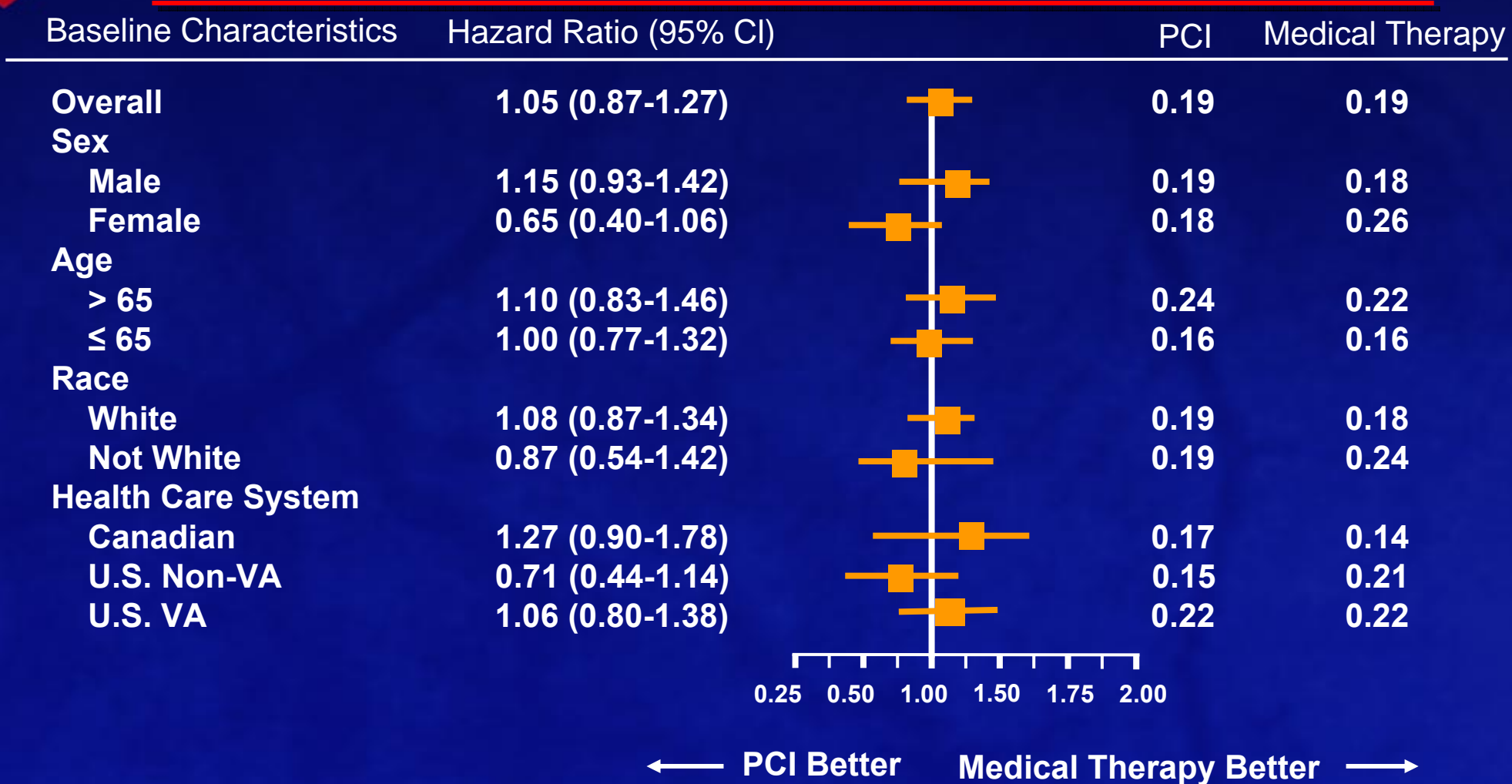
Freedom from Angina During Long-Term Follow-up

Characteristic	PCI + OMT	OMT
CLINICAL		
Angina free – no.		
Baseline	12%	13%
1 Yr	66%	58%
3 Yr	72%	67%
5 Yr	74%	72%

The comparison between the PCI group and the medical-therapy group was significant at 1 year ($P < 0.001$) and 3 years ($P = 0.02$) but not at baseline or 5 years.

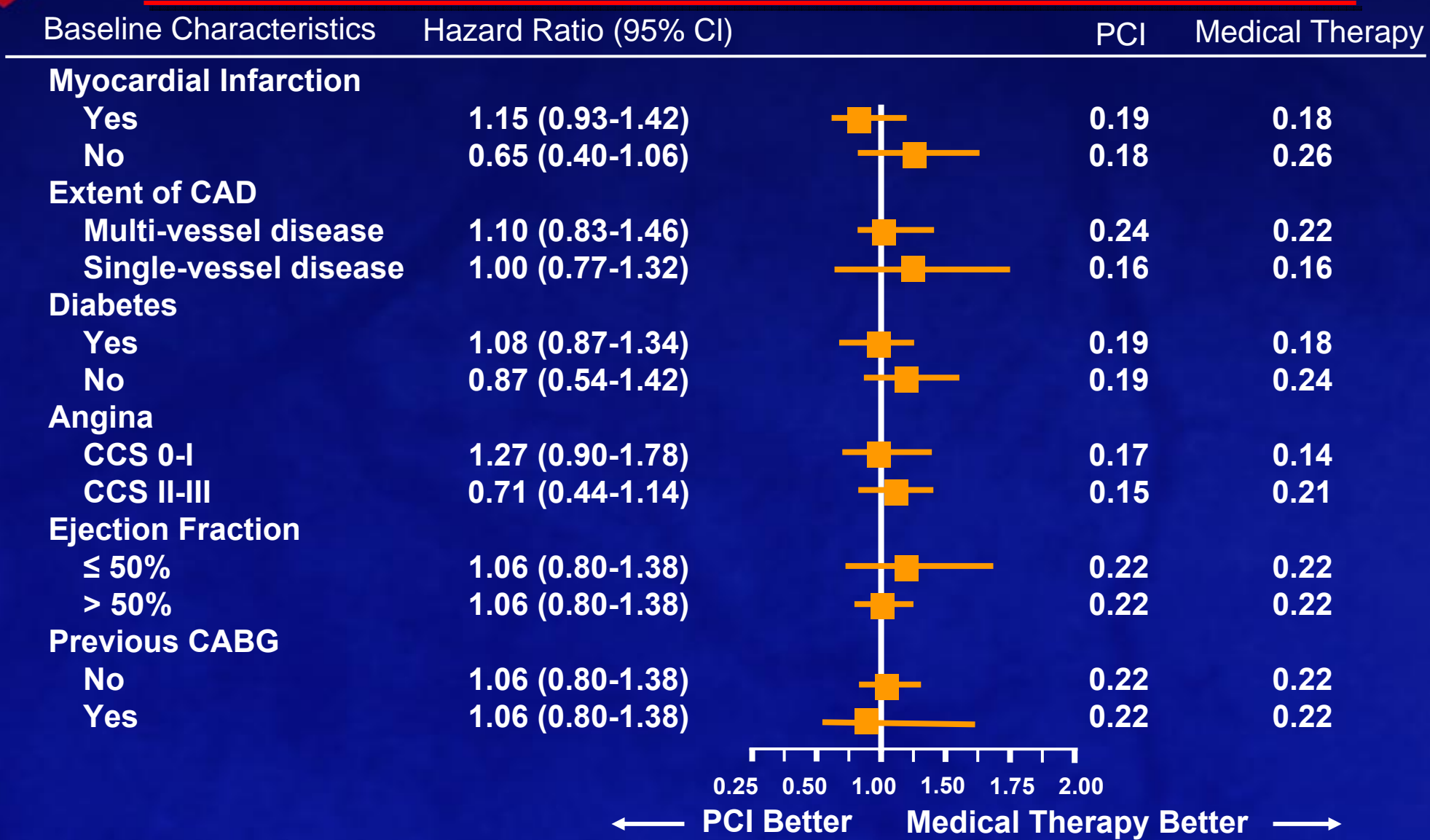


Subgroup Analyses





Subgroup Analyses





Conclusions

- As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to optimal medical therapy
- As expected, PCI resulted in better angina relief during most of the follow-up period, but medical therapy was also remarkably effective, with no between-group difference in angina-free status at 5 years



Implications

- Our findings reinforce existing ACC/AHA clinical practice guidelines, which state that PCI can be safely deferred in patients with stable CAD, even in those with extensive, multivessel involvement and inducible ischemia, provided that intensive, multifaceted medical therapy is instituted and maintained
- Optimal medical therapy and aggressive management of multiple treatment targets without initial PCI can be implemented safely in the majority of patients with stable CAD—two-thirds of whom may not require even a first revascularization during long-term follow-up