The Interventional Trials of the Year: 2006-2007 (TCT, AHA, and ACC)

Roxana Mehran, MD
Associate Professor of Medicine

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

The best of…LBCT

- Adjunct Pharmacology ACS, AMI (ACUITY 30-day, 1 Year, ISAR-REACT 2)

- DES in AMI (TYPHOON, PASSION), DES in the real world (SORT OUT), DES in Bifurcations (Nordic Bif study)

- New Drug-Eluting Stents (ZOMAXX I, SPIRIT III, ENDEAVOR Safety, RESOLUTE, and ABSORB)

- Anti PCI Trials! (OAT and COURAGE)

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ACUITY

A Prospective, Randomized Trial of Bivalirudin in Acute Coronary Syndromes

30- day (ACC-06), and Final One-Year Results (ACC-07) from the ACUITY Trial

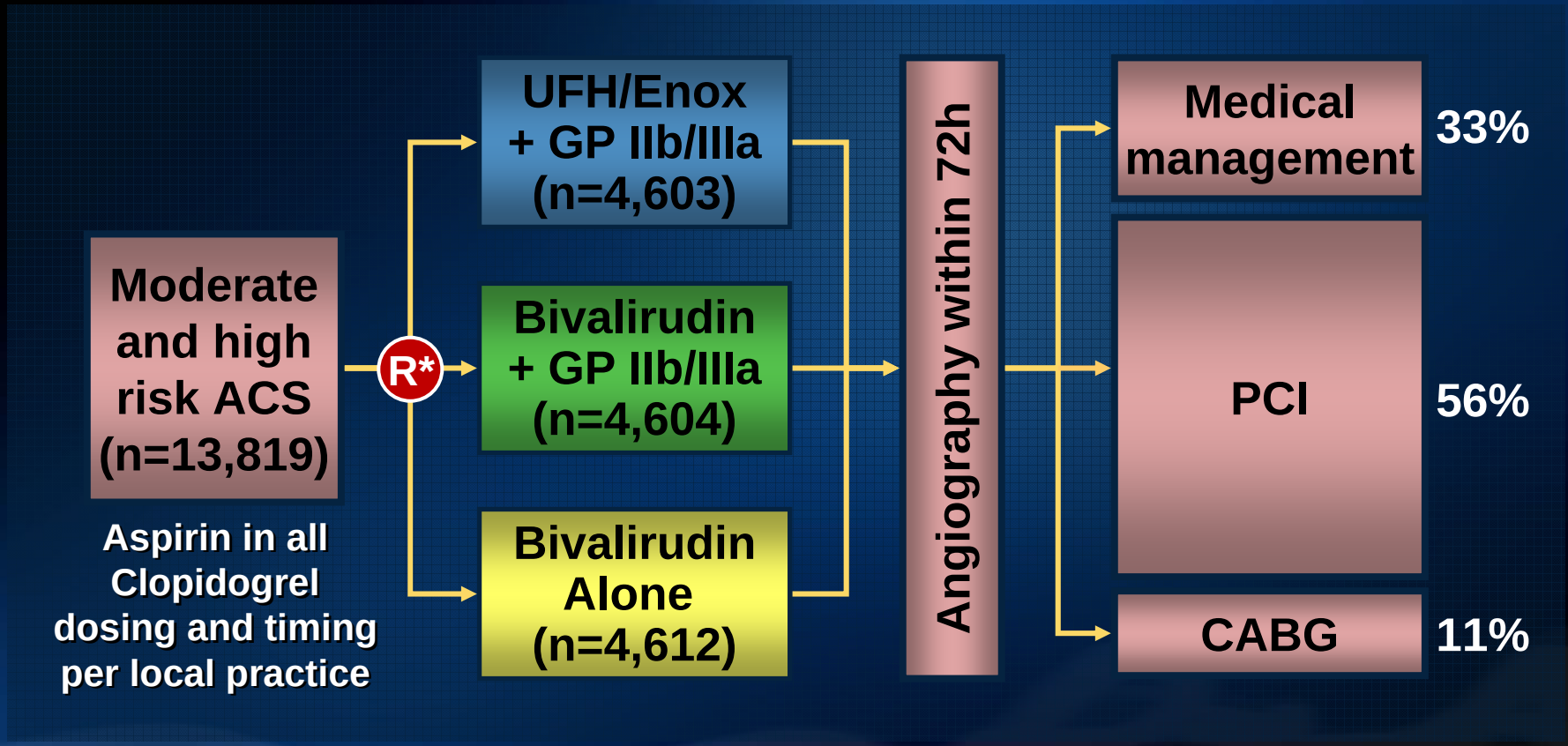
Gregg W. Stone MD

for the **ACUITY Investigators**

ACUITY

Study Design – First Randomization

Moderate and high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,819)



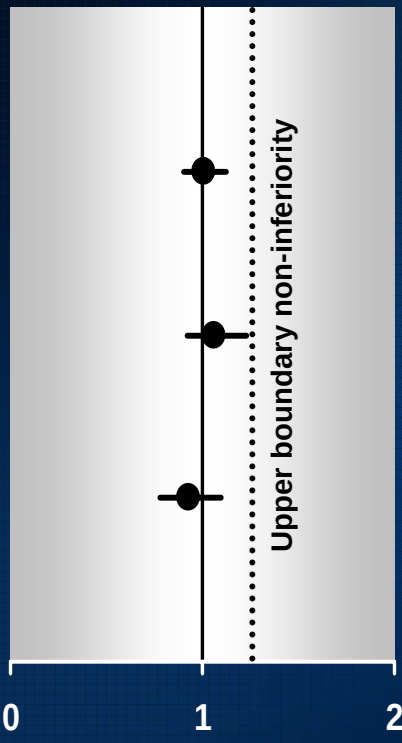
*Stratified by pre-angiography thienopyridine use or administration

ACUITY

Primary Endpoint Measures (ITT) – 30 Days

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI

Primary endpoint	Risk ratio ±95% CI	Bival + IIb/IIIa	UFH/Enox + IIb/IIIa	RR (95% CI)	p value (non inferior) (superior)
Net clinical outcome		11.8%	11.7%	1.01 (0.90-1.12)	<0.001 0.93
Ischemic composite		7.7%	7.3%	1.07 (0.92-1.23)	0.015 0.39
Major bleeding		5.3%	5.7%	0.93 (0.78-1.10)	<0.001 0.38

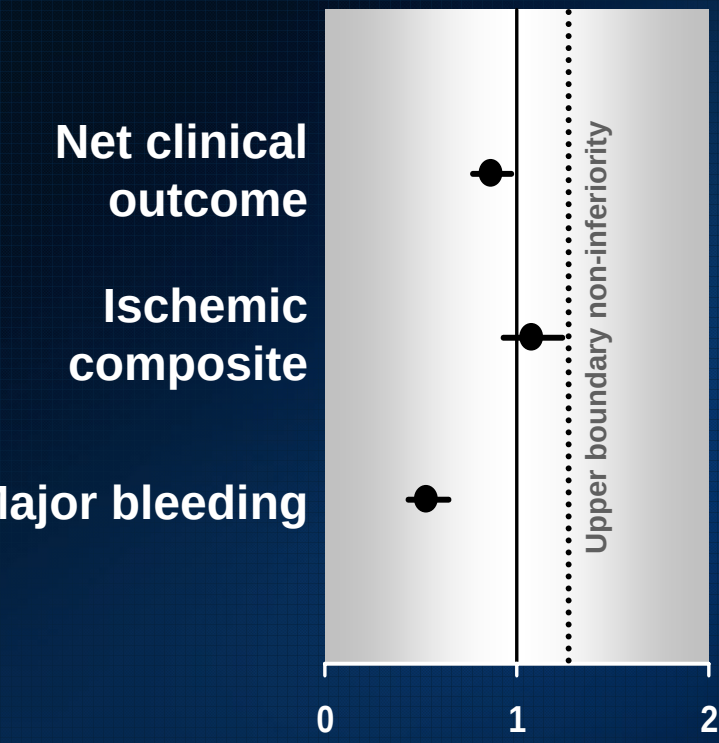


Bivalirudin + IIb/IIIa better UFH/Enox + IIb/IIIa better

Primary Endpoint Measures (ITT) – 30 Days

UFH/Enoxaparin + GPI vs. Bivalirudin Alone

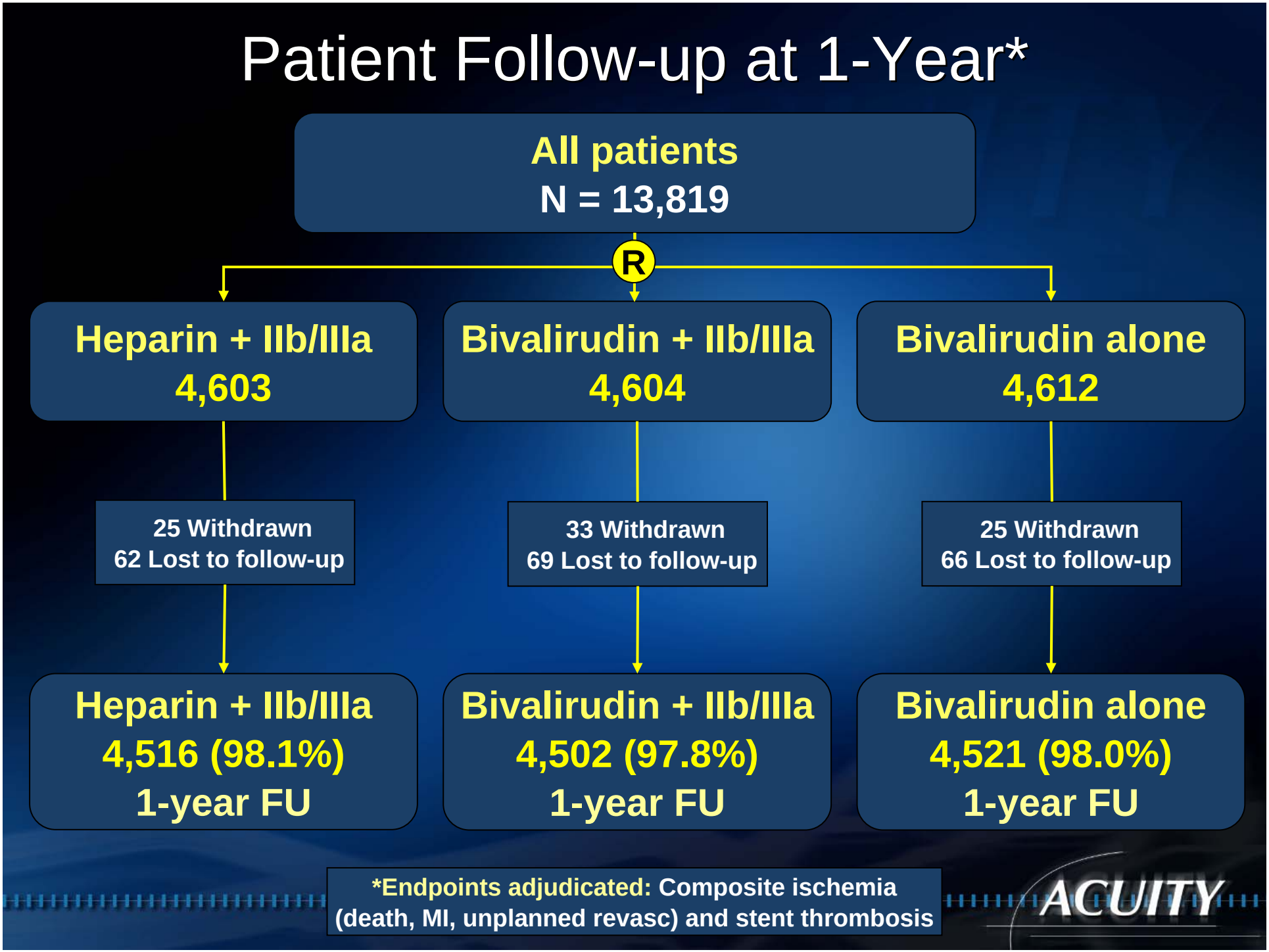
Primary endpoint	Bival alone	UFH/Enox + IIb/IIIa	RR (95% CI)	p value (non inferior) (superior)
Net clinical outcome	10.1%	11.7%	0.86 (0.77-0.97)	<0.001 0.015
Ischemic composite	7.8%	7.3%	1.08 (0.93-1.24)	0.01 0.32
Major bleeding	3.0%	5.7%	0.53 (0.43-0.65)	<0.001 <0.001



Stone GW et al. NEJM 2006;355:2203-16

ACUITY

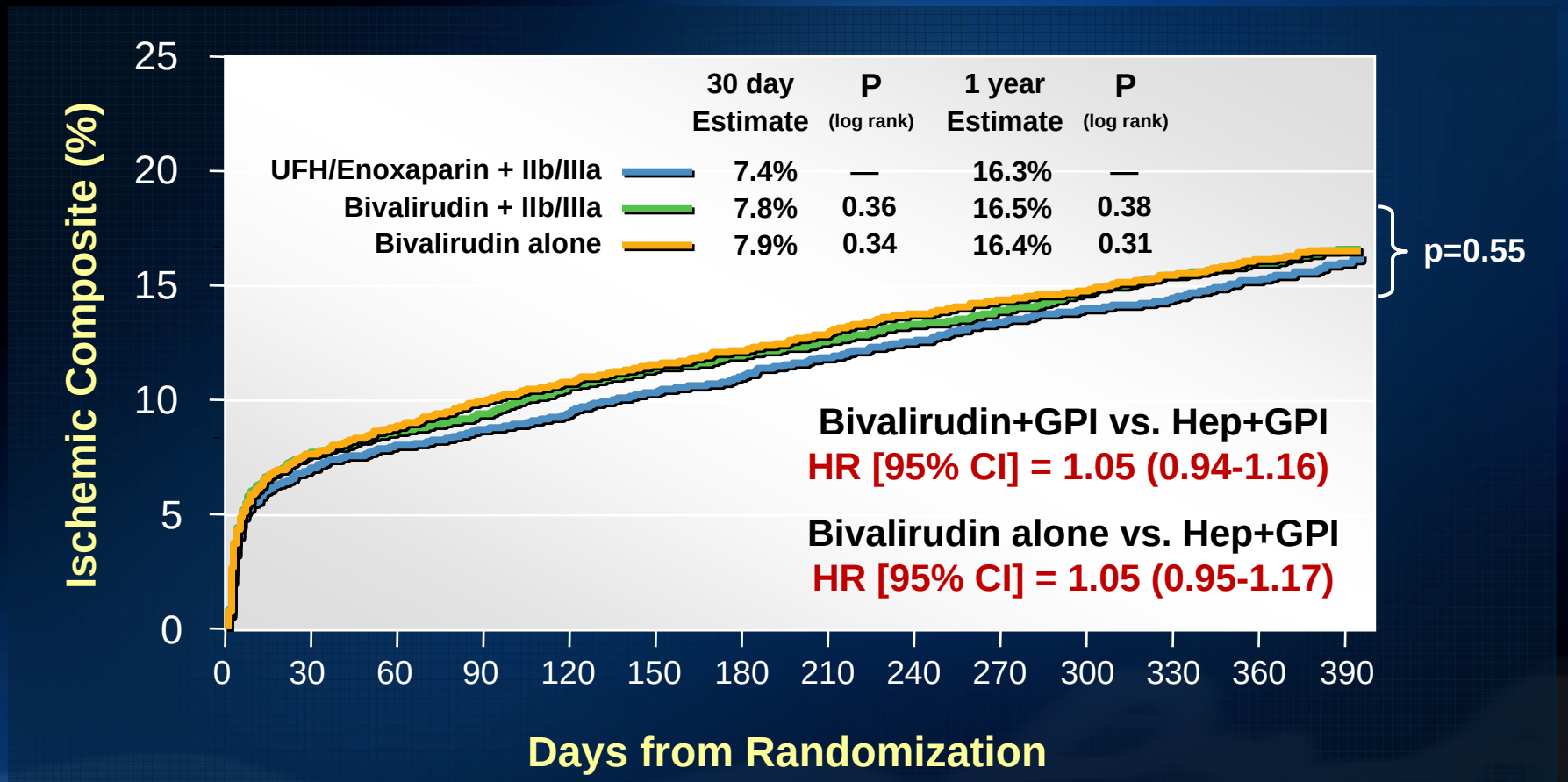
Patient Follow-up at 1-Year*



Ischemic Composite Endpoint

(Death, MI, unplanned revascularization for ischemia)

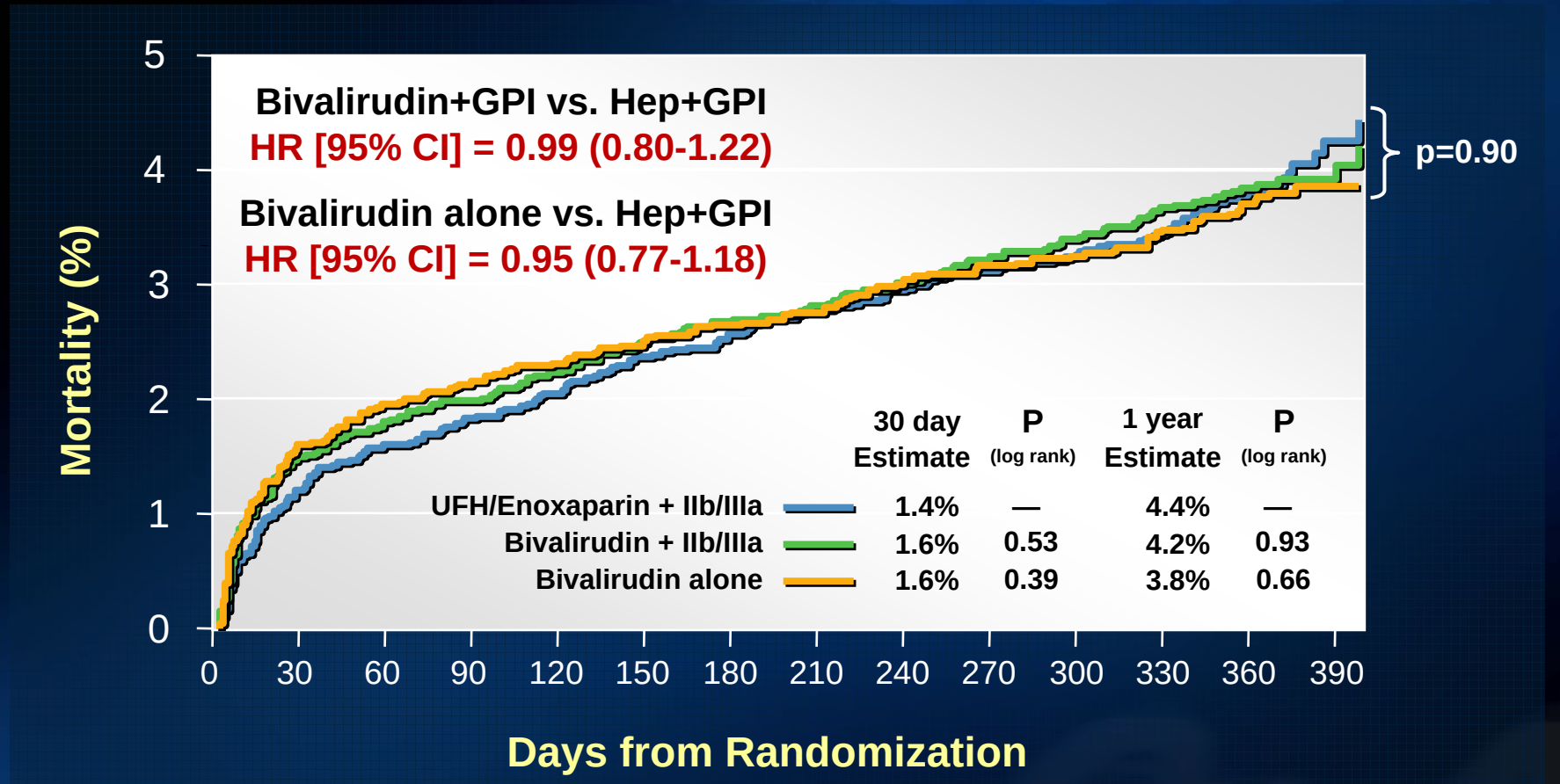
UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone



ACUITY

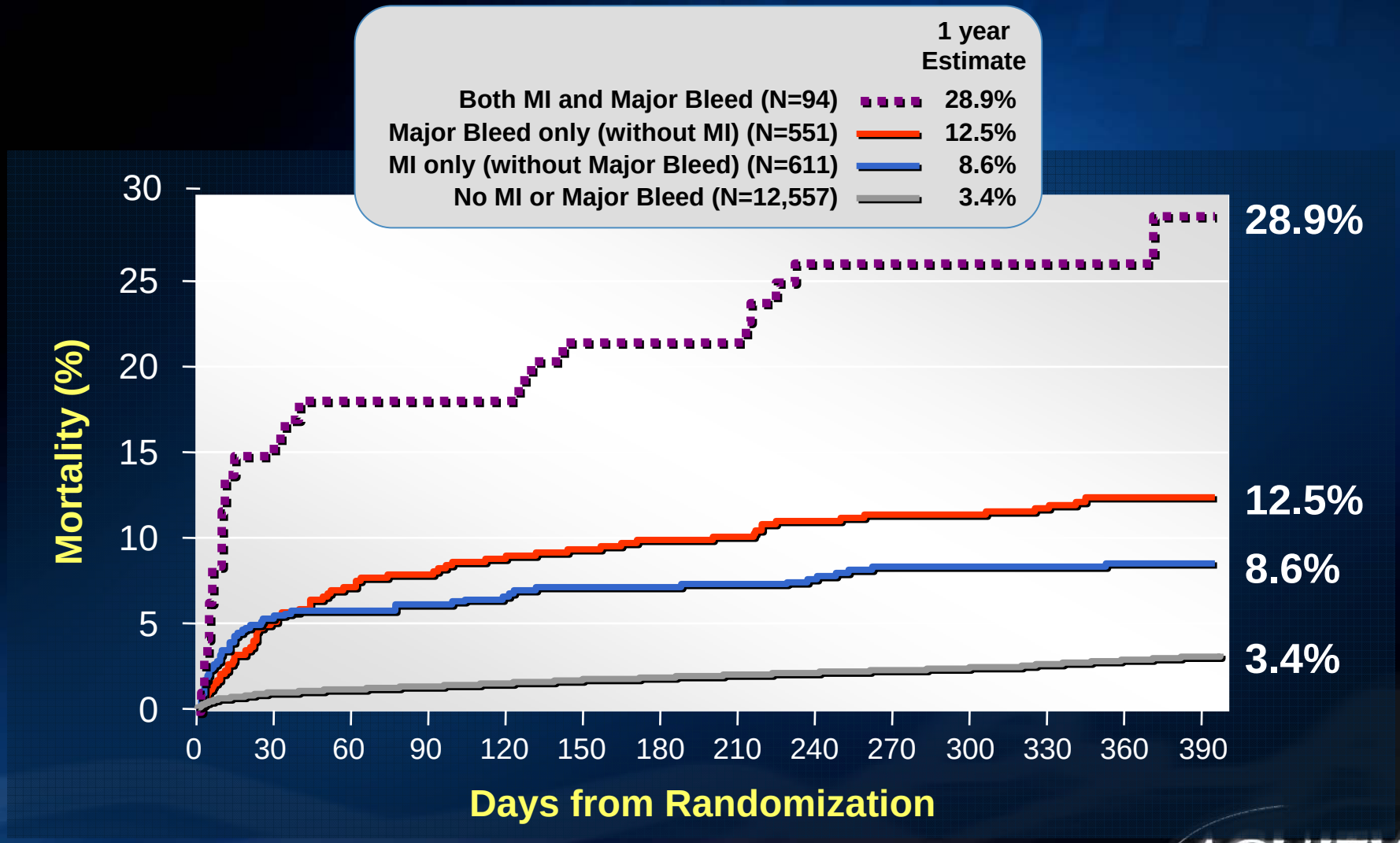
Mortality: 524 total deaths at 1-year

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone



ACUITY

Impact of MI and Major Bleeding (non-CABG) in the First 30 Days on Risk of Death Over 1 Year



ACUITY

ISAR-REACT 2 Trial

2022 High Risk ACS patients undergoing PCI

Accelerating or rest angina within 48 hours with either: (1) Tn-T > 0.03 ugL or (2) new ischemic EKG changes

Clopidogrel
600 mg x 1 (> 2 hr pre PCI)
75 mg/d x 30 days

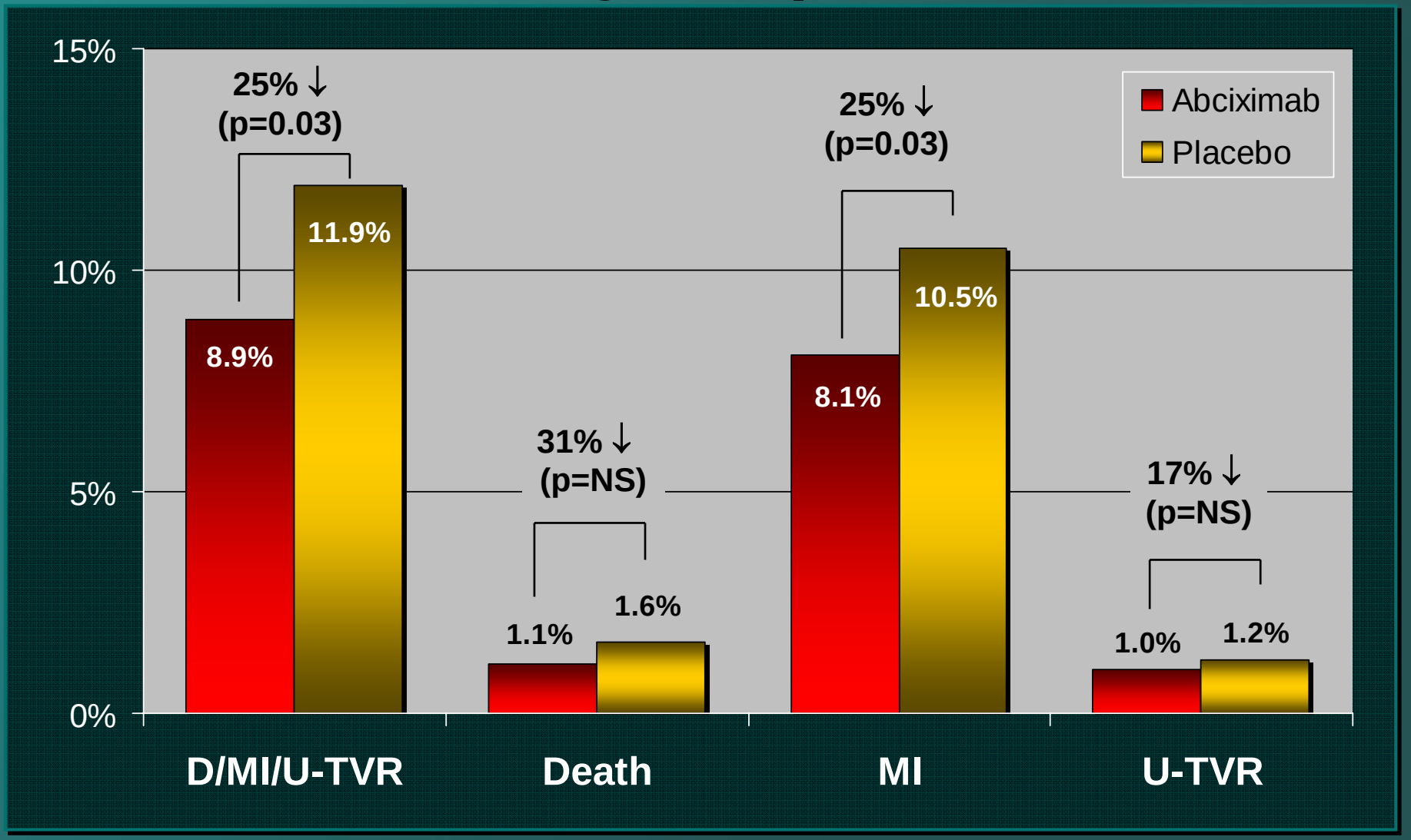
Abciximab (n=1012)

Placebo (n=1010)

Primary endpoint
30-day death, MI, U-TVR

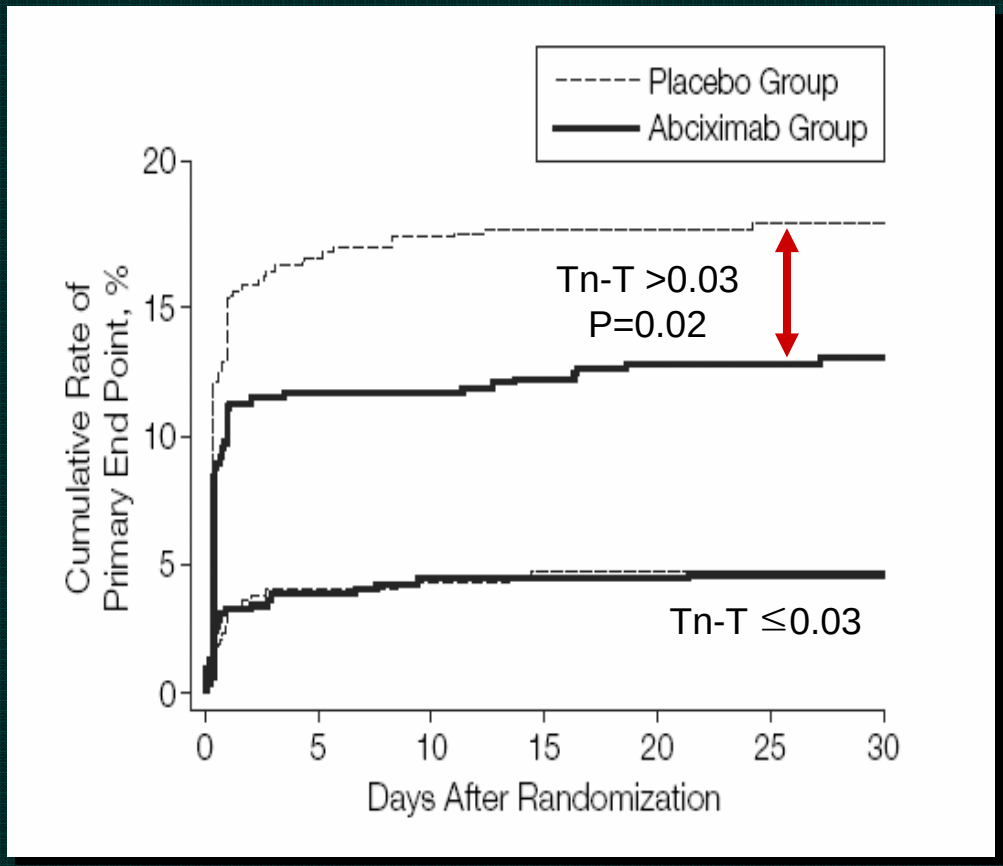
ISAR-REACT 2

30-day endpoints



ISAR-REACT 2

1ry endpt benefit with IIb/IIa and troponin elevation



- **Benefit of abciximab restricted to subgroup with elevated Troponin at time of PCI**
  - **TnT > 0.03 RR = 0.71**
  - **TnT ≤ 0.03 RR = 0.99**
- **Similar findings in PURSUIT, CAPTURE, TACTICS**

Kastrati A et al. JAMA 2006;295:1531-8

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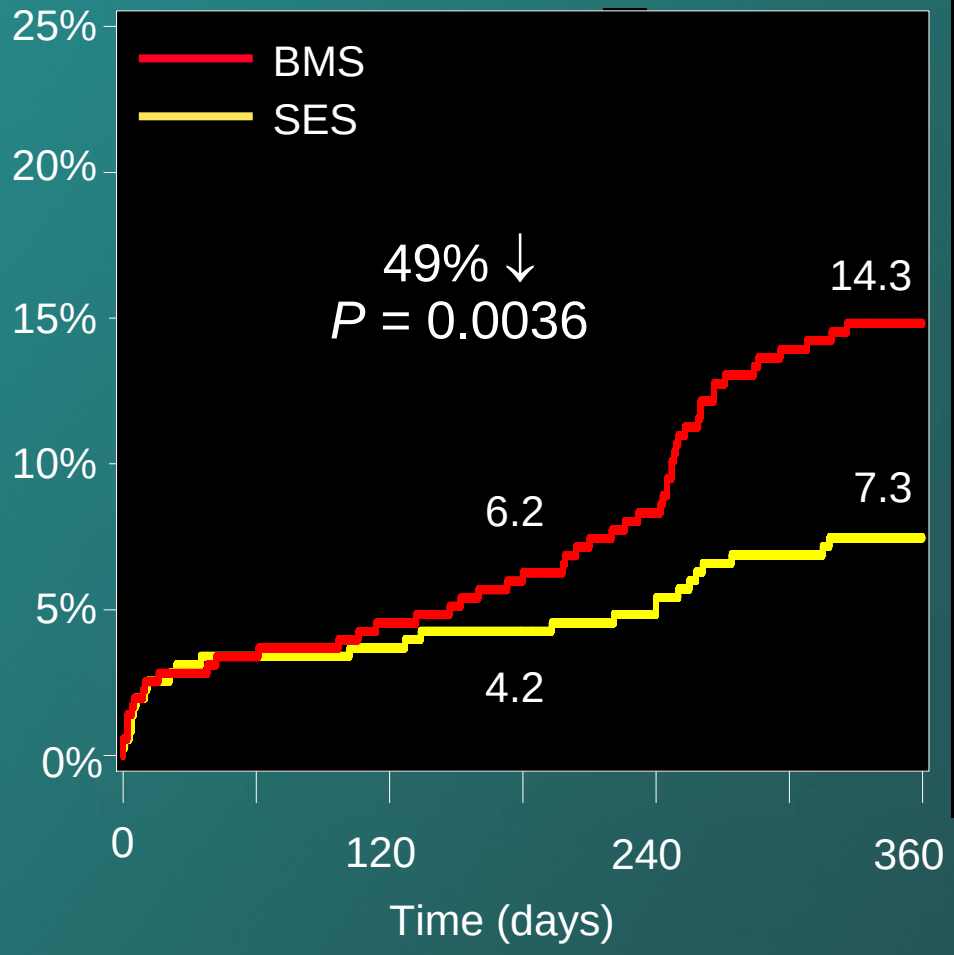
TYPHOON

1° Endpoint: Target Vessel Failure

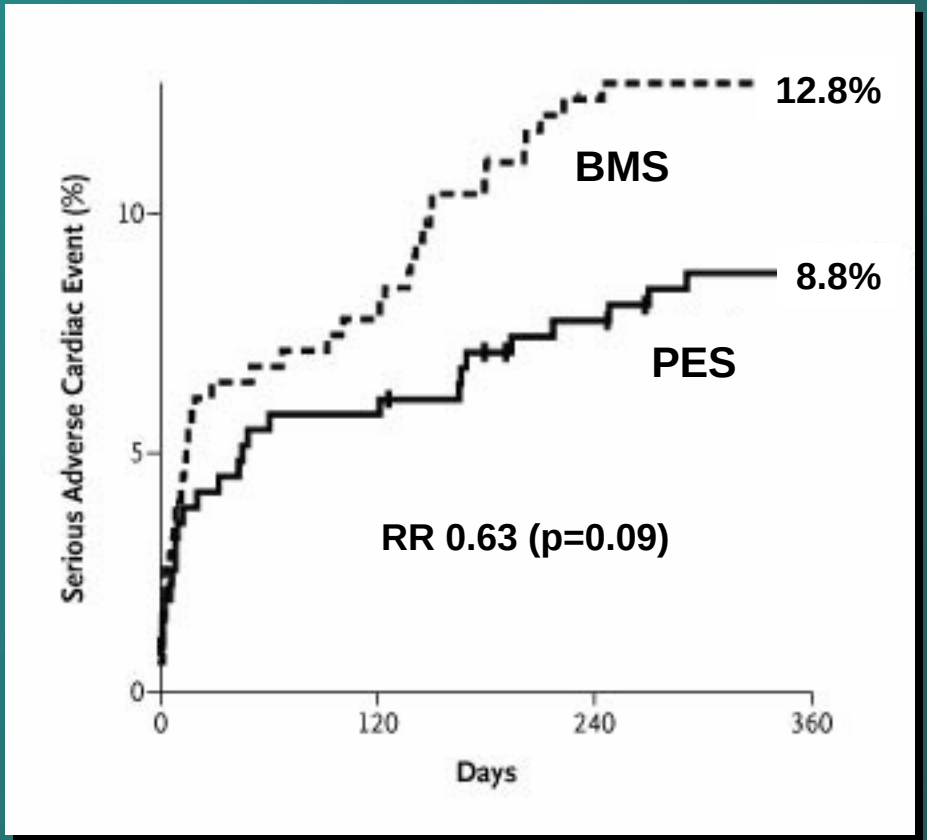


Spaulding C et al. NEJM 2006;355:1093-1104

- **712 pts within 12 hrs of AMI**
- **Randomized to SES vs. any approved BMS**
- **Primary endpoint: Target vessel failure (TV-related death, re-MI, or TVR) at 1 year**
- **Key issues**
  - ***Dual antiplatelet >6 months***
  - ***Angio. Substudy at 8 months in 210 pts (29% of overall)***
- ***Benefit entirely due to reduced TLR (3.7 vs. 12.6%)→ no excess late MI or stent thrombosis***

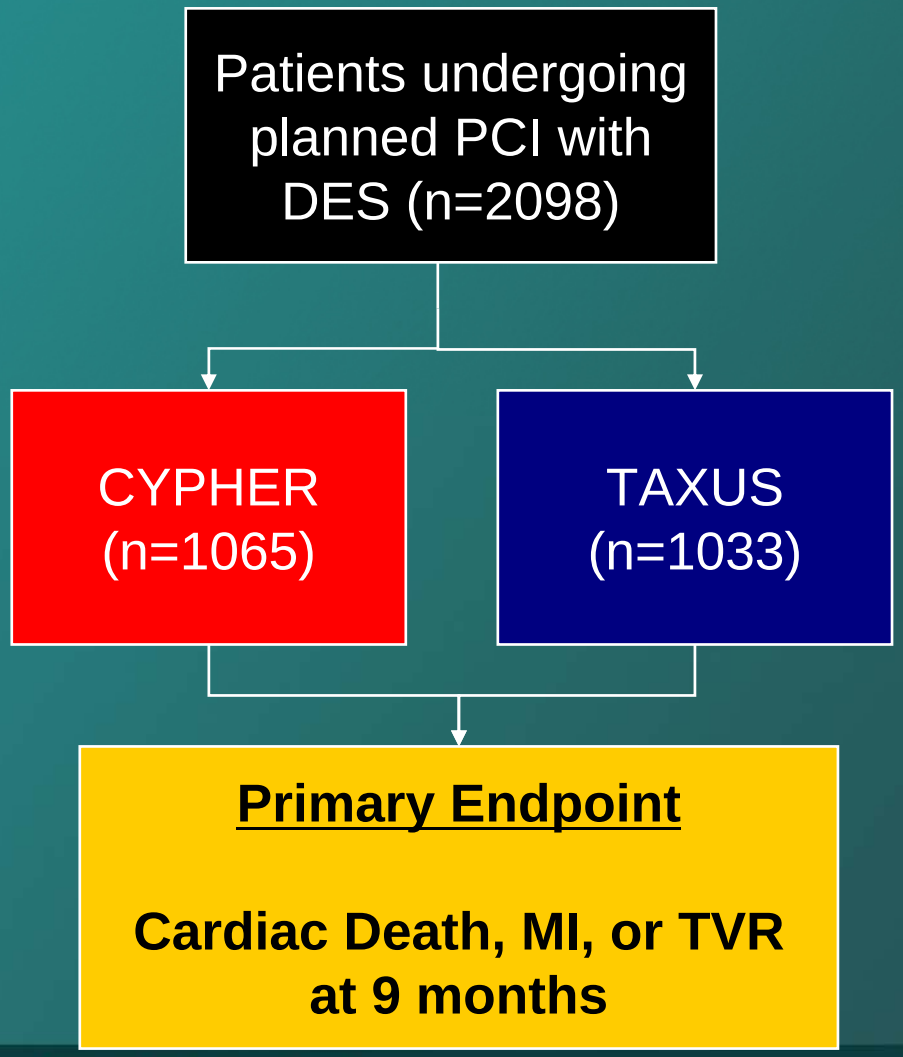
PASSION

1° Endpoint: Death/MI/TLR



- 619 pts presenting within 6 hrs or AMI at 2 study centers
- Randomized to PES vs. Bare Express Stent (double-blind)
- Primary endpoint: Composite of death, MI, or TLR
- Patients managed according to standard practice without routine angiographic f/u
- Main Result: No benefit on primary endpoint although trends toward lower TLR

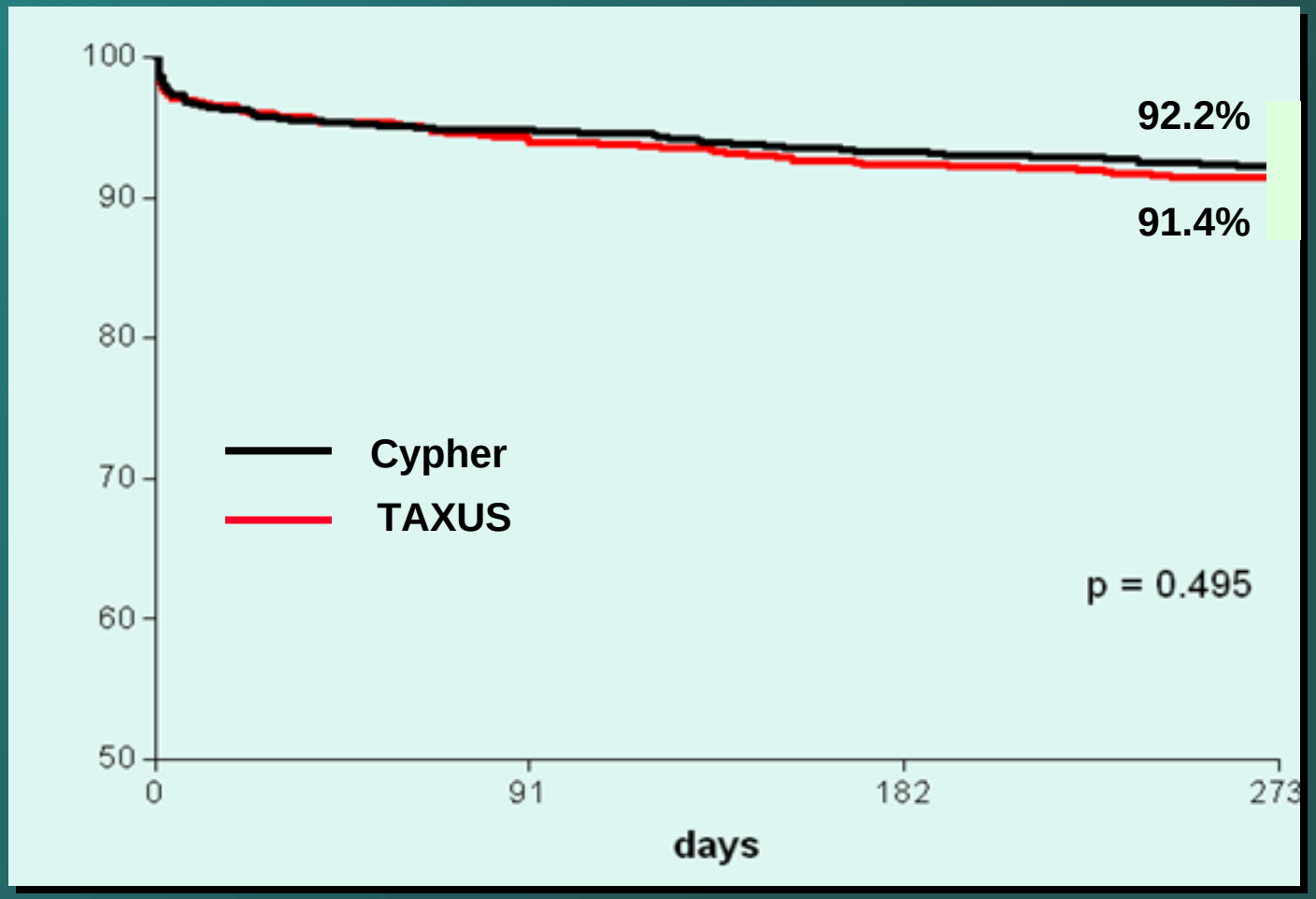
SORT-OUT Trial



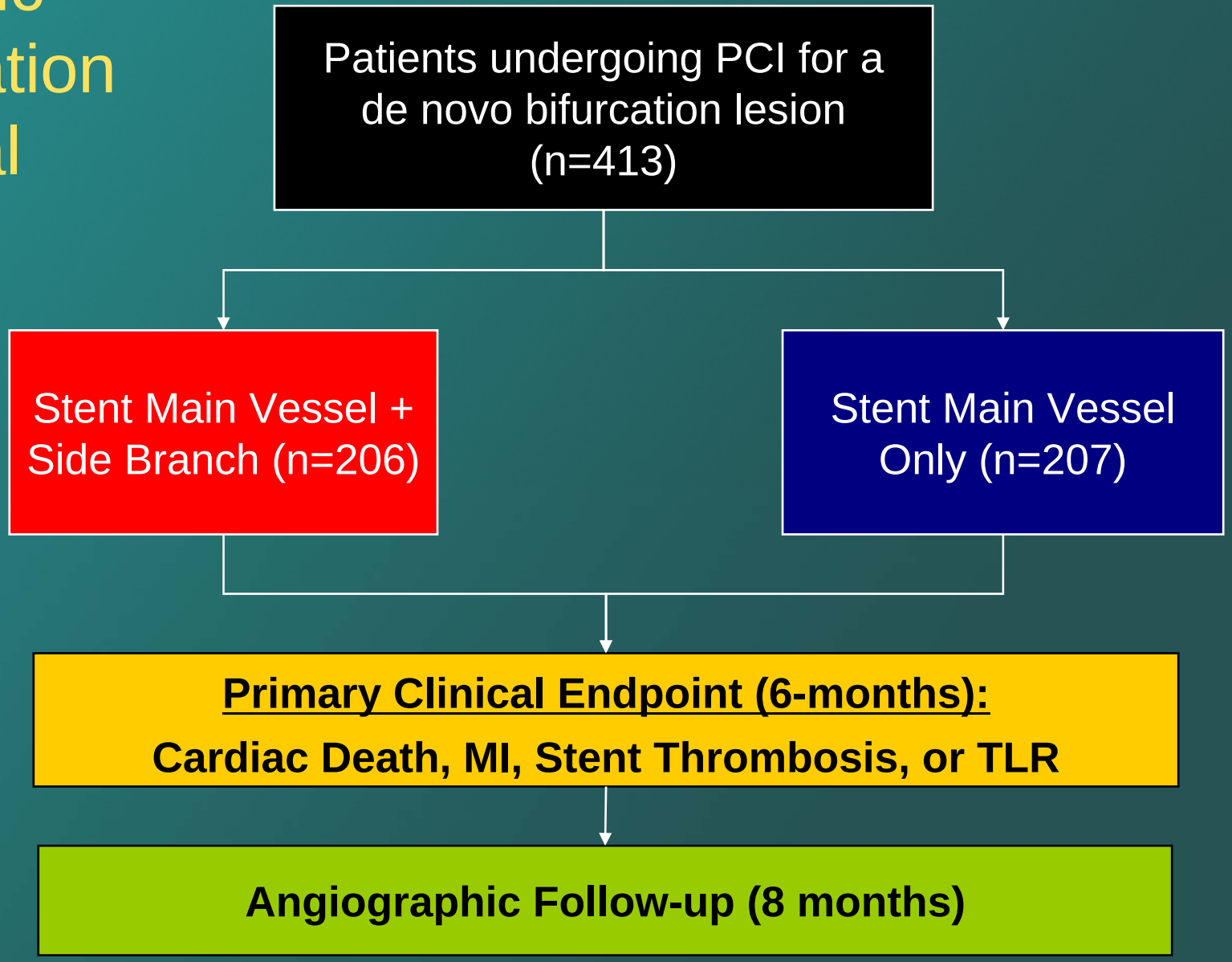
Key Trial Features

- **Involved all 5 university centers in Denmark**
- **Very high participation→ ~20% of all pts enrolled during recruitment period**
- **No mandatory angiographic or clinical f/u at all→ all events ascertained through national health database and death registry (true "real world" trial)**

Primary Endpoint: Cardiac Death, MI, TLR at 9 months



Nordic Bifurcation Trial



Thuesen L et al. Circulation 2006;114:1955-61

6-month Clinical Outcomes

Outcome	MV + SB	MV only	P-value
1° Composite	3.4%	2.9%	NS
Cardiac Death	1.0%	1.0%	NS
MI	0.5%	0.0%	NS
TVR	1.9%	1.9%	NS
Stent thrombosis	0.5%	0.0%	NS
Periprocedural MI (CKMB>3x)	18%	8%	0.011
CCS class > 1 at 6 mos	8.6%	9.2%	NS

Thuesen L et al. Circulation 2006;114:1955-61

Angiographic Outcomes

Outcome	MV + SB	MV only	P-value
Mai… rest…			…S
Side… rest…			.06
Any…			…S
Sidebranch occlusion	0.0%	0.5%	NS

Implications

For treatment of bifurcation lesions, stenting the main vessel alone is equally effective as stenting both branches, yet offers substantial advantages in terms of risk, time, and cost

Thuesen L et al. Circulation 2006;114:1955-61

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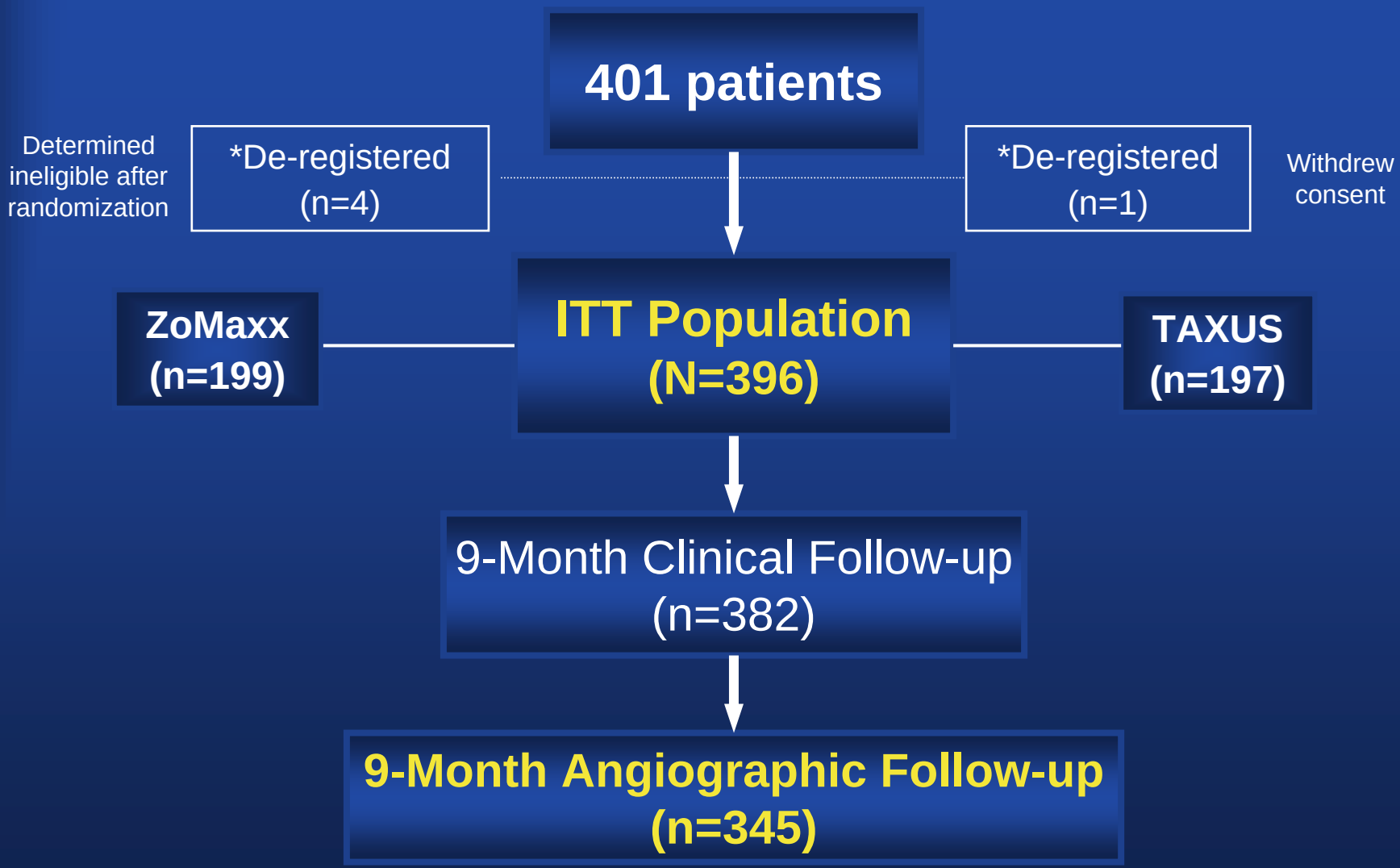
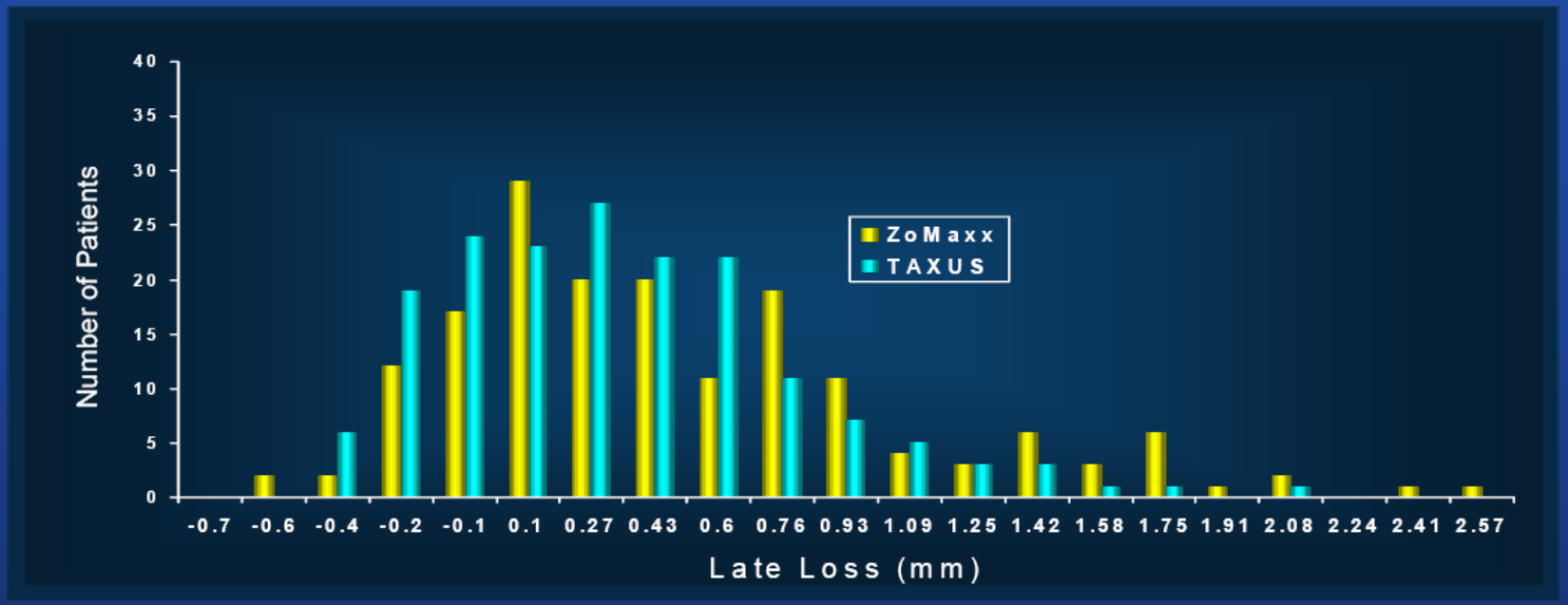
ZOMAXX I


401 patients
Determined ineligible after randomization
*De-registered (n=4)
*De-registered (n=1)
Withdrew consent
ZoMaxx (n=199)
ITT Population (N=396)
TAXUS (n=197)
9-Month Clinical Follow-up (n=382)
9-Month Angiographic Follow-up (n=345)
*no stent implantation attempted
ZOMAXX I

Angiographic Results



Primary Endpoint	ZoMaxx (median)	TAXUS (median)	Median difference	Upper 95% CI
In-segment late loss	0.29 mm	0.22 mm	0.12*	0.21*

*** Met primary non-inferiority endpoint (based on non-parametric testing)**

ZOMAXX I

Angiographic Results

	ZoMaxx (n=170)	Taxus (n=175)	P-Value
In-stent			
Late loss (mm)	0.67 ± 0.57	0.45 ± 0.48	<0.001
Restenosis	12.9%	5.7%	0.03
In-segment			
Late loss (mm)	0.43 ± 0.60	0.25 ± 0.45	0.003
Restenosis	16.5%	6.9%	0.007

ZOMAXX I

Clinical, Angiographic, and IVUS Results from the Pivotal U.S. Randomized SPIRIT III Trial of the XIENCE™ V Everolimus-eluting Coronary Stent System

Gregg W. Stone, MD
for the SPIRIT III Investigators

Study Algorithm

1002 pts enrolled at 65 U.S sites

RVD ≥2.5 mm - ≤3.75 mm; Lesion length ≤28 mm

Max. 2 lesions each in a different epicardial vessel

Pre-rand: ASA ≥ 300 mg, clopidogrel ≥300 mg load unless on chronic Rx

Randomized 2:1 XIENCE V:TAXUS

Stratified by diabetes and intent for 1 vs. 2 lesion treatment

Pre-dilatation mandatory

Everolimus-eluting

XIENCE V

Paclitaxel-eluting

TAXUS

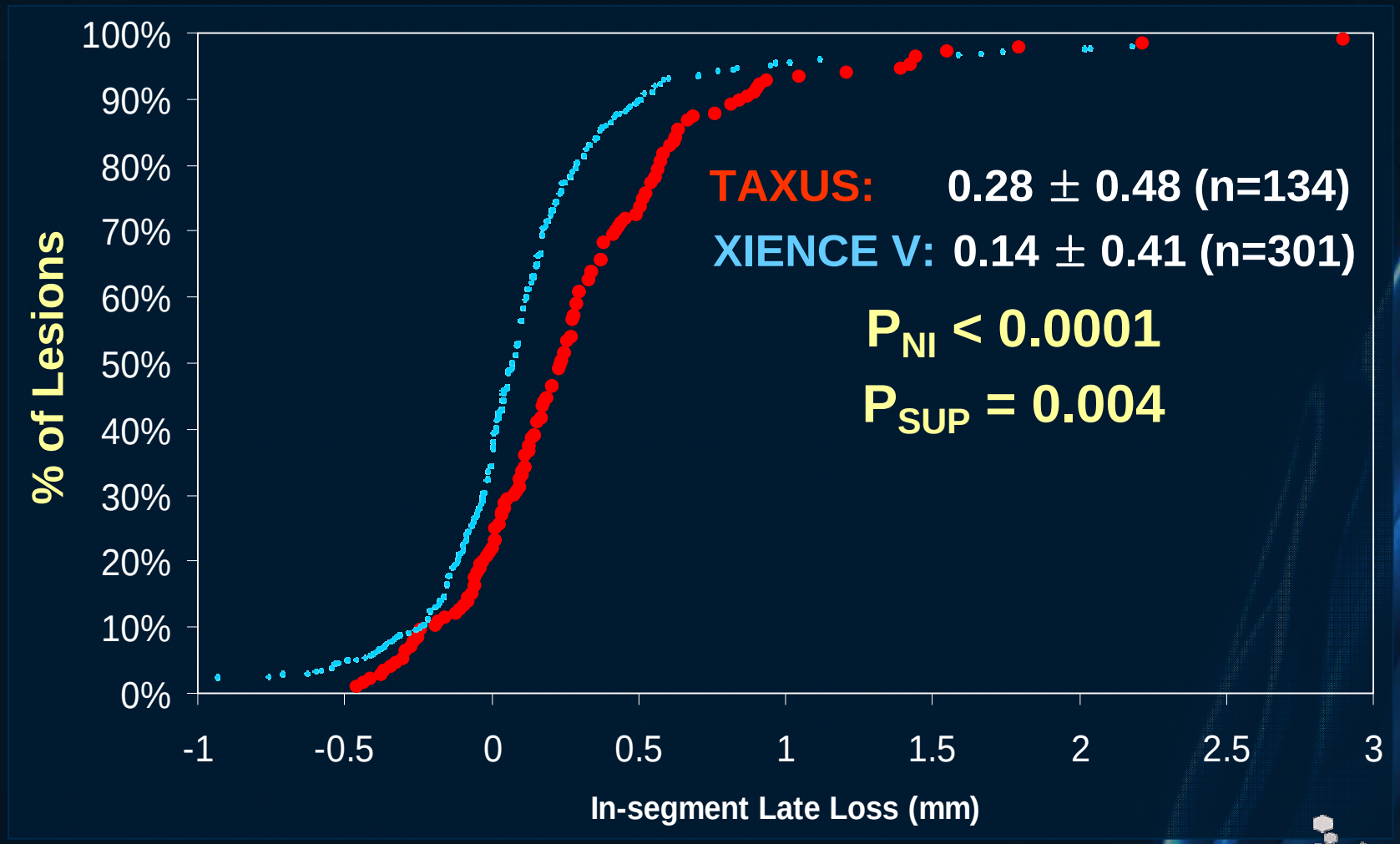
Aspirin ≥ 80 mg QD for 5 years; Clopidogrel 75mg QD for ≥6 months

Clinical f/u: 1, 6, 9 months and yearly for 1-5 years

Angio f/u (N=564) @ 8 mos; IVUS f/u (N=240) @ 8 mos

Primary Endpoint: In-segment LL at 8 Months*

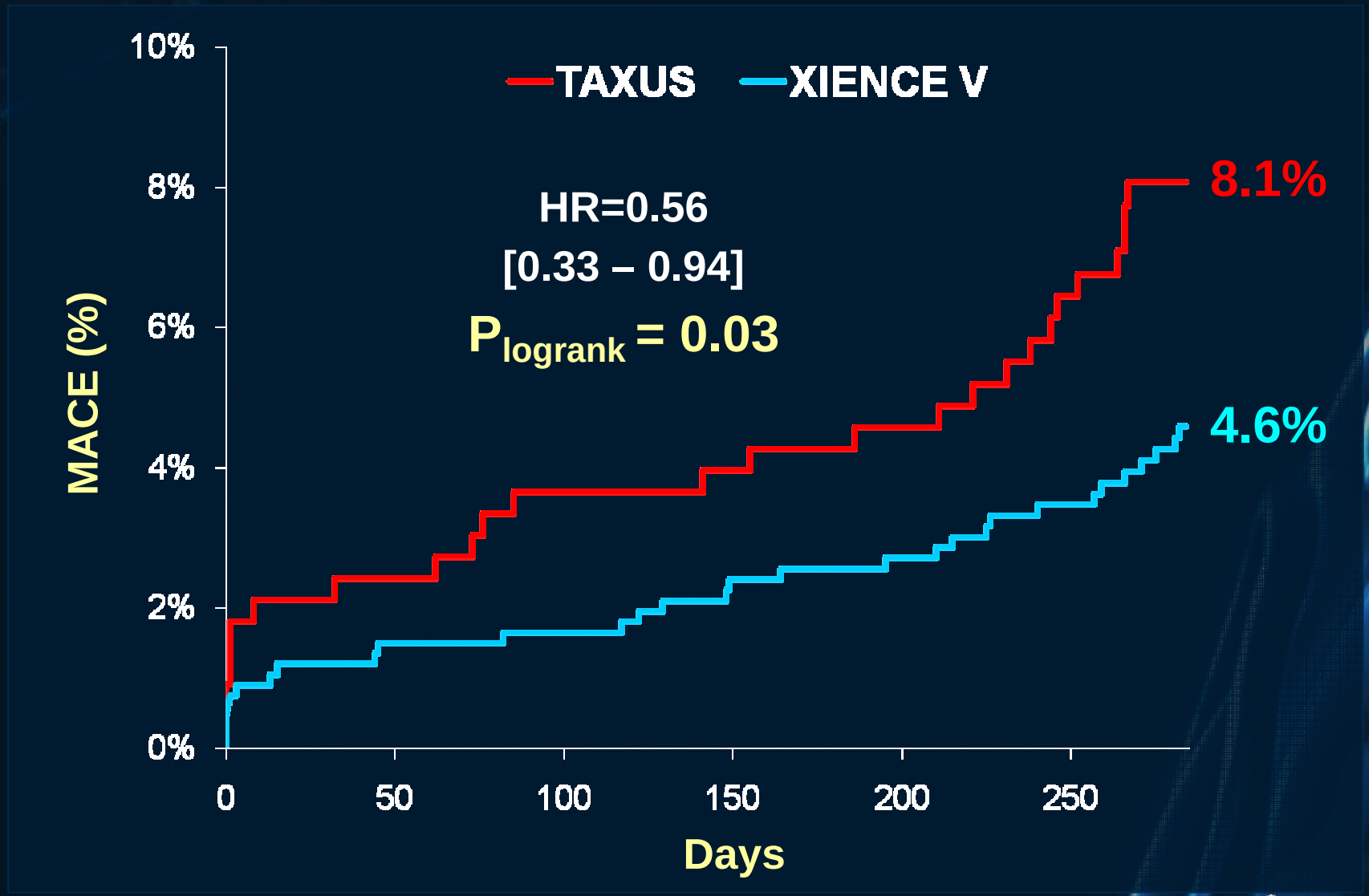
(Analysis Lesion)



*F/U window ±28 days.

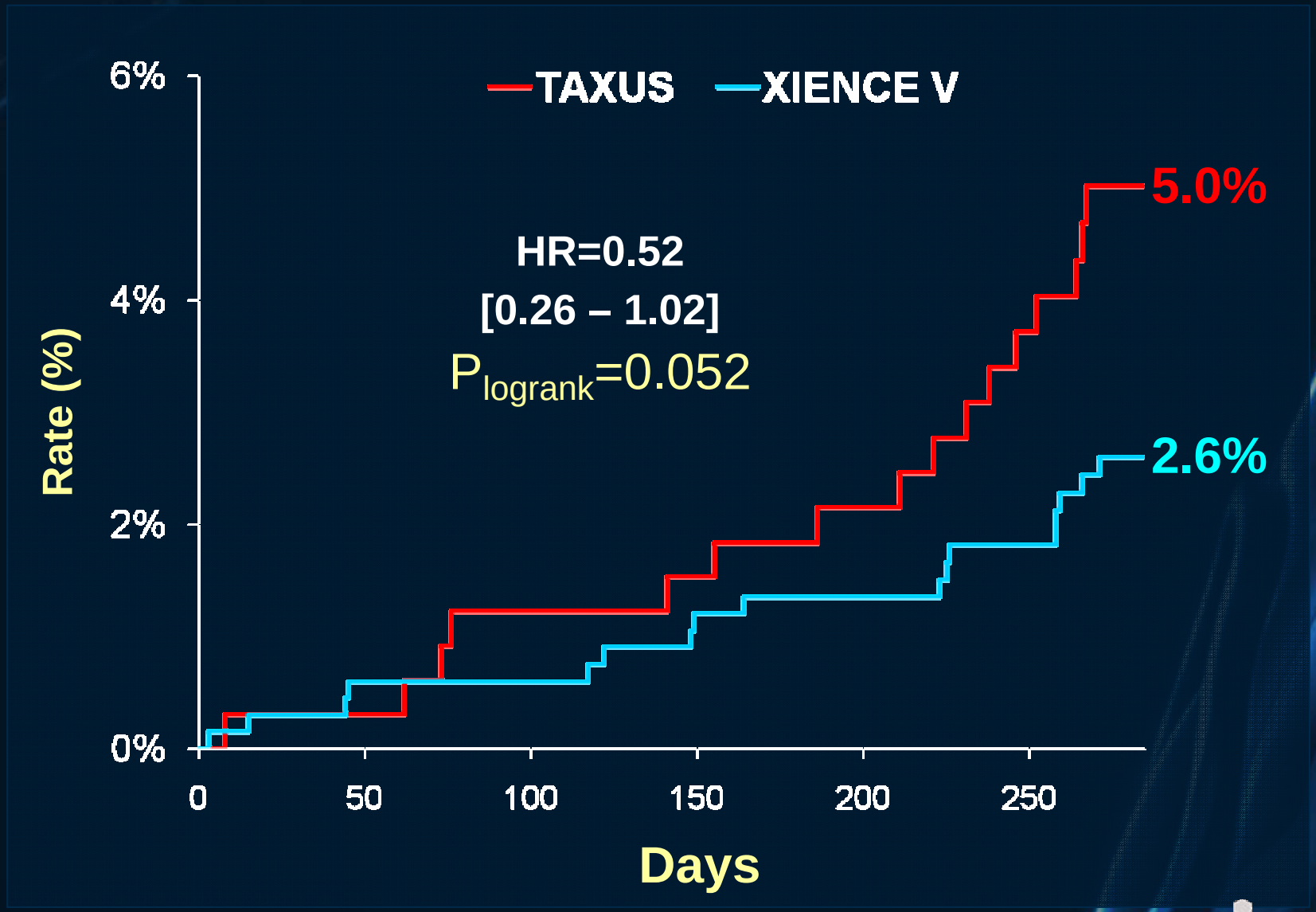
Spirit III

MACE Through 284 Days



Spirit III

Ischemia-driven TLR Through 284 Days



Spirit III

Two-Year Outcomes from the ENDEAVOR III Trial: A Randomized Trial of the Endeavor Zotarolimus-Eluting Stent Compared with the Cypher–Eluting Stent

Martin B. Leon, MD

For the Endeavor III Investigators

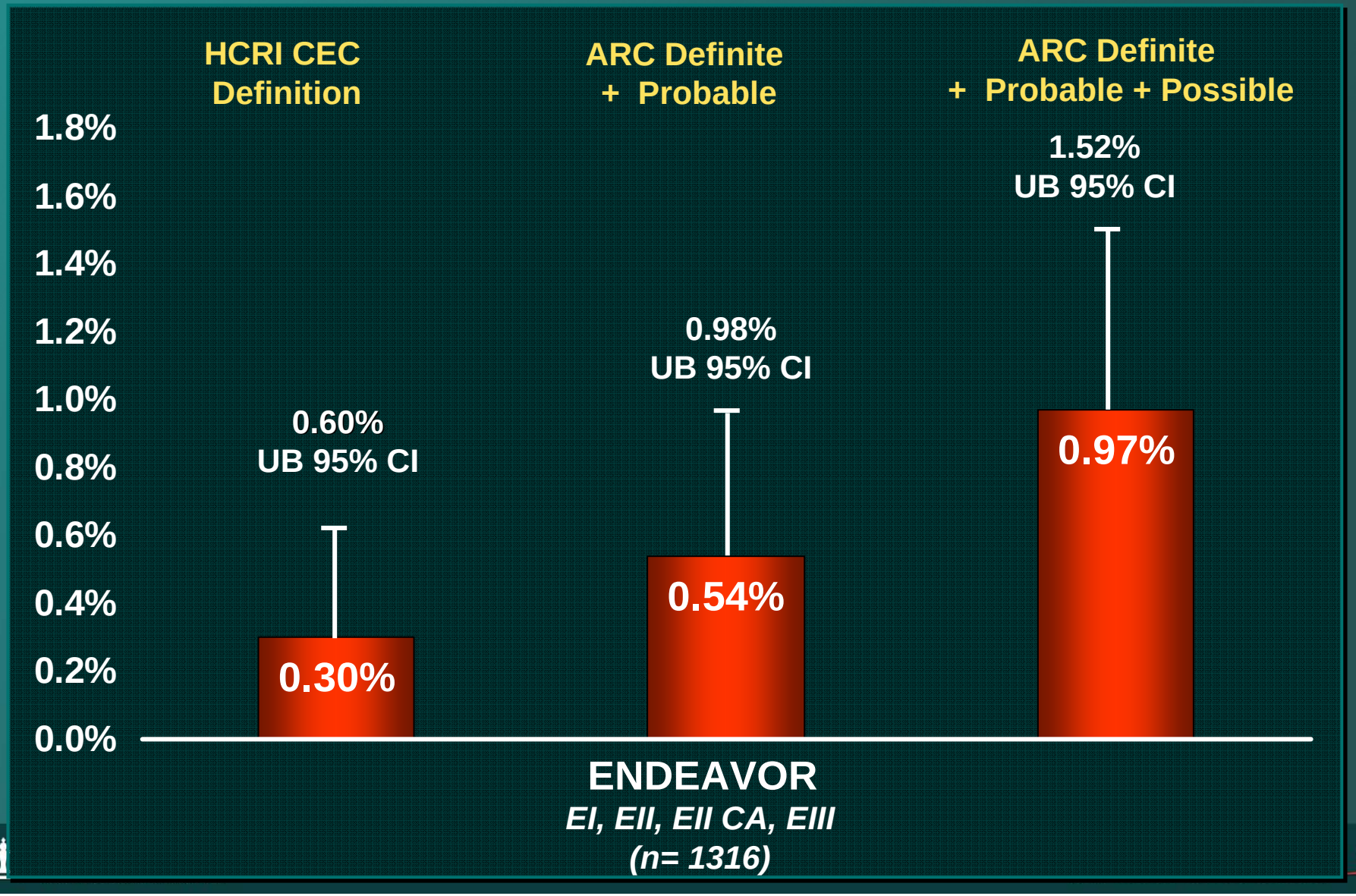
ACC 2007 i2 Symposium
March 26, 2007
New Orleans, LA

Endeavor Clinical Trial Program

ENDEAVOR I	→	Phase I FIM 36 month results
ENDEAVOR II	→	Double-blind Randomized Trial 24 month results
ENDEAVOR II CA Registry	→	Continued Access Safety 24 month results
ENDEAVOR III	→	Endeavor vs. Cypher 24 month results
ENDEAVOR IV	→	Endeavor vs. Taxus 30 day results
Endeavor Japan	→	Single Arm Trial Enrollment completed
E-Five Registry	→	Real-World Performance and Safety Evaluation Enrollment completed
PROTECT	→	Endeavor vs. Cypher Safety Study 8,000 patient RCT

Endeavor Safety Analysis

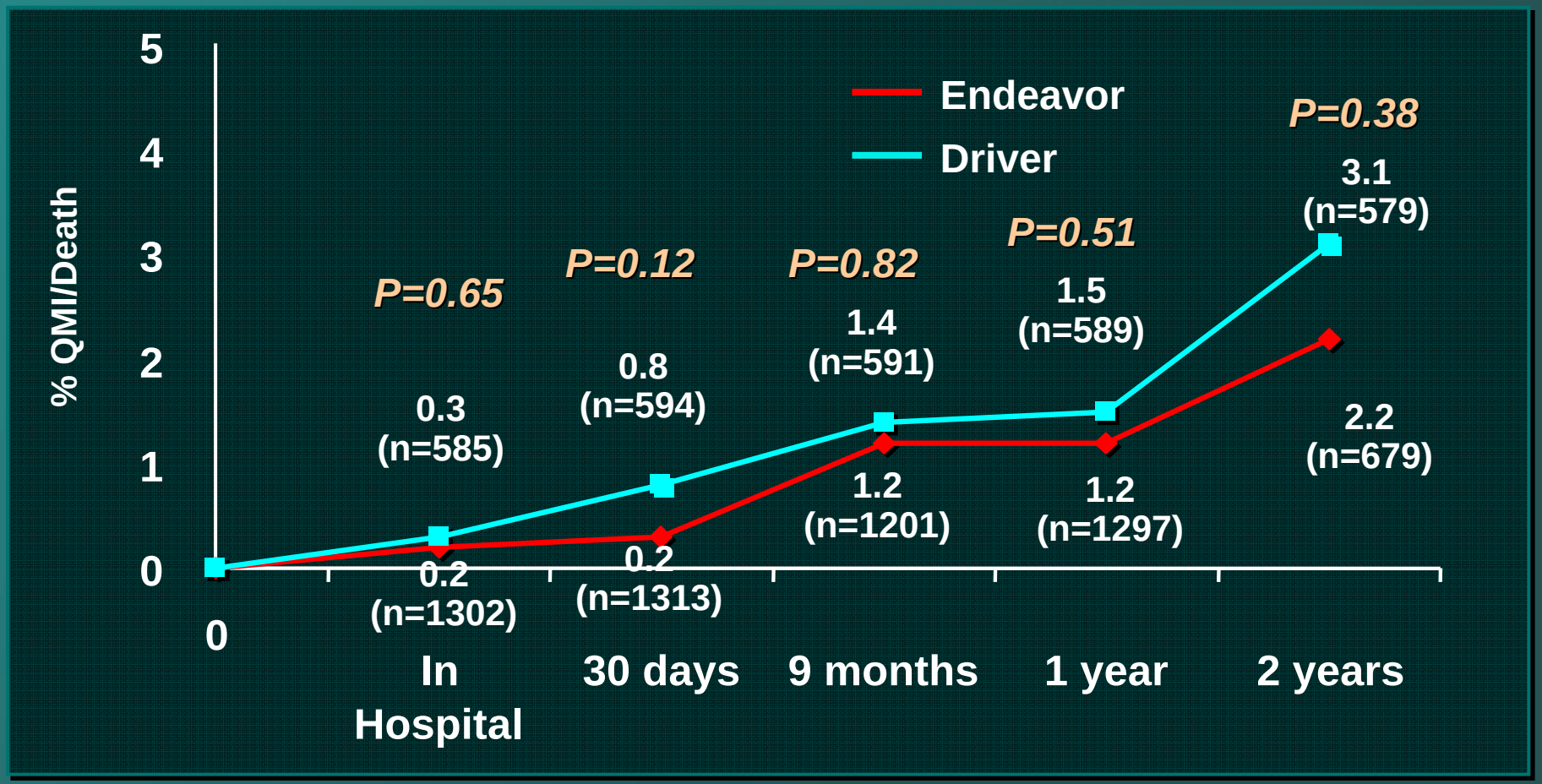
HCRI CEC and ARC Definitions 2yr K-M estimate



Endeavor Safety Analysis

Composite of Death and QMI

EI, EII, EII CA, and EIII vs. EII Driver



RESOLUTE

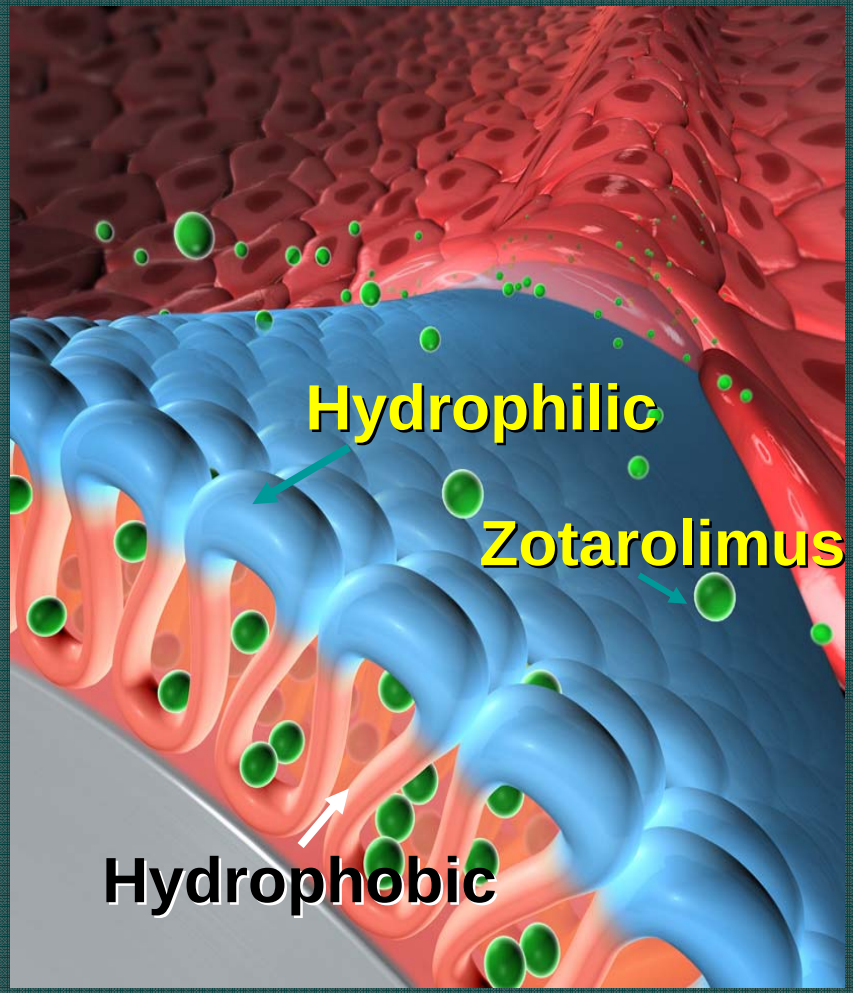
4 month Angiographic and IVUS Subset

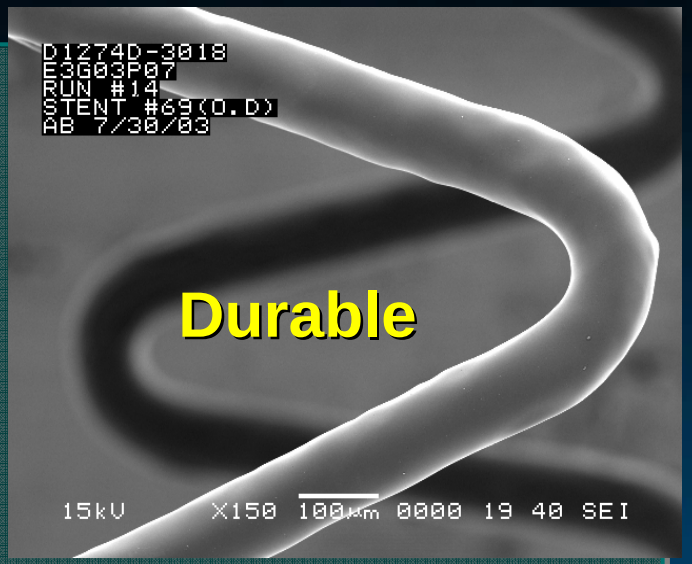
Professor Ian Meredith
M.D., Ph.D., FACC, FRACP, FSCAI
Monash Medical Centre and Monash University
Melbourne, Australia

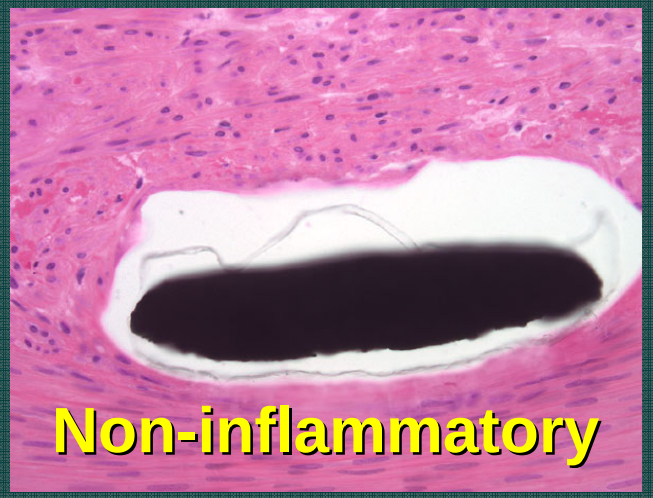
Principal Investigator
On behalf of the RESOLUTE Investigators

Endeavor Resolute

BioLinx Polymer System





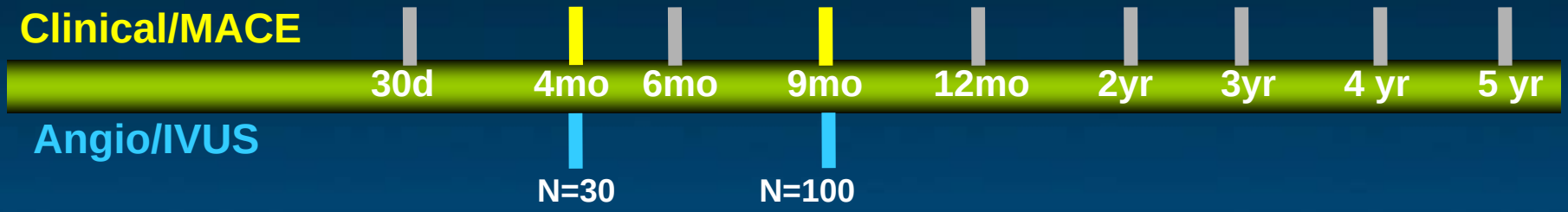


Clinical Trial Design

Single *De Novo* Native Coronary Artery Lesions
Lesion Length: 14-27mm
Stent Diameters: 2.5, 3.0, 3.5mm
Stent Lengths: 18, 24, 30mm (8/9mm bailout)
Drug Dose: 1.6 μg/mm^2 stent surface area
Antiplatelet therapy for 6 months
Pre-dilatation required

Endeavor Resolute Stent

130 Patients (includes 30 PK Sub-Study Patients)
12 Sites (New Zealand and Australia)



Primary Endpoint: Late lumen loss (in-stent) at 9 mths by QCA

Secondary Endpoints: MACE at 30 days, 6, 9 and 12mths and IVUS and angiographic parameters at 9mths

30 pt Subset: 4mth MACE and angiographic, IVUS parameters

9 month results will be compared to an ENDEAVOR II DES cohort

Angiographic Results

4 Month Subset

n=30		In-stent	In-segment
RVD (mm)			2.90±0.38
Lesion Length (mm)			15.16±5.38
MLD (mm)	pre		0.83±0.34
	post	2.81±0.36	2.43±0.45
Acute Gain		1.98±0.45	1.61±0.59
MLD (mm)	4 mo f/u	2.68±0.39	2.38±0.40
Late Loss (mm)		0.12±0.26	0.05±0.20
Late Loss Index		0.06±0.17	0.01±0.18
% DS		7.18±7.86	17.74±7.57
ABR (%)		0	0

Late Breaking Clinical Trials I

The ABSORB Trial

Six Month Angiographic and IVUS results from this First-in-Man Evaluation of a Fully Bioabsorbable Everolimus-Eluting Coronary Stent

Patrick W. Serruys, MD, PhD and John A. Ormiston, MD

On behalf of the ABSORB Investigators

Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands

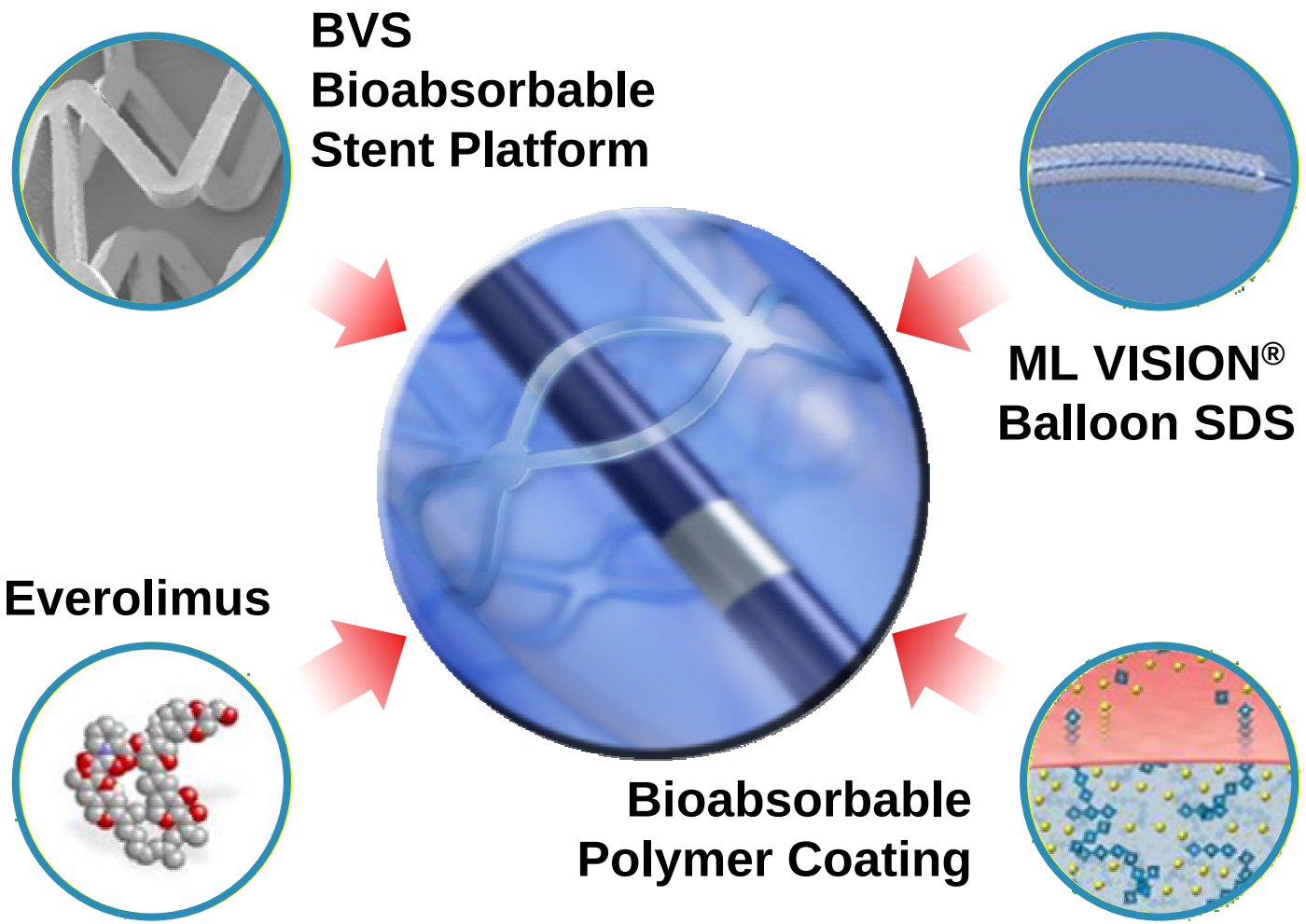
Auckland City Hospital, Auckland, New Zealand

24th March 2007

11:00-11:10

La Nouvelle Orleans C

BVS Stent Components



Note: BVS is currently in development at Abbott Vascular. Not available for sale

ABSORB: Study Design

Single, *de-novo* lesion → **3.0 mm n = 30** → **BVS Stent**

Sponsor: Abbott Vascular

Primary Investigators:

- J Ormiston MD
- PW Serruys MD, PhD

DSMB: J Tijssen PhD,
T Lefèvre MD, P Urban MD

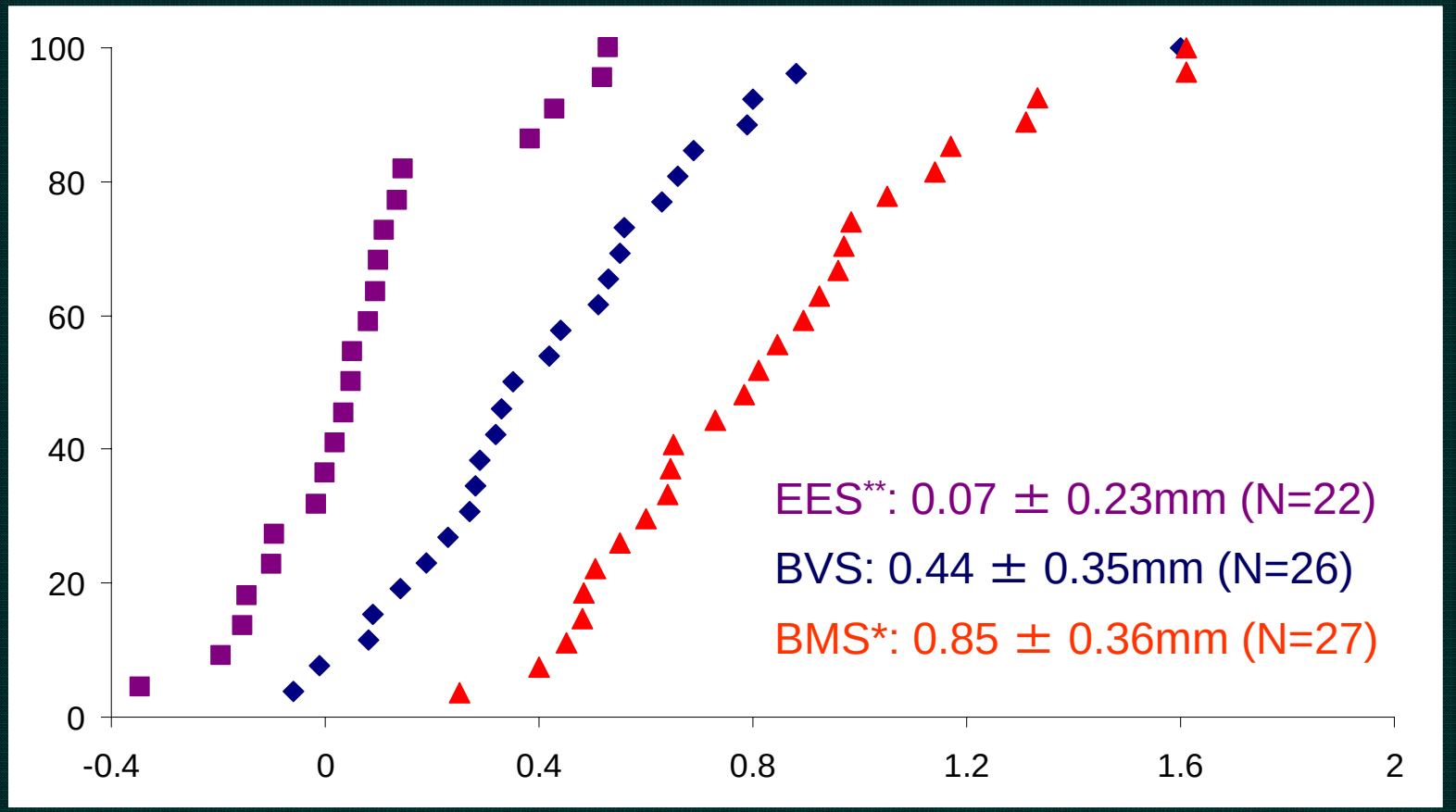
CEC: C Hanet MD,
D McClean MD, V Umans MD

Angiographic and IVUS Corelab:
Cardialysis (Rotterdam, NL)

- Prospective, open label, FIM
- 3.0 x 12mm stents (3.0 x 18mm* stents available after enrolment start and used in 2 pts)
- 6 sites EU, NZ

Rotterdam, NL, Patrick Serruys (16)
Krakow, PL, Dariusz Dudek (6)
Auckland, NZ, John Ormiston (5)
Arhus, DN, Leif Thuesen (3)
Aalst, BE, Bernard de Bruyne
St Denis, F, Bernard Chevalier

ABSORB
Angiographic Late Loss



*** BMS loss from SPIRIT FIRST (n=27)**

**** EES loss of pts with 3.0 x 18mm for single lesion from SPIRIT FIRST and II (n=22)**

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- New Drug-Eluting Stents (ZOMAXX I, SPIRIT III, ENDEAVOR Safety, RESOLUTE, and ABSORB)

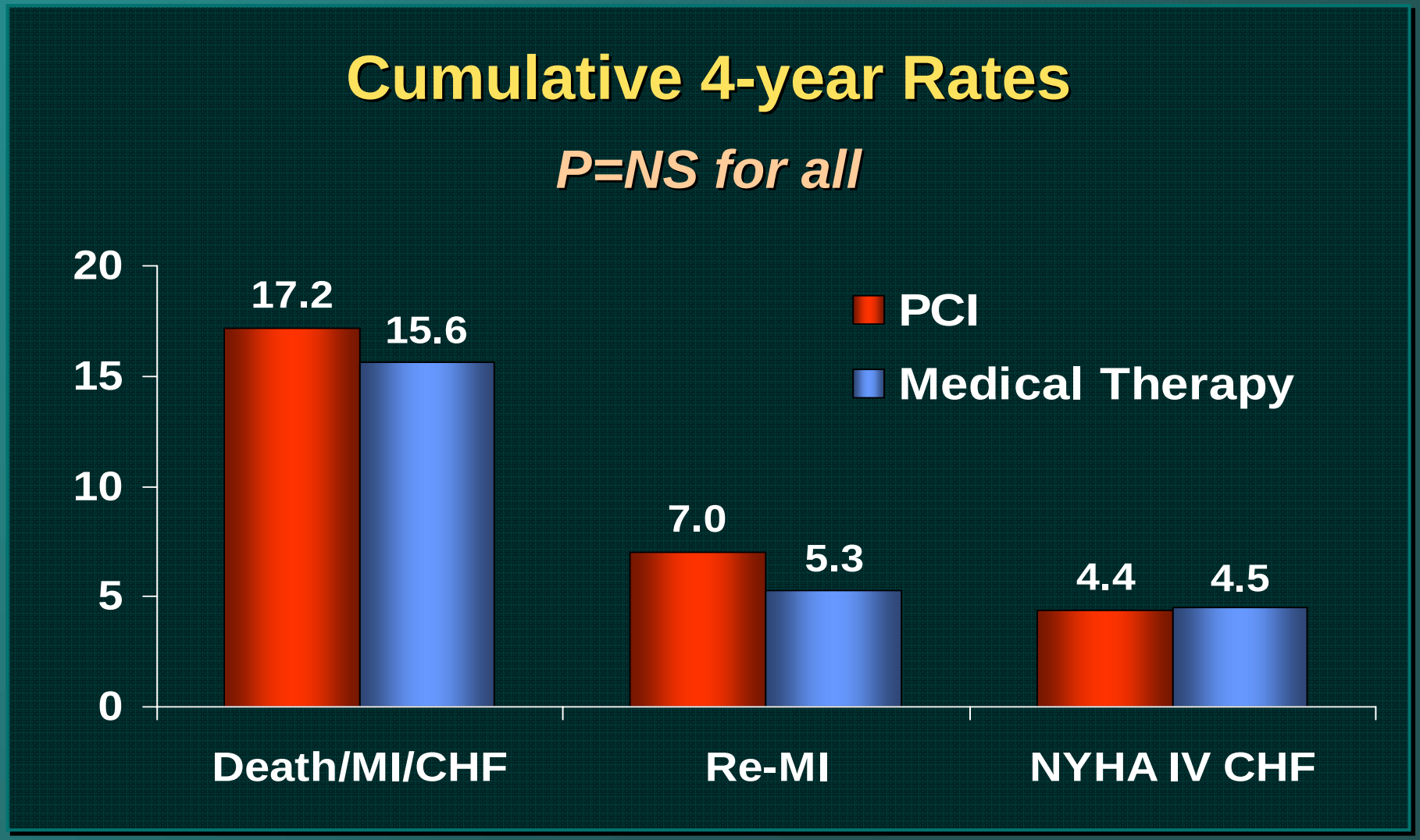
- *Anti PCI Trials! (OAT and COURAGE)*

OAT Trial

- 2166 stable patients with total occlusion of the Infarct-Related Artery at 3-28 days following MI
- Patients at “increased risk”, defined as an EF<50%, proximal occlusion of a major epicardial vessel with a large risk region, or both
- Randomization to PCI vs. Medical Therapy
- Primary Endpoint: death, reinfarction, or Class IV heart failure at 4 years

Hochman et al, NEJM 2006; 355:2395-2407

OAT Trial



Hochman et al, NEJM 2006; 355:2395-2407

OAT Trial

- 2166 stable patients
- 3-28 days post MI
- 100% occlusion
- 4 year F/U

	PCI	Med
Death MI Class IV CHF	17.2%	15.6%

OAT: Who Were They?

Age	58
Class I	83%
Throm. Therapy	20%
Time from MI to Randomization	8 days
Stress test	27%
Ischemia mild/none	90%
SVD	82% (50% RCA)

Stable, untreated, non-ischemic, single vessel, 1 week out of an MI

Nothing to do with CTOs

COURAGE

COURAGE

Clinical **O**utcomes **U**tilizing

Revascularization and

Aggressive **G**uideline-Driven

Drug **E**valuation

A North American Trial

19 US Non-VA Hospitals

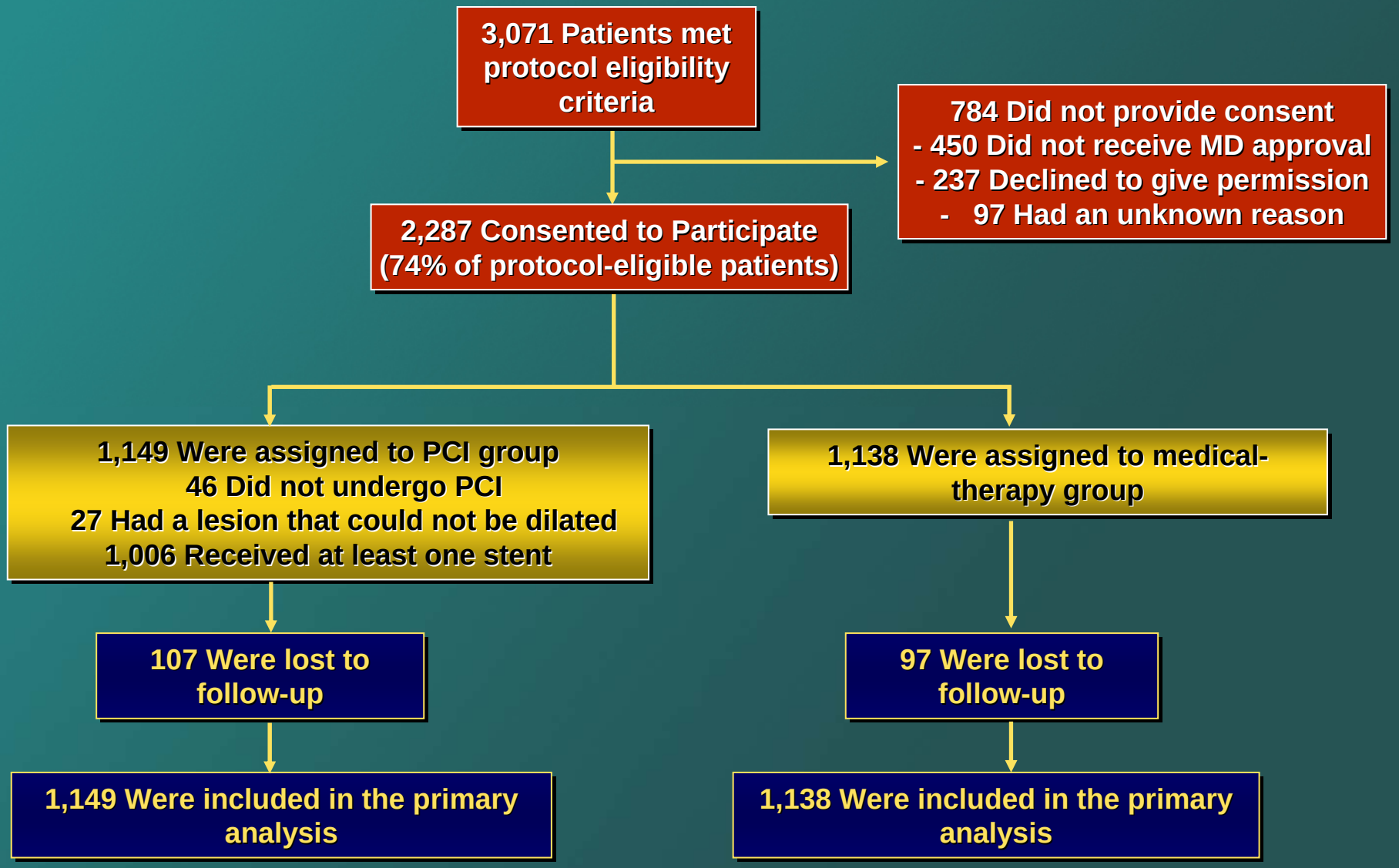
15 VA Hospitals

16 Canadian Hospitals

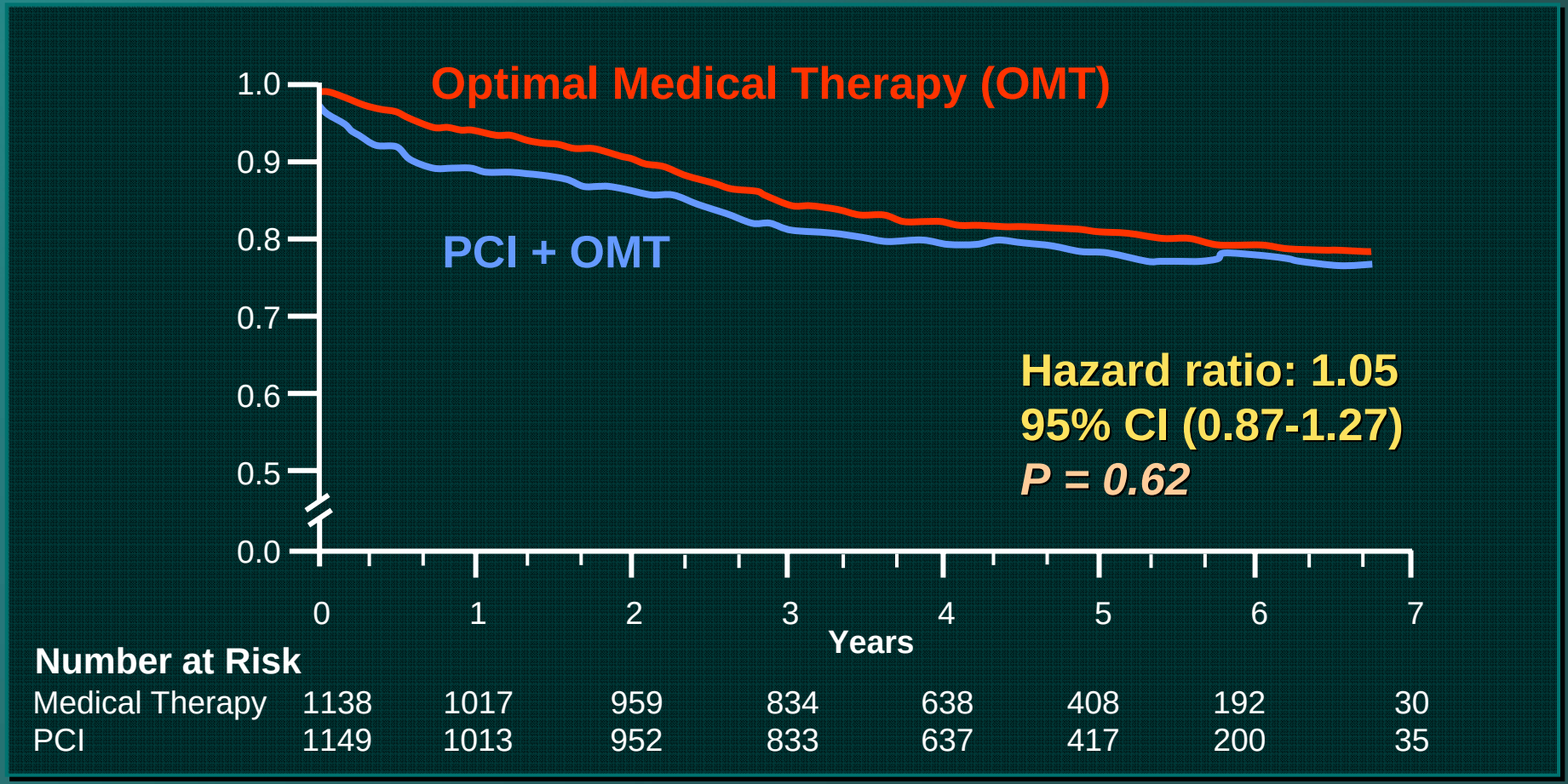
50 Hospitals

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

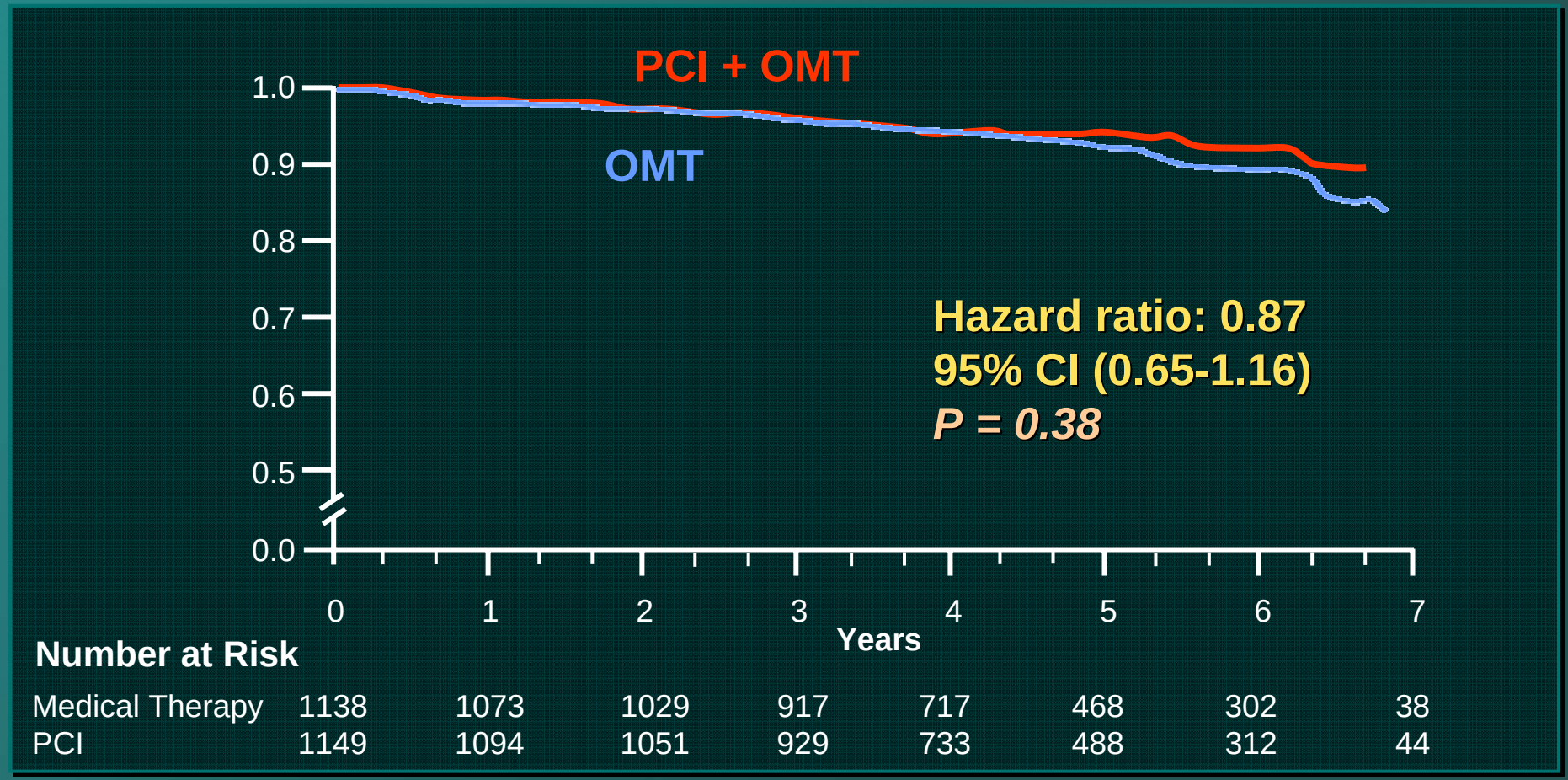
Enrollment and Outcomes



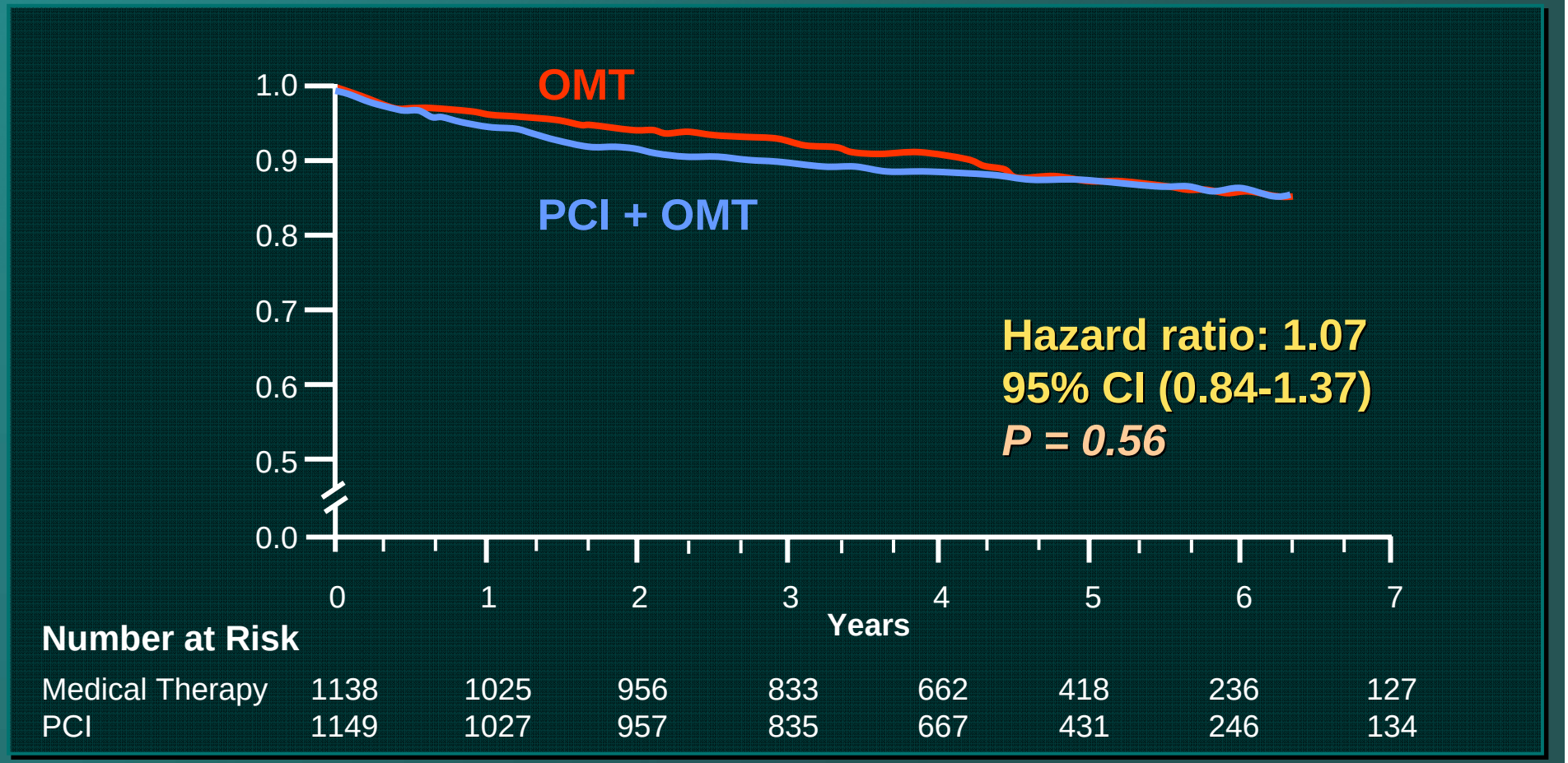
Survival Free of Death from Any Cause and Myocardial Infarction



Overall Survival



Survival Free of Hospitalization for ACS



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

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.

Important LBCTs Summary

- ***Trends in adjunctive pharmacology:*** **stress value of clopidogrel, downgrade IIb/IIIa inhibitors, consider bivalirudin as preferred anti-thrombin.**
- ***DES in AMI/Real world/Bifurcations:*** ***early and intermediate results favor DES in AMI, and in real world patients, and for treating bifurcations use of one stent with provisional stenting of the SB seems more favorable***
- ***New DES:*** **Favor Xience V for efficacy and Endeavor for safety (preliminary); watch out for bioresorbables in the future**
- ***Anti PCI:*** **Patient selection/endpoint definitions will influence clinical outcomes. Read between the lines! There are no new findings in COURAGE, PCI relieves symptoms and improves QOL.**