Resolute in the DES era:

Indications & Limitations

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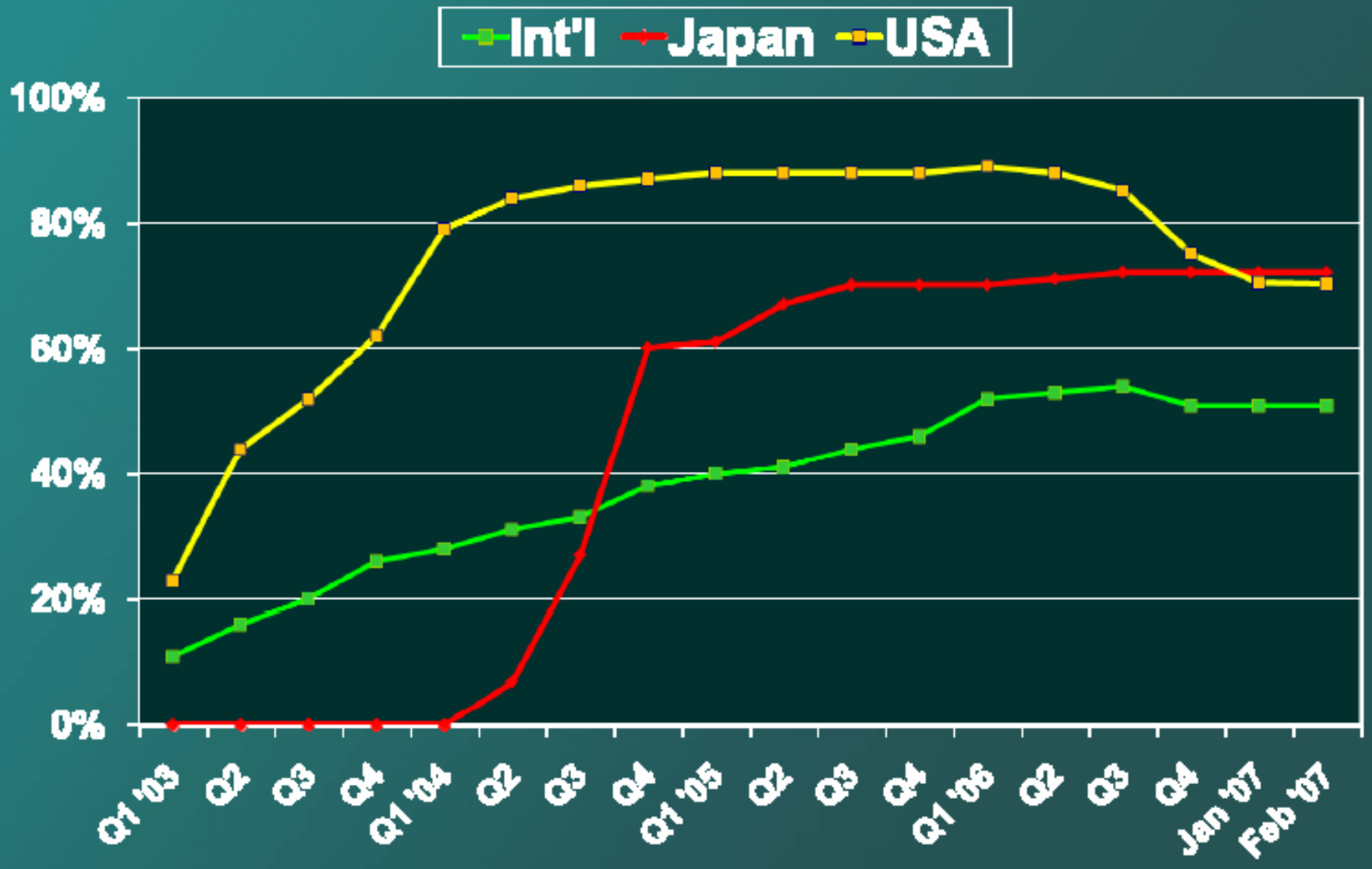
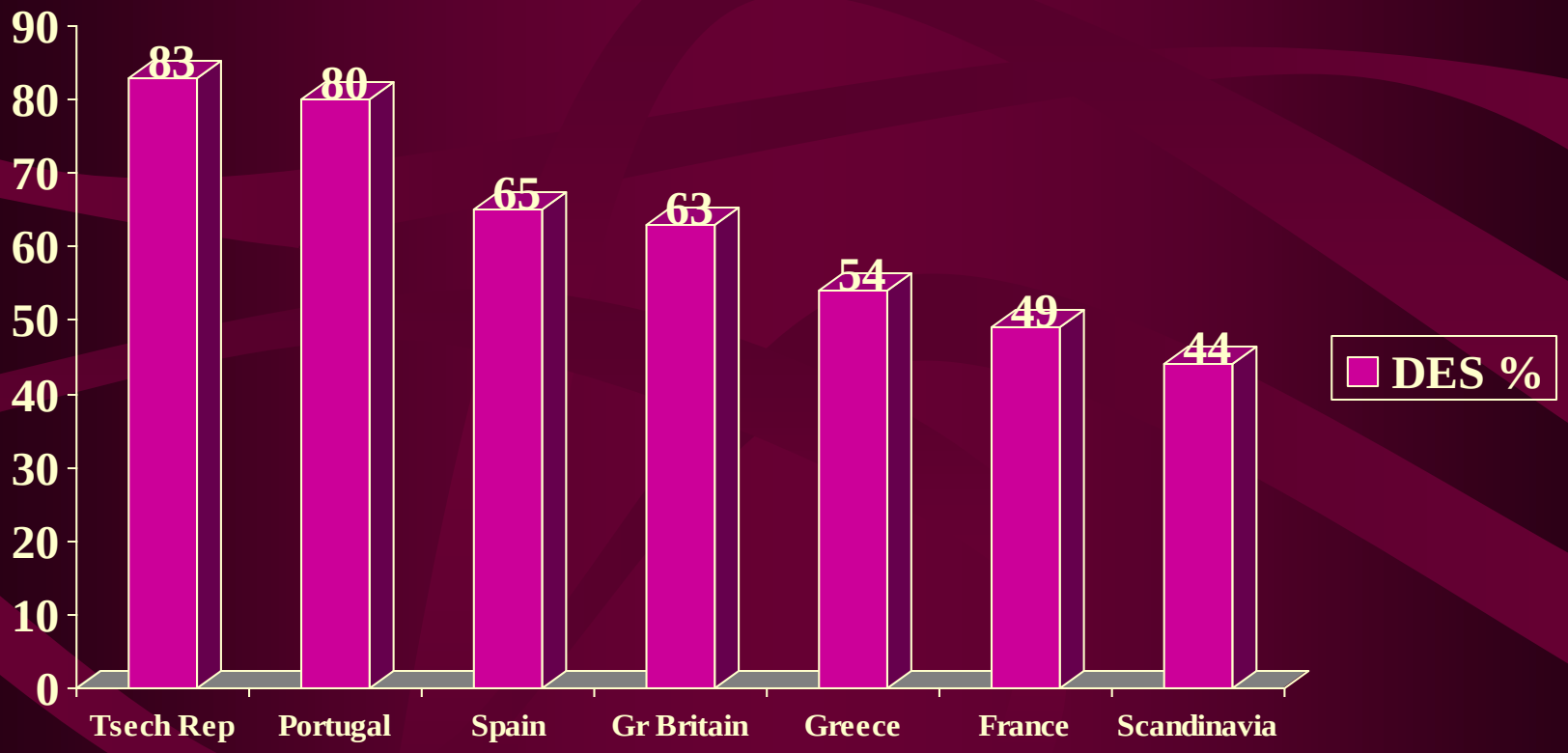
Cardiac Catheterization Laboratory

11/6/2009

DES Penetration



Use of DES in Europe in 2007

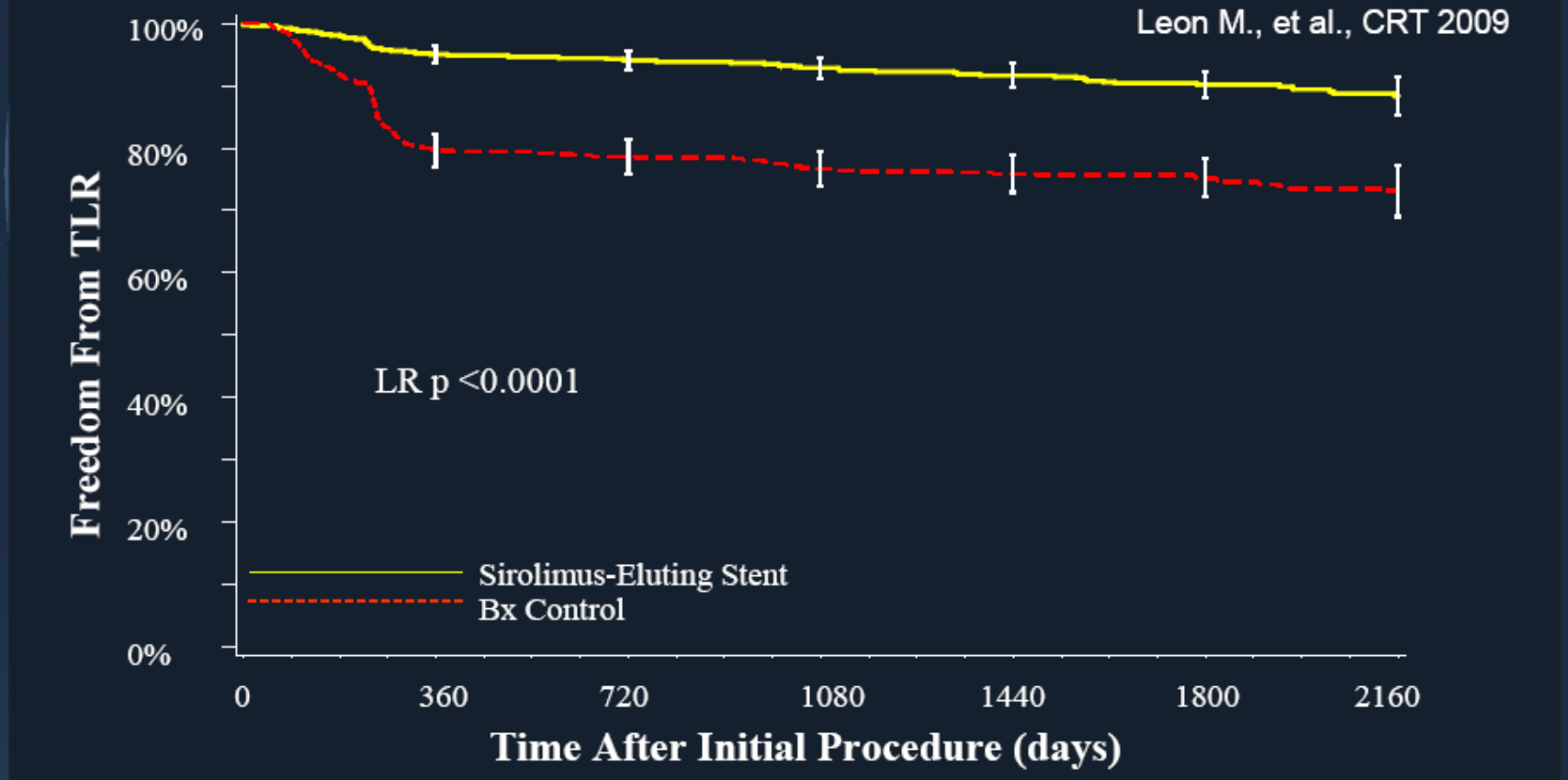


Current "On-Label" Definitions

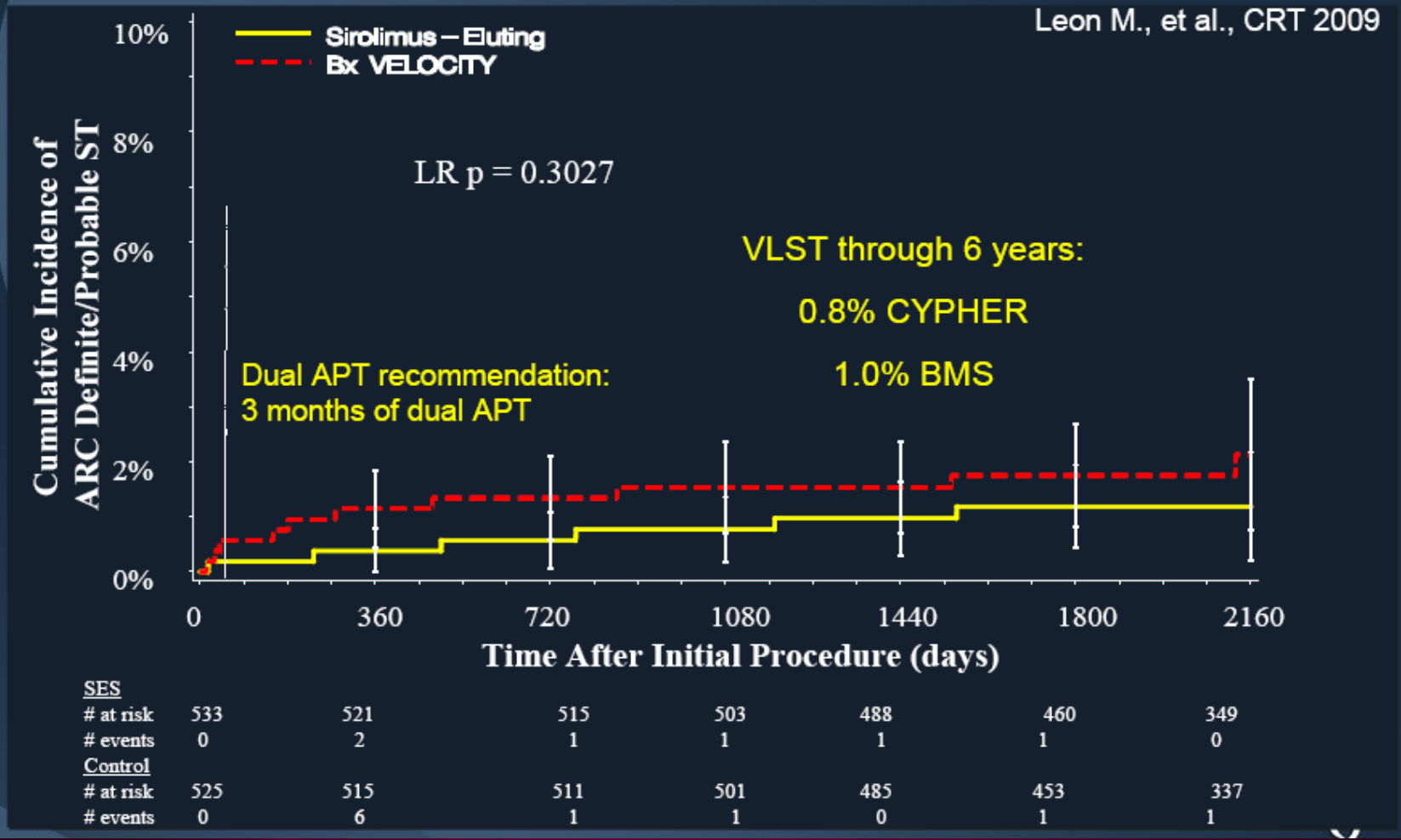
Individual Stent IFUs:

- **CYPHER:** symptomatic de novo native lesions 2.5 – 3.5 mm in diameter and ≤30 mm in length
- **TAXUS:** de novo native lesions 2.5 – 4.0 mm in diameter and ≤28 mm in length
- **ENDEAVOR:** de novo native lesions 2.5 – 3.5 mm in diameter and ≤27 mm in length
- **XIENCE V/Promus:** symptomatic de novo native lesions 2.5 – 4.25 mm in diameter and ≤28 mm in length

SIRIUS Trial: 6Y Follow-Up
Freedom from TLR



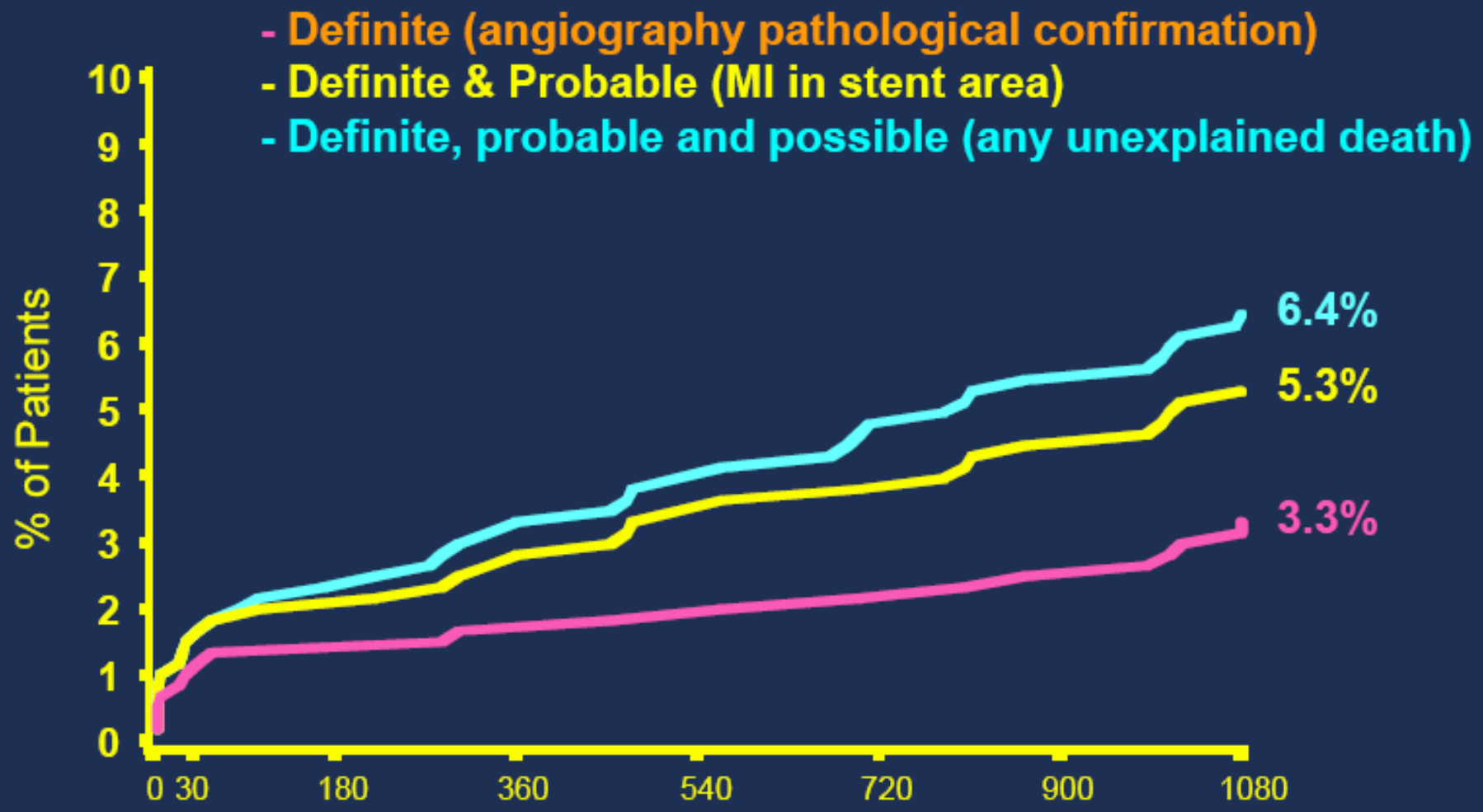
SIRIUS Trial: 6Y Follow-Up
ARC Def./Prob. Stent Thrombosis



CENTRO CUORE COLUMBUS

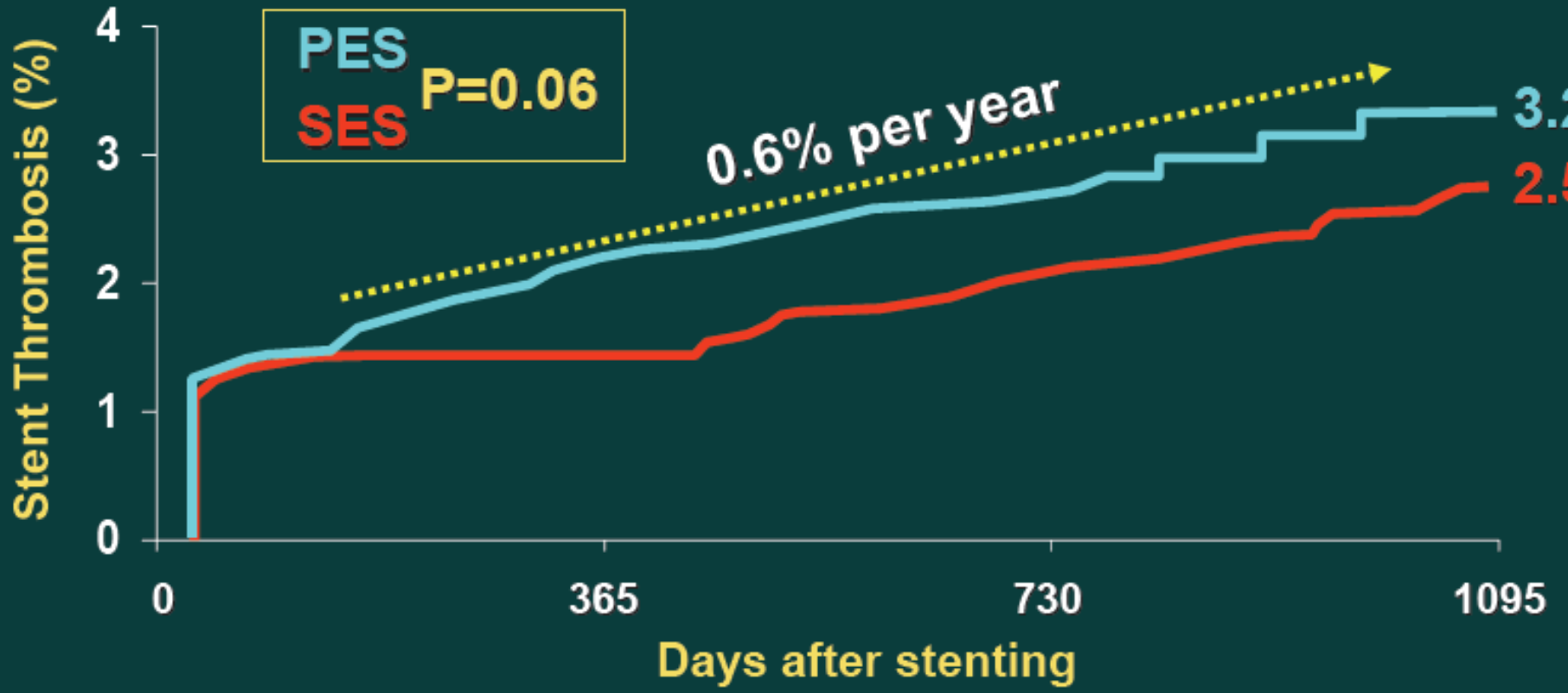
ARTS II – Stent thrombosis up to 3 years *

* Re-adjudication according to Dublin definitions



ARTS II was performed with SES

Bern/Rotterdam 2 Center Experience

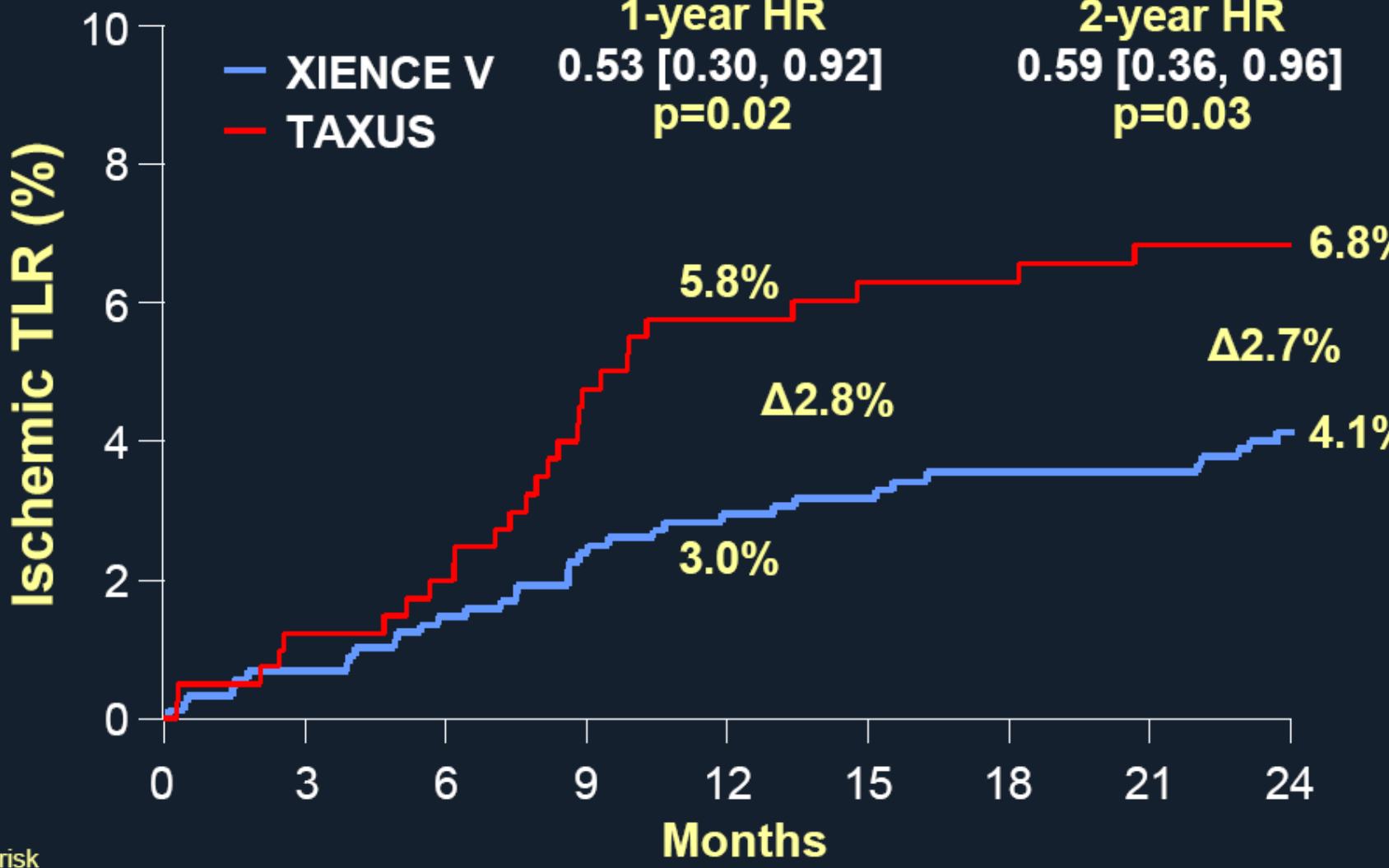


Days after PCI	9	30	365	730	1095
Incidence SES (%)	1.0	1.1	1.3	1.9	2.5
Incidence PES (%)	1.2	1.3	2.0	2.7	3.2
Pts at risk	8146	7162	7002	2841	971

Daemon J et al. Lancet 2007;369:667–78

Spirit

SPIRIT II + III: Ischemic TLR

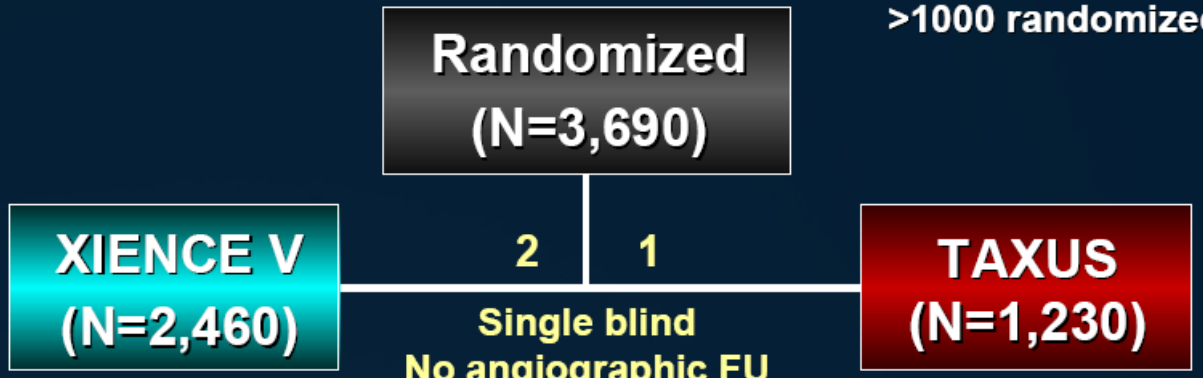


Number at risk

XIENCE V	892	880	869	852	840	819	816	808	801
TAXUS	409	397	392	375	366	354	349	348	346

Spirit

SPIRIT IV Trial



Up to 3 lesions in 1, 2 or 3 separate vessels (2 max per vessel)

Primary endpoint: MACE at 12 months

(cardiac death, MI,

Primary Endpoint Results
TCT September 2009
San Francisco

TCT 2009

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COLUMBIA UNIVERSITY MEDICAL CENTER

ENDEAVOR Clinical Trial Program

Enrollment Complete / In Follow Up	1yr	2yr	3yr	4yr	5yr
ENDEAVOR I	Single Arm First-in-Man (n = 100)				5yr
ENDEAVOR II	1:1 RCT vs. BMS (E = 598,D = 599) PK (n = 106)			4yr	
ENDEAVOR II CA	Continued Access Single Arm (n = 296)			4yr	
ENDEAVOR III	3:1 RCT vs. Cypher® (E = 323,C = 113)		3yr		
ENDEAVOR IV	1:1 RCT vs.Taxus® (E = 773,T = 775)	2yr			
ENDEAVOR PK	Pharmacokinetic Study (n = 43)	2yr			
ENDEAVOR Japan	Single Arm (n = 99)	2yr			
E-FIVE	Open Label Single Arm (n = 8300)	1yr			

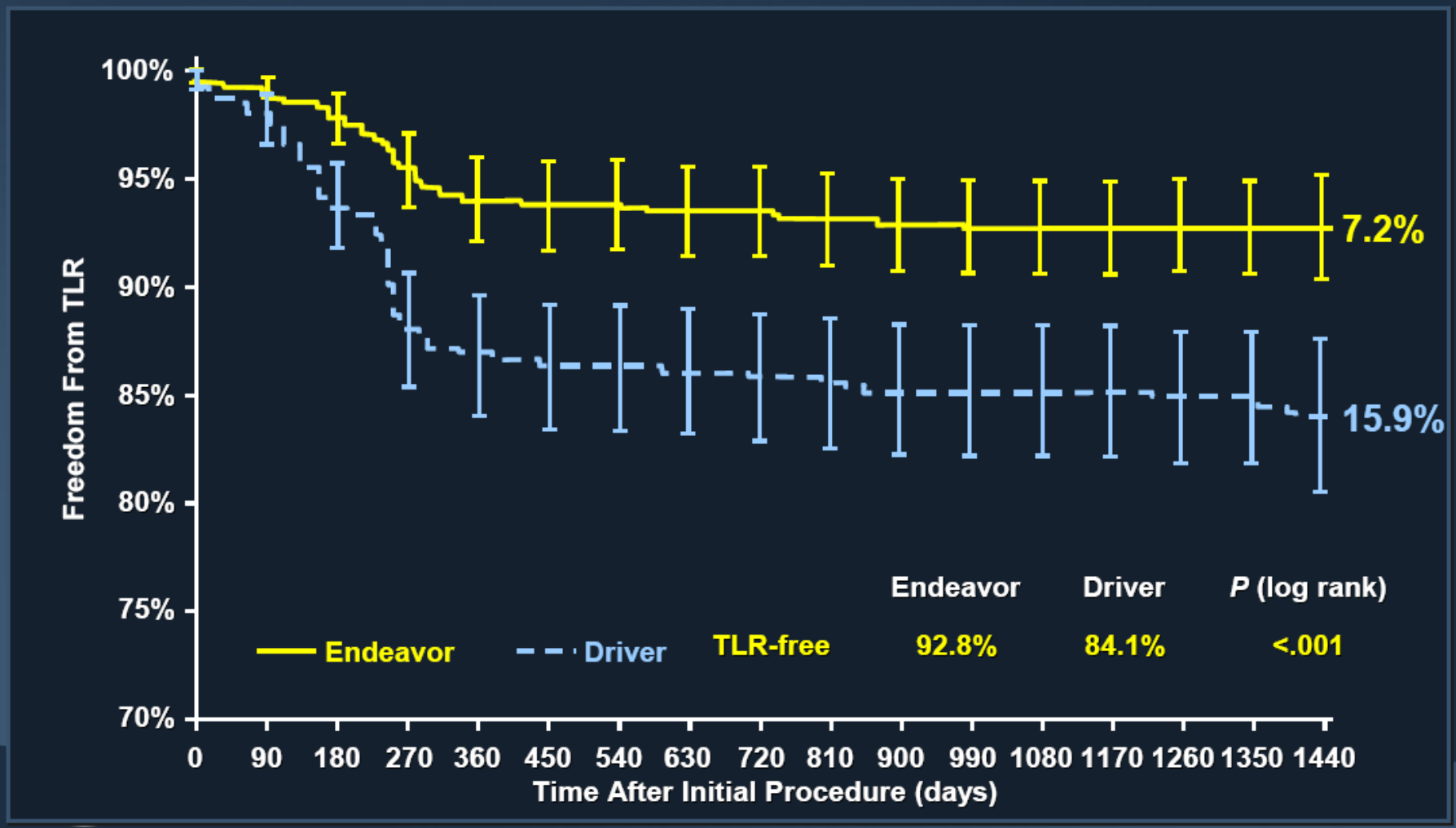
Enrolling / Planning

PROTECT	1:1 RCT vs. Cypher (E = 4400,C = 4400)
ENDEAVOR SVS	Small Vessel Single Arm (n ≈ 250)
PROTECT CA NA	Post Mkt Registry Single Arm (n ≥ 1000)
E-Japan PMS	Post Mkt Registry Single Arm (n ≈ 2000)

~24,000 patients
~$250M
Projected
Investment

ENDEAVOR II

TLR thru 4 years



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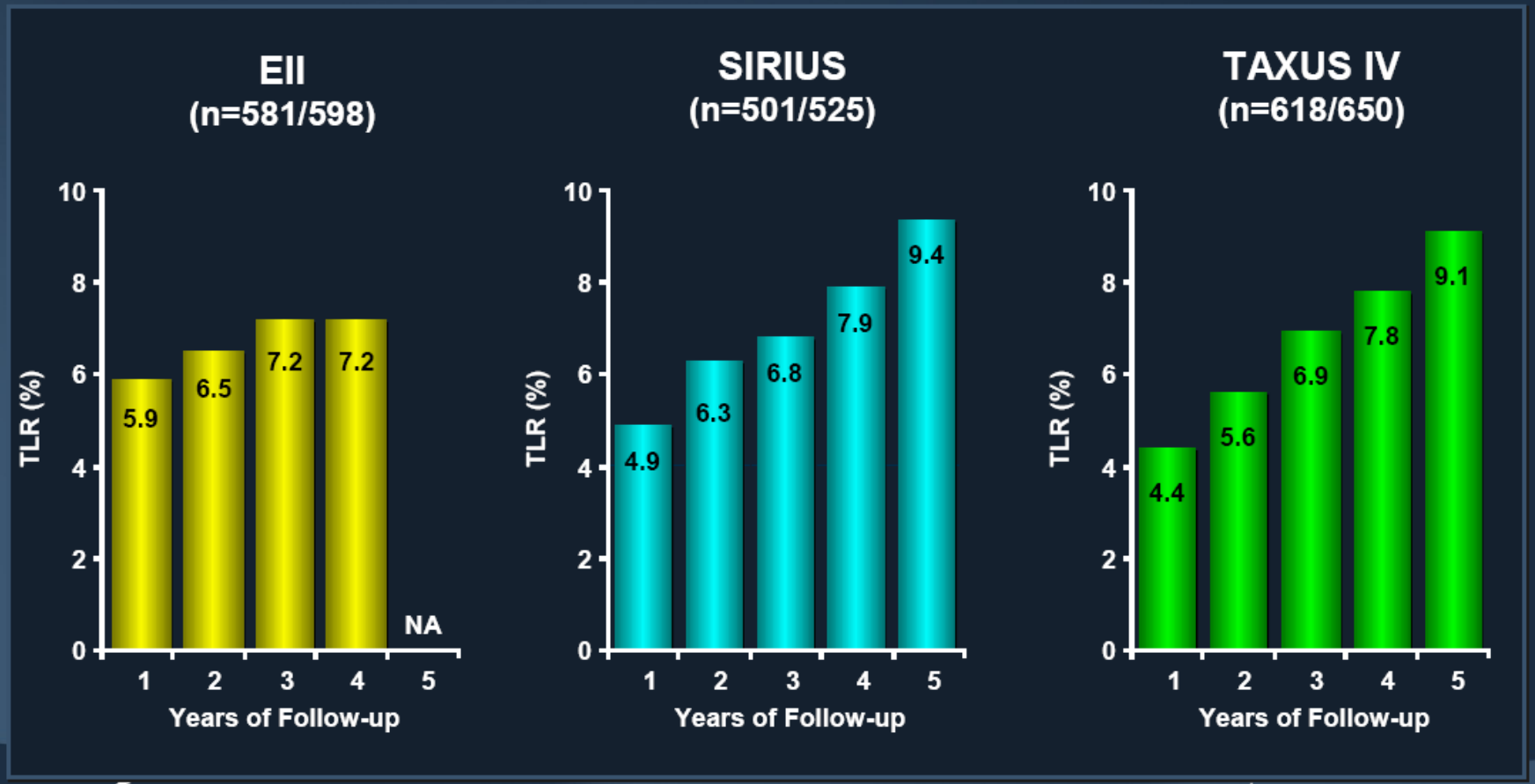
The University Hospital of Columbia and Cornell

Pivotal Trials TLR - DES Arms
ENDEAVOR II, SIRIUS, and TAXUS IV



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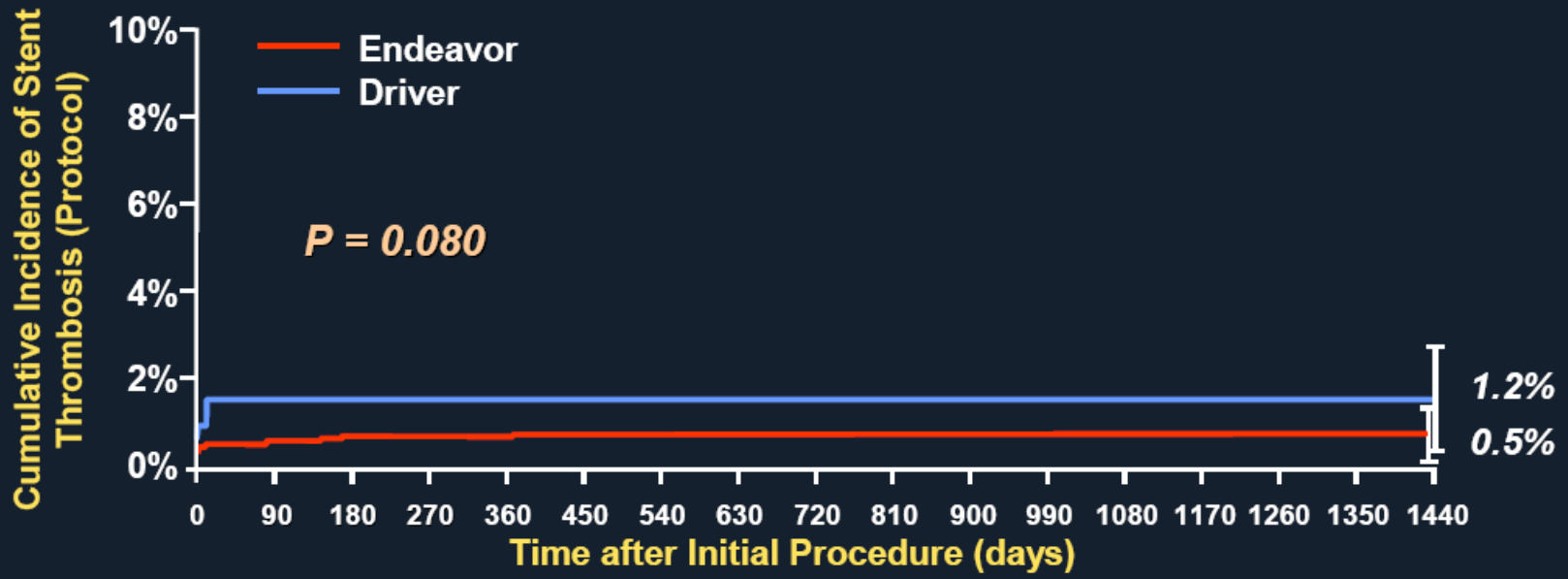
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Endeavor Safety Analysis

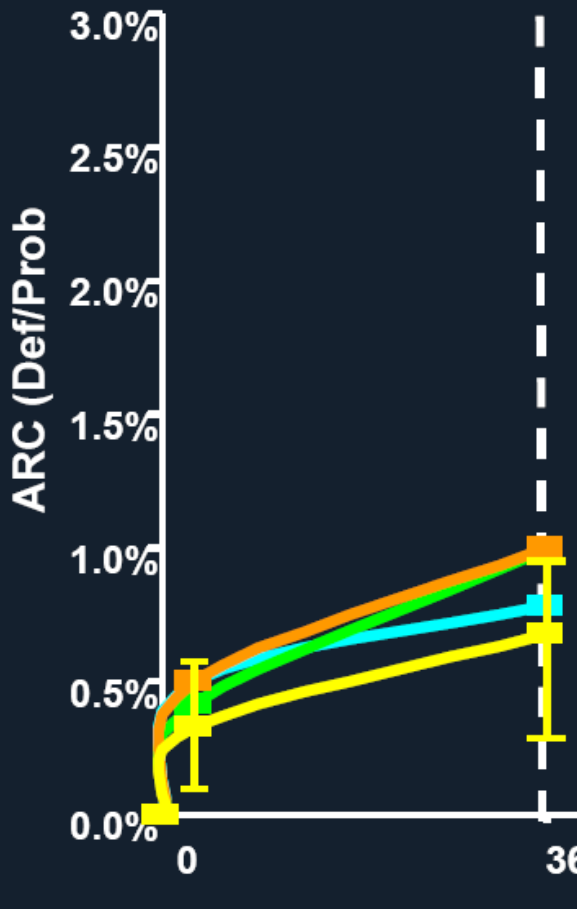
Cumulative Incidence of Stent Thrombosis (Protocol) to 1440 days



Days	0	30	270	360	720	1080	1440
Endeavor	2132	2131	2114	2069	2038	1651	1087
# Events	1	6	3	0	1	0	0
% CI	0.0%	0.3%	0.5%	0.5%	0.5%	0.5%	0.5%
Driver	596	595	587	577	571	560	545
# Events	1	6	0	0	0	0	0
% CI	0.2%	1.2%	1.2 %	1.2%	1.2%	1.2%	1.2%

DES In Perspective: LAST

ARC Def/Prob ST Landmark Analysis



Pooled Data	No. at Risk 1 Year	2 Years	3 Years	4 Years
Endeavor	2068	2036	1650	1087
Cypher	863	848	824	789
Taxus	1351	1300	1117	715
Xience V /Promus	892	865	NA	NA

There are no important differences in stent thrombosis rates among 1st and 2nd generation DES during the first year after stent implantation

CARDIOVASCULAR RESEARCH FOUNDATION

1. Mauri et al. TCT 2008.
2. Mauri L et al. *N Engl J Med.* 2007;356:1020-1029.
3. Serruys PW et al. *ACC* 2008
3. Stone GW et al. *PCR* 2008.

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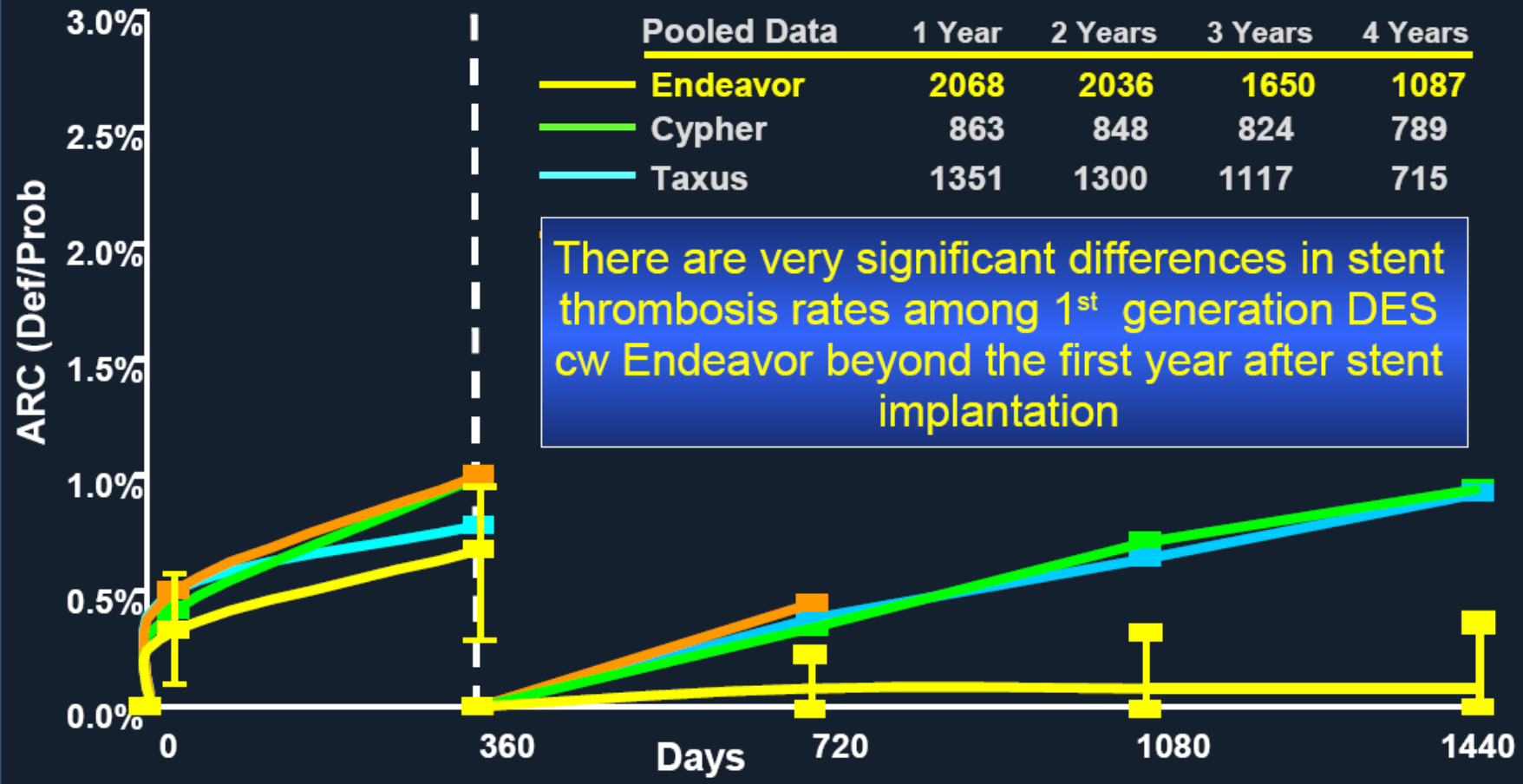
DES In Perspective: VLST

ARC Def/Prob ST Landmark Analysis



Pooled Data	No. at Risk 1 Year	2 Years	3 Years	4 Years
Endeavor	2068	2036	1650	1087
Cypher	863	848	824	789
Taxus	1351	1300	1117	715

There are very significant differences in stent thrombosis rates among 1st generation DES cw Endeavor beyond the first year after stent implantation

CARDIOVASCULAR RESEARCH FOUNDATION

1. Mauri et al. TCT 2008.
2. Mauri L et al. *N Engl J Med*. 2007;356:1020-1029.
3. Serruys PW et al. *ACC* 2008
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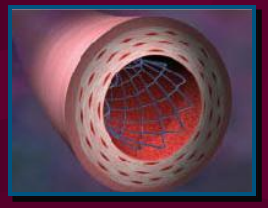
Combining Proven DES Components with Innovative Technologies

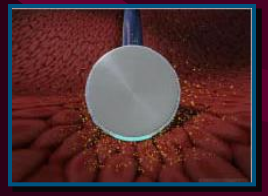
Proven Components

- **Driver stent offers uniform vessel support**



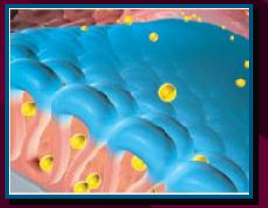
- **Sprint delivery system offers outstanding low-profile advantage**

- **Potent antiproliferative drug allows effective inhibition of neointima growth**



Innovative Technologies

- **BioLinx biocompatible polymer allows for rapid, complete and functional healing**



Effective drug-release kinetics inhibit neointima growth

RESOLUTE Clinical Program

RESOLUTE	Single Arm First-in-Human (n=139) 2yr
RESOLUTE AC*	1:1 RCT** vs. Xience® (R=1,150,X=1,150)
RESOLUTE Intl	Non-RCT Observational (R=2,464)
RESOLUTE US	2.5 – 3.5 Clinical Non-RCT vs. Hx Control (R=1,112)
	2.5 – 3.5 Angio / IVUS Non-RCT vs. Hx Control (R=100)
	2.25 Angio Non-RCT (R = 129)
	4.0 Angio Non-RCT (R = 58)
	38 mm+ – Long Lesion Non-RCT (R = TBD)
RESOLUTE Japan	Non-RCT (R ≈ 100)

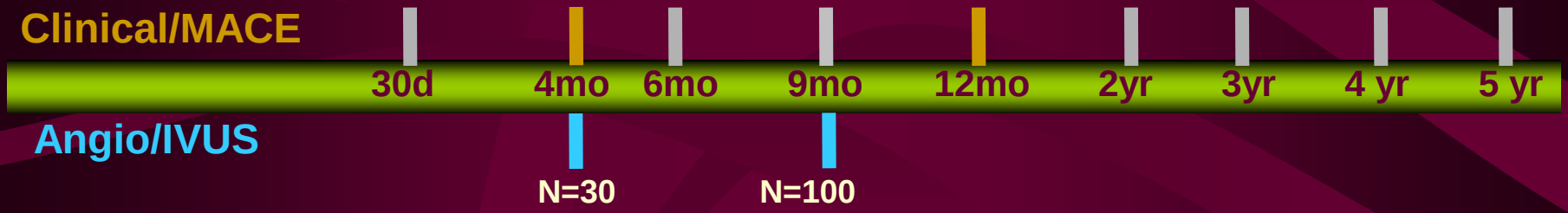
** Resolute AC: Resolute All Comers; **: RCT: Randomized Clinical Trial*

RESOLUTE

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/mm² stent surface area
Antiplatelet therapy for 6 months
Pre-dilatation required

Endeavor Resolute Stent

130 Patients (9 additional PK Sub-Study Patients enrolled after original 130 patients)
12 Sites (New Zealand and Australia)

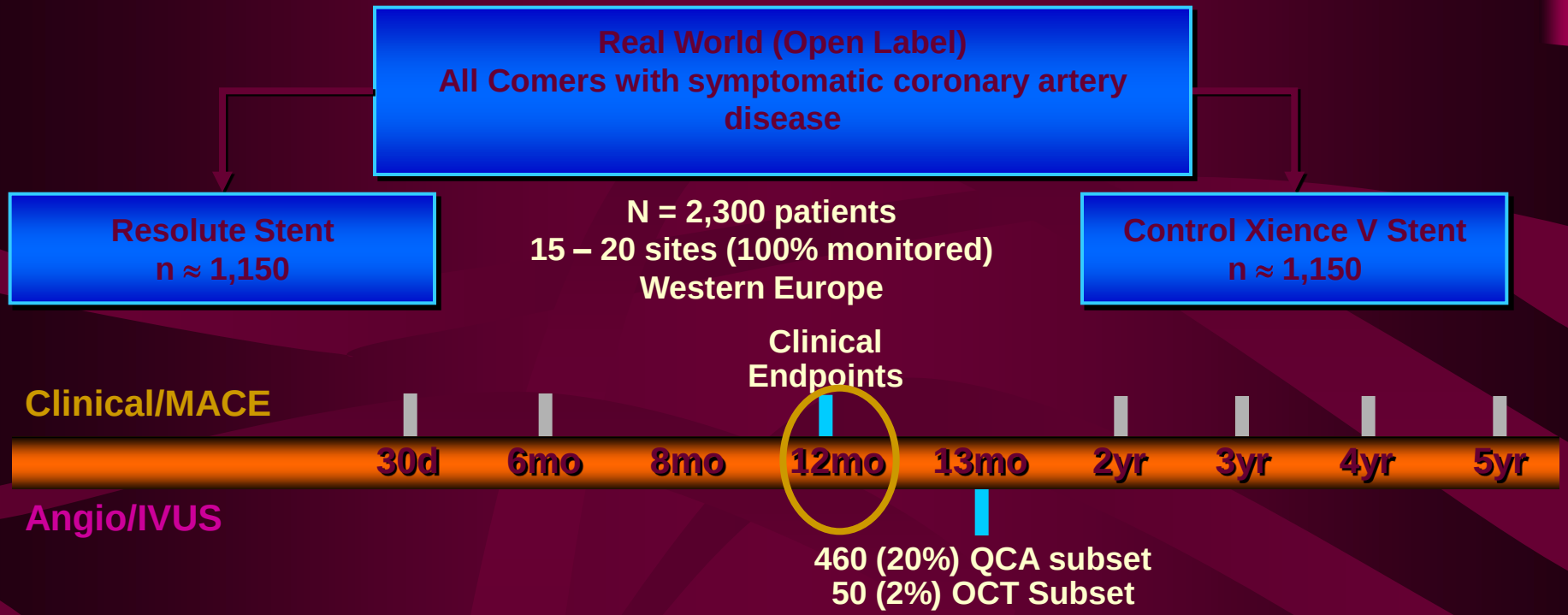


Primary Endpoint: Late lumen loss (in-stent) at 9 months by QCA

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

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

RESOLUTE All Comers



Primary Endpoint: Composite - Cardiac Death, Target Vessel MI, TLR @ 12mo
Secondary Endpoints: Composite @ 30d, 6mo, 2 – 5 yr; angiographic & optical coherence tomography (OCT) parameters @ 13 mo
Drug Therapy: ASA and clopidogrel/ticlid ≥6 months (per guidelines)

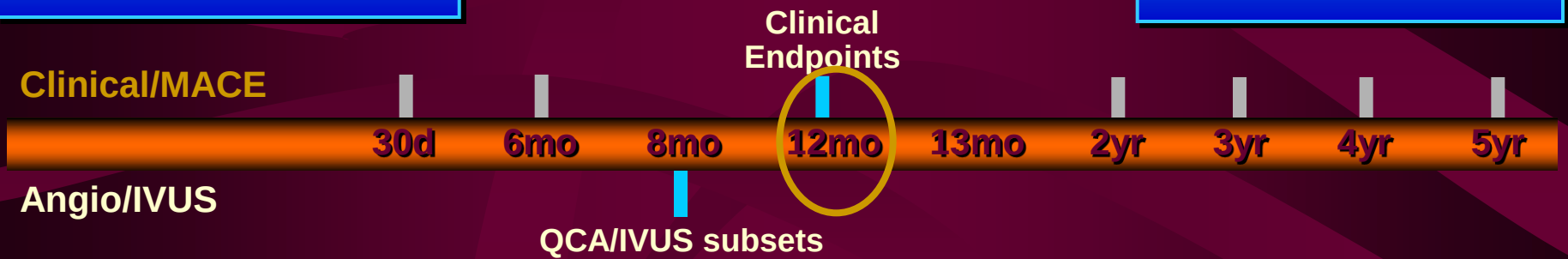
RESOLUTE US

***De Novo* Native Coronary Lesion**
Vessel Diameter: 2.25-4.2 mm
Lesion Length: ≤ 27 mm

Resolute Stent
2.25 Angio (n = 129)
2.5 – 3.5 Clinical (n = 1,112)
2.5 – 3.5 Angio/IVUS (n = 100)
4.0 Angio (n = 58)

N = 1,399 patients
125 sites
United States

Hx Controls
Performance Goals



Primary Endpoints:
2.25 Angio → In-Segment %DS @ 8 mo / Key 2°EP TLF @ 12 mo
2.5 – 3.5 Clinical →Target Lesion Failure @ 12 mo
2.5 – 3.5 Angio/IVUS → In-Stent LLL @ 8 mo
4.0 Angio → In-Segment LLL @ 8 mo
Drug Therapy: ASA and clopidogrel/ticlid ≥6 months (per guidelines)

RESOLUTE International

Real World (Open Label)
All Comers with symptomatic coronary artery disease

N = 2,464 patients
~100 sites
International

Primary Endpoint: Composite - Cardiac Death & Target Vessel MI @ 12mo
Secondary Endpoints: ARC Definite and Probable Stent Thrombosis @ 12 mo
Drug Therapy: ASA and clopidogrel/ticlid ≥6 months (per guidelines)

Angiographic Results

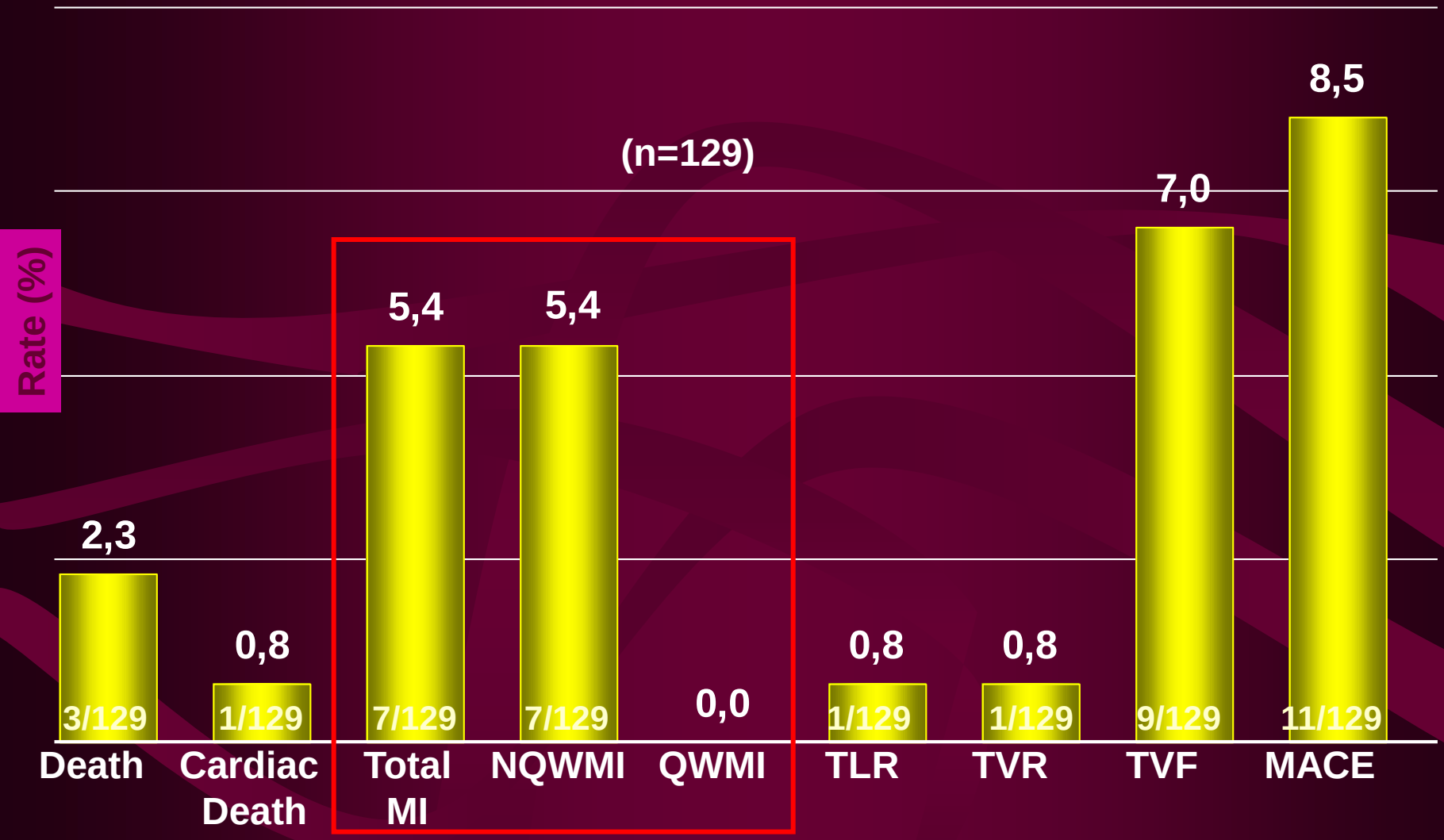
9 Month Cohort

n=96	In-stent	In-segment
Pre-procedure RVD (mm)		2.79 ± 0.40
Lesion Length (mm)		15.87 ± 6.51
MLD (mm) pre		0.82 ± 0.35
post	2.74 ± 0.41	2.33 ± 0.44
Acute Gain	1.91 ± 0.47	1.51± 0.50
9 mo f/u MLD (mm)	2.51 ± 0.48	2.21 ± 0.45
Late Loss (mm)	0.22 ± 0.27	0.12 ± 0.27
Late Loss Index	0.12 ± 0.16	0.08 ± 0.21
9 mo f/u % DS	10.13 ± 12.63	21.08 ± 10.62
ABR n (%)	1 (1%)	2 (2.1%)

As presented at TCT 2007

RESOLUTE

Clinical Events at 12 months



Clinical Events to 24 Months

	9 months n = 130 patients 131 lesions	12 months n = 130 patients, 131 lesions	24 months n = 130 patients, 131 lesions
Death (all) – % (n)	1.5 (2)	2.3 (3)	3.1 (4)
Cardiac	0.8 (1)	0.8 (1)	0.8 (1)
MI (all) – % (n)	5.4 (7)	5.4 (7)	5.4 (7)
Q Wave	0	0	0
Non Q wave	5.4 (7)	5.4 (7)	5.4 (7)
Death (cardiac) + MI (all) – % (n)	6.2 (8)	6.2 (8)	6.2 (8)
Stent Thrombosis (all) – % (n)	0	0	0
0-30 days	0	0	0
31-360 days	0	0	0
TLR – % (n)	0	0.8 (1)	1.5 (2)
TVR (non-TL) – % (n)	0	0	0
TVR – % (n)	0	0.8 (1)	1.5 (2)
MACE – % (n)	6.9 (9)	8.5 (11)	10 (13)
TVF – % (n)	6.2 (8)	6.9 (9)	7.7 (10)

Endeavor Resolute Stent

Caution: Investigational product in the United States. Limited by Federal (US) law to investigational use.

RESOLUTE

Dual Antiplatelet Therapy (DAPT) Usage

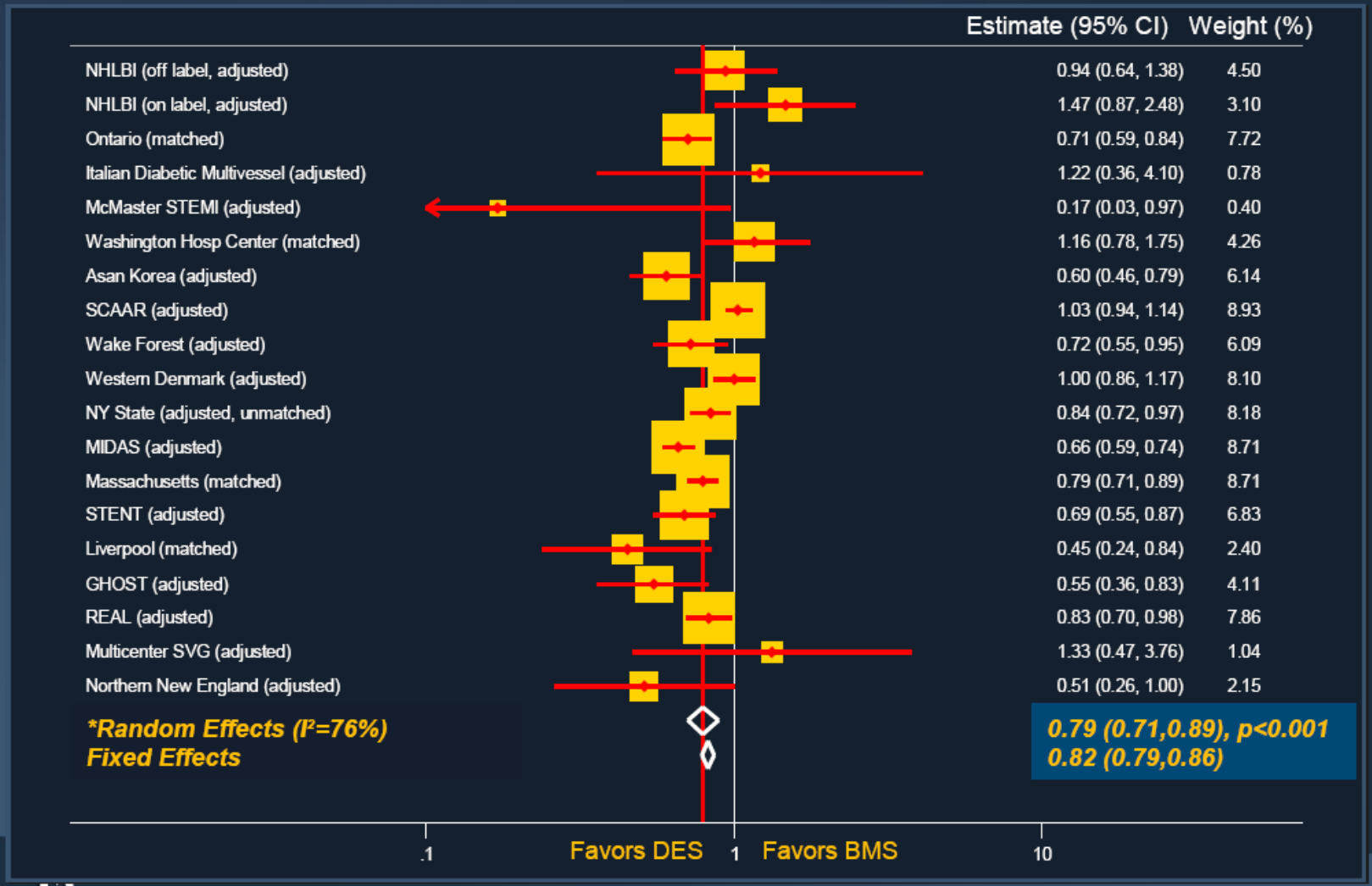
Percent of patients on DAPT at:	6 months	9 months	1 year	2 years
RESOLUTE	77.7% (101/130)	58.1% (75/129)	55.1% (70/127)	43.3% (55/127)

DES Current Questions

- “Off - label” use
- Use in ACS

All-Cause Mortality: Adjusted Registries

136,558 patients, 19 registries , mean F/U 2.7 years



CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

Outcomes Following Coronary Stenting:

A National Study of Long Term, Real-World Outcomes of Bare-Metal and Drug-Eluting Stents

Pamela S. Douglas, J. Matthew Brennan, Kevin J. Anstrom, Eric L. Eisenstein, David Dai, Ghazala Haque, David F. Kong, Ralph Brindis, Art Sedrakyan, David Matchar, Eric D. Peterson

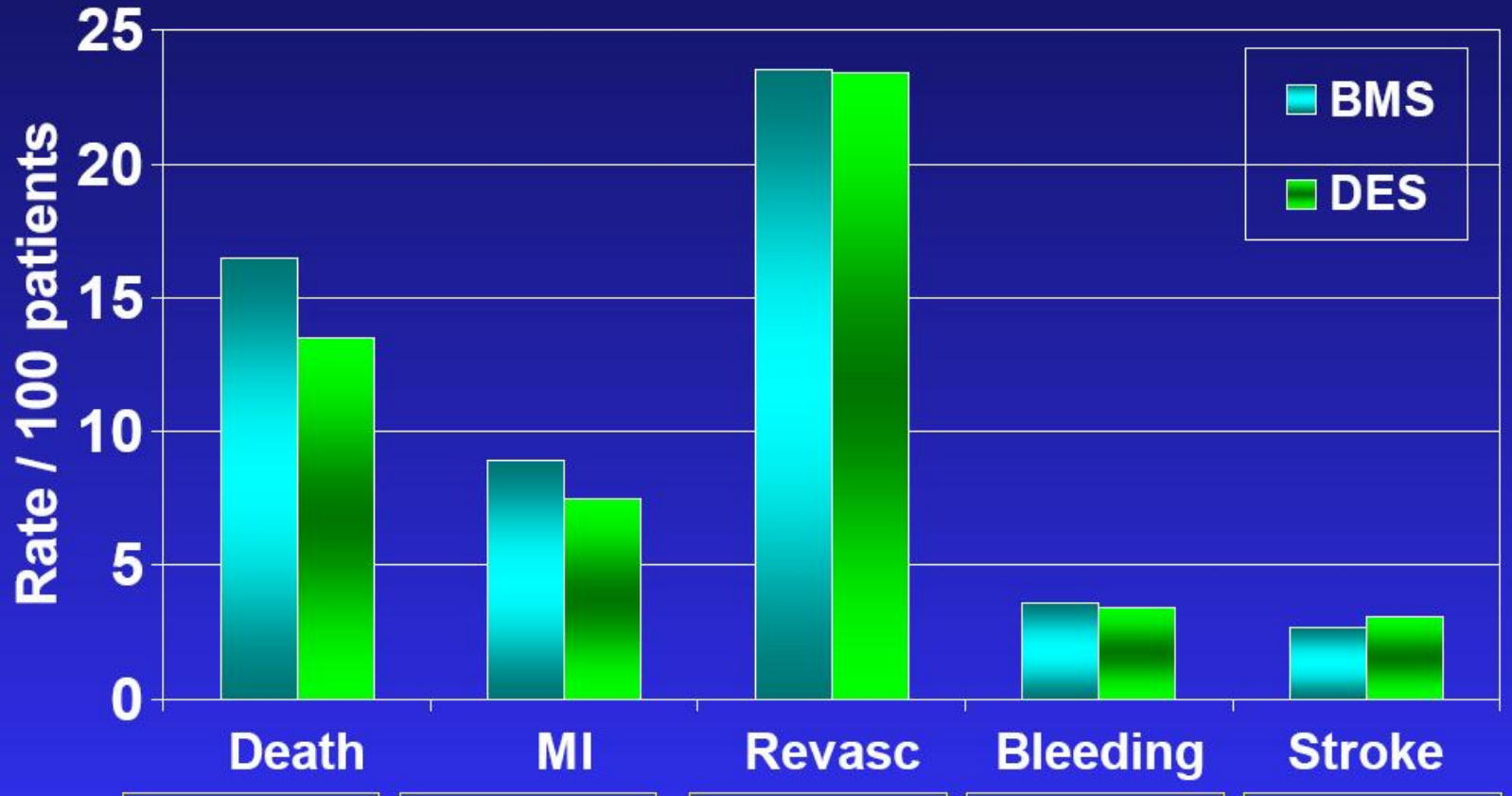
Duke Clinical Research Institute
Duke University Medical Center

Methods

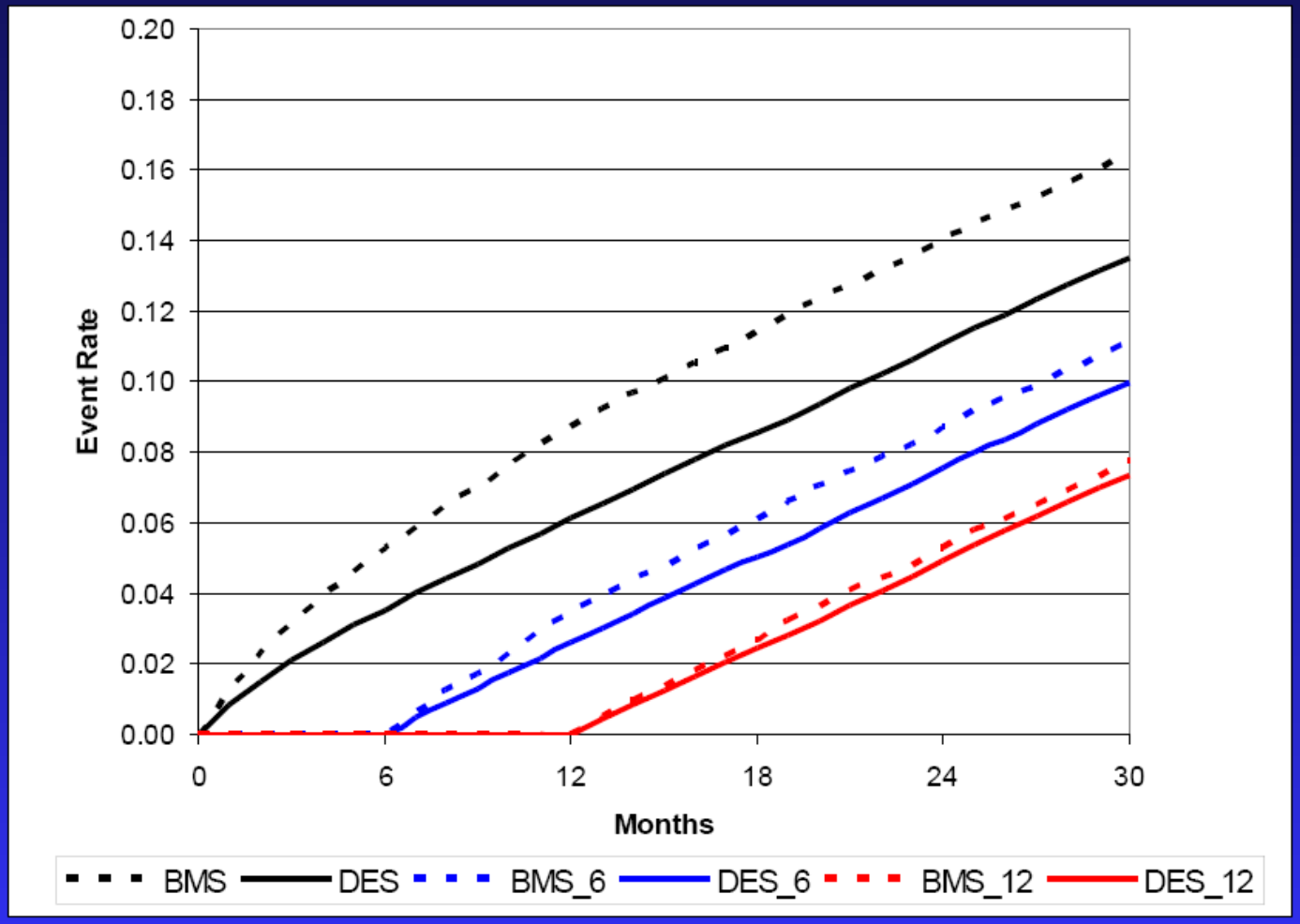
- **Objective:** To examine comparative effectiveness and safety of DES vs BMS in a national PCI cohort
- **Population:** All NCDR PCI pts 1/04-12/06
- **Follow up:** Linkage to CMS inpatient claims data using indirect identifiers; 76% matched
- **Final cohort:** 262,700 pts
  - 83% DES; 46% Cypher, 55% Taxus
- **Analysis:** Inverse propensity weighted model
  - 102 covariates; Cox PH to verify mortality

AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov
Duke Clinical Research Institute
NCDR™ CathPCI Registry
National Cardiovascular Data Registry

DES and BMS Event Rates: 30-month Adjusted



Landmark Display: Mortality



Conclusions

- Linkage of clinically rich NCDR data to claims data is feasible; Data analysis allows a robust, longitudinal assessment of clinical effectiveness
- Comparing outcomes of DES to BMS at 30 mo:
  - No identifiable DES safety concerns
  - Lower death and MI rates in DES patients
  - Slightly lower revasc, bleeding; Similar stroke rates
- Results consistent among all patient subgroups
- Caveat: The apparent 'benefit' of DES may be affected by selection bias and unmeasured confounders present in this real world cohort

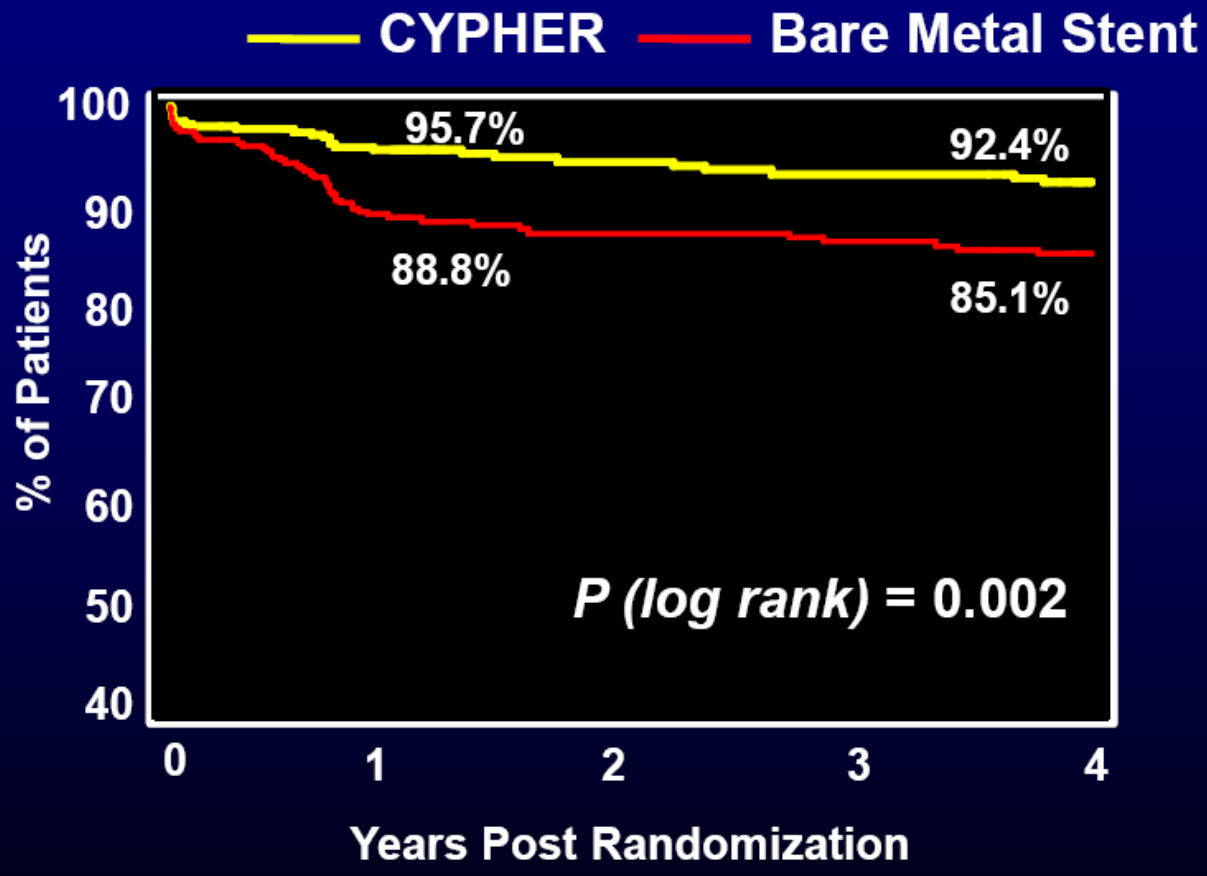
4-Year Extension

- By study design, TYPHOON was closed after 1-year follow-up
- TYPHOON was reopened in 2007 to ascertain 4-year follow-up due to concerns about very late stent thrombosis, especially in high-risk patients such as ST-elevation myocardial infarction
  - Resubmission to ethics committees was necessary
  - Patients were contacted an average of 3 years after inclusion to sign an informed consent for the extension
  - Events were adjudicated by an independent Critical Events Committee using the Academic Research Consortium (ARC)/Dublin definitions
  - Data management and analysis was performed by Cardialysis (Rotterdam, The Netherlands)

TYPHOON 4 yr FU

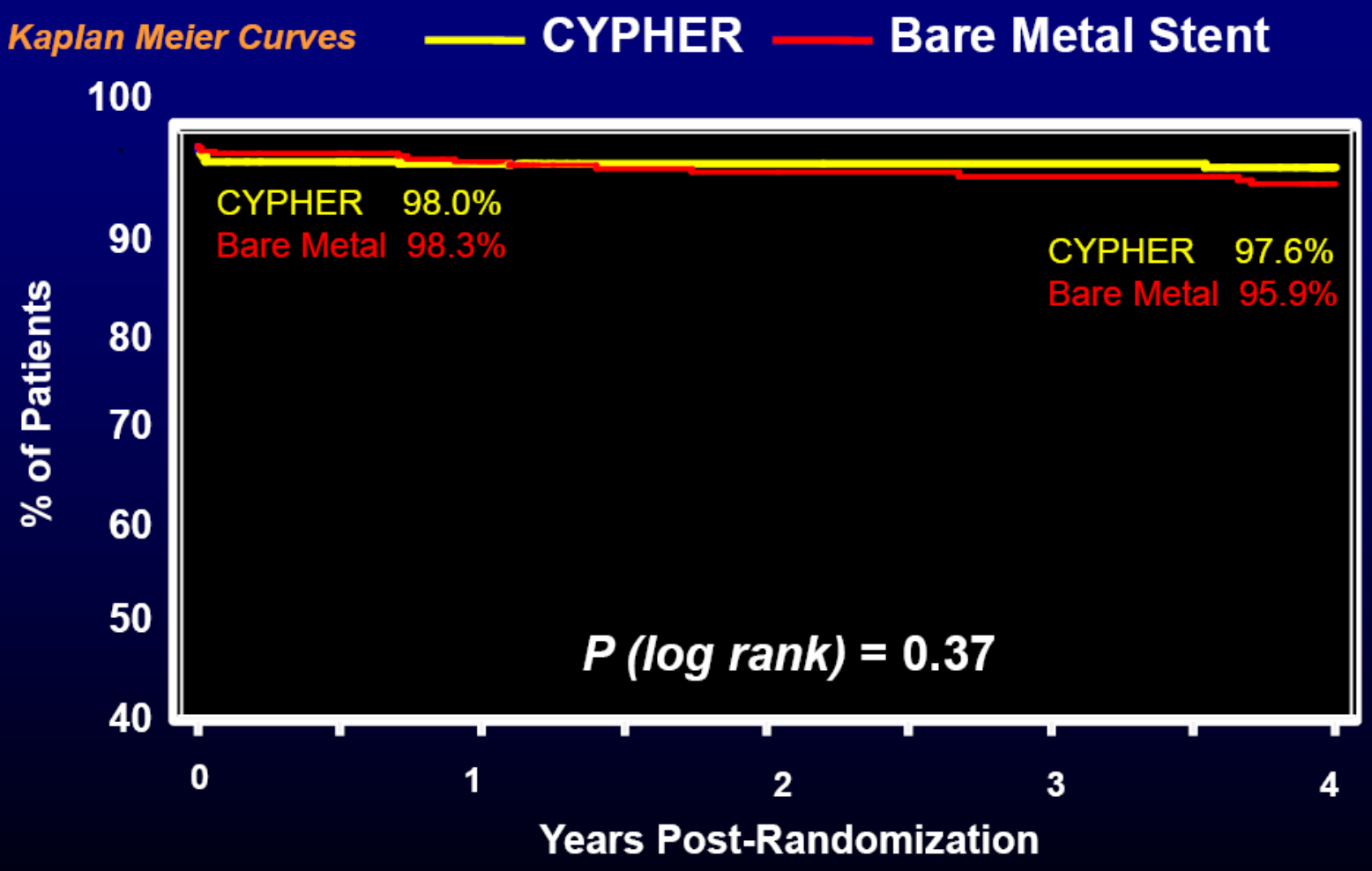
Freedom from Target Lesion Revascularization

Kaplan Meier Curves



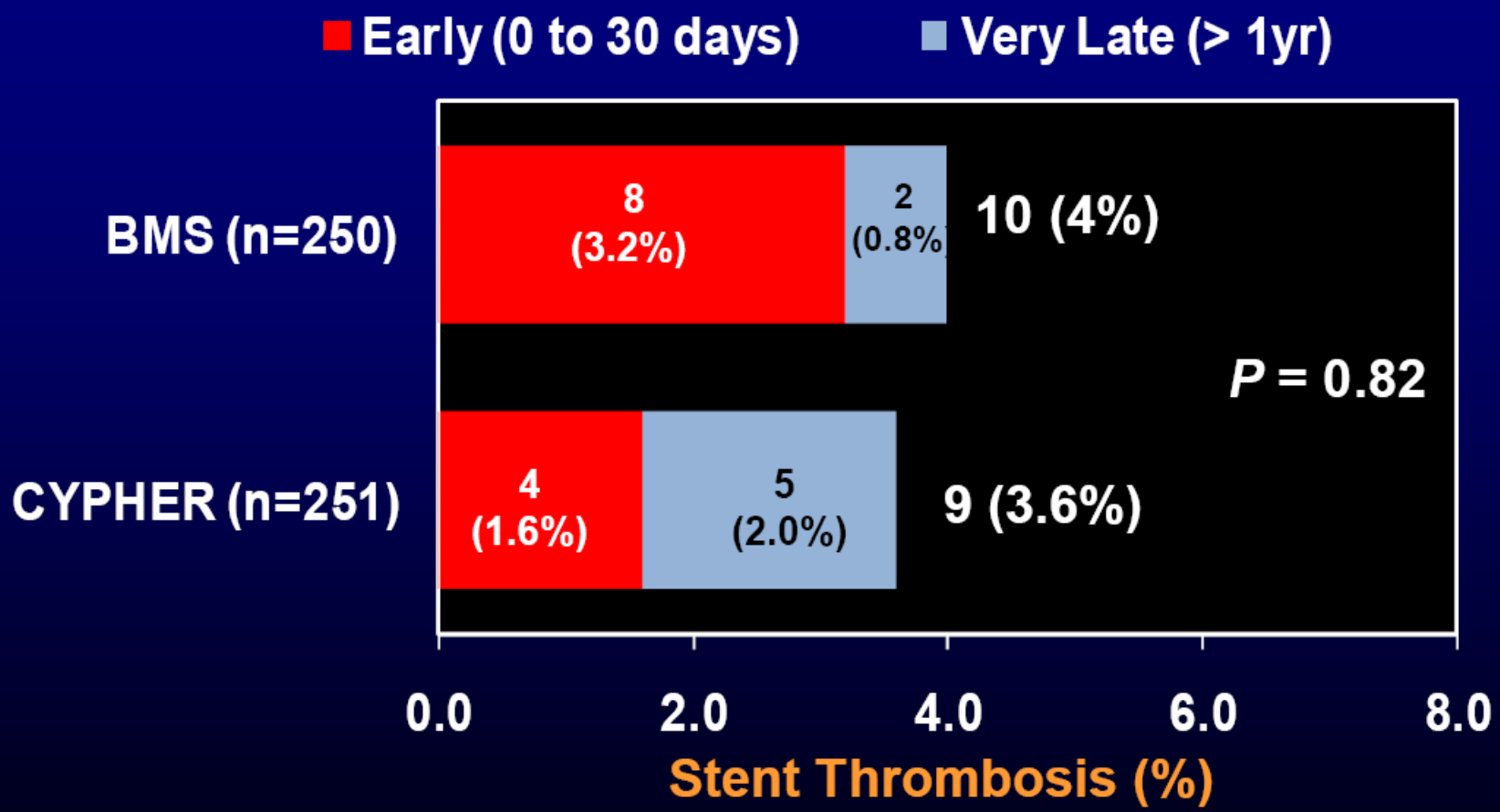
TYPHOON 4 yr FU

Freedom from Cardiac Death



TYPHOON 4 yr FU

ARC Definite Stent Thrombosis at 4 Years

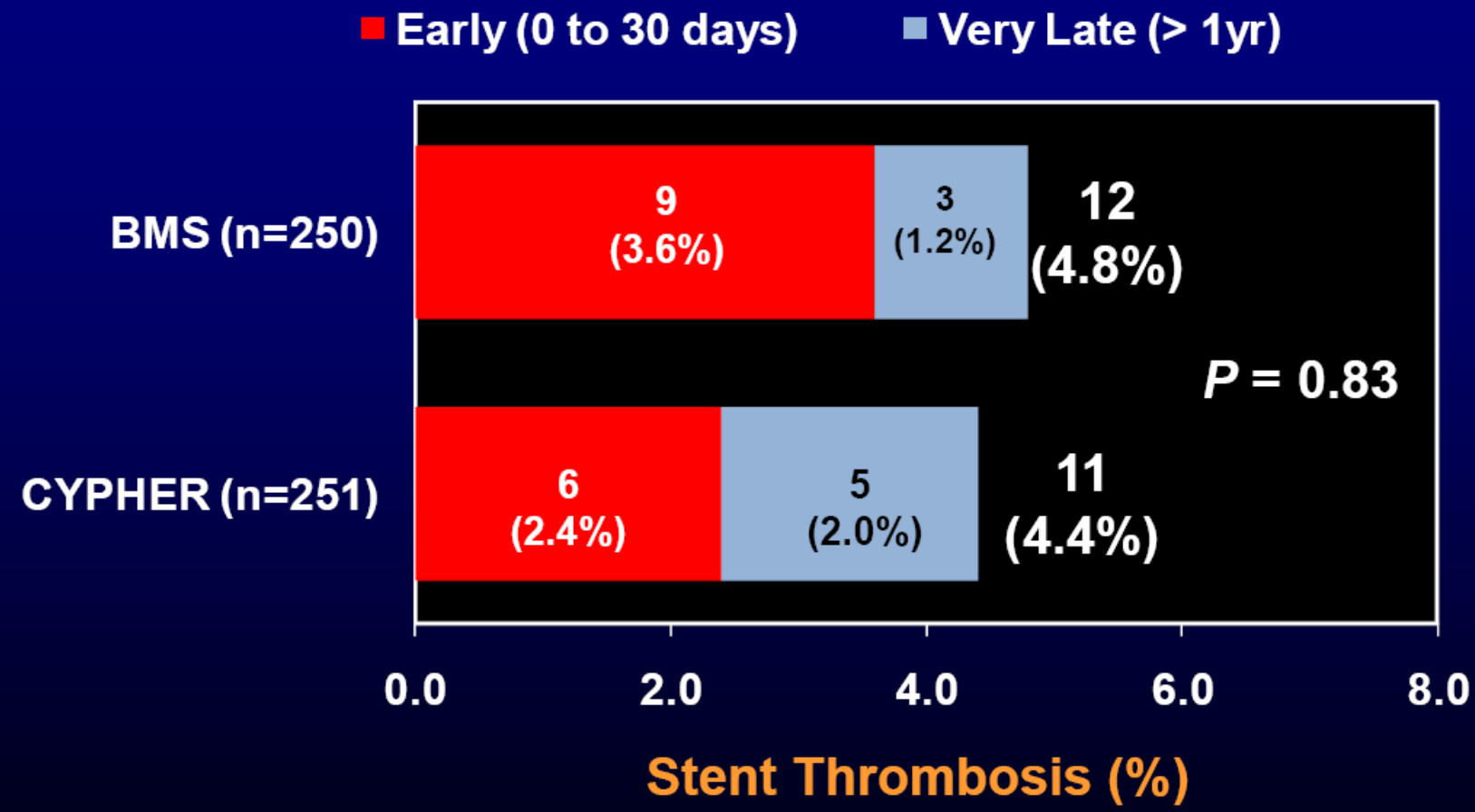


No late (>30 days to 1 yr) definite stent thrombosis

ARC/Dublin definitions. Hierarchical events

TYPHOON 4 yr FU

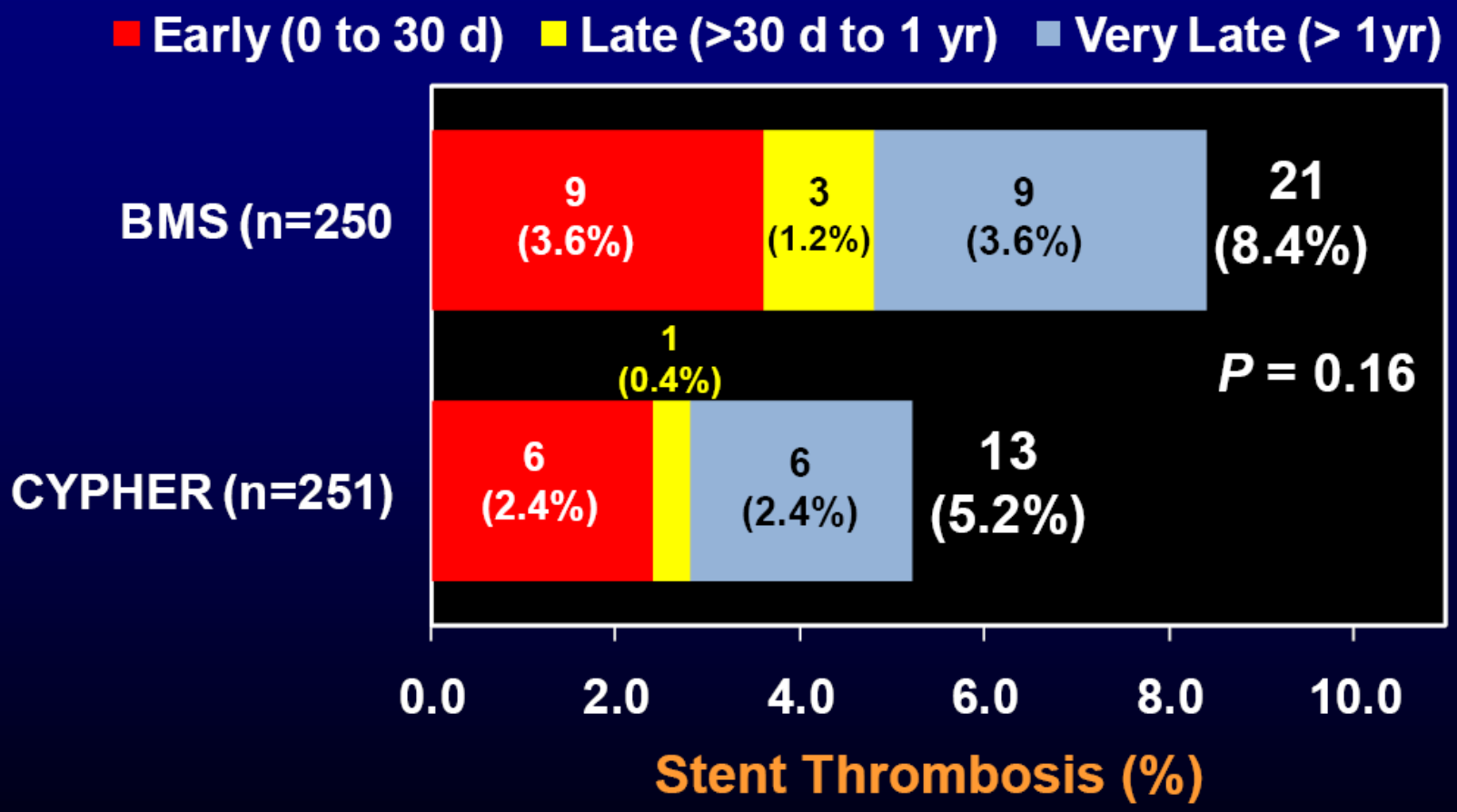
ARC Definite/Probable Stent Thrombosis at 4 Years



No late (>30 days to 1 yr) definite/probable stent thrombosis

ARC/Dublin definitions. Hierarchical events

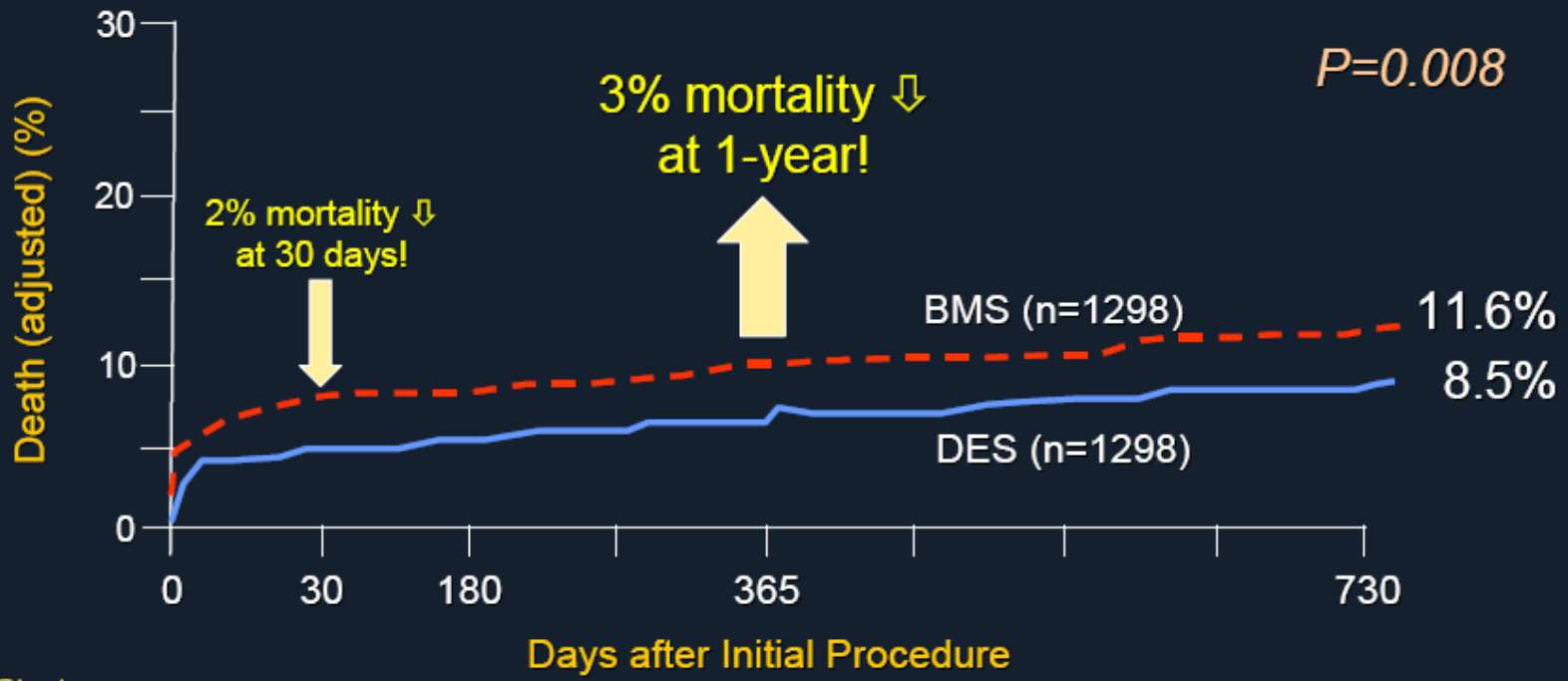
Any ARC-Defined Stent Thrombosis (Definite/Probable/Possible) at 4 Years



ARC/Dublin definitions. Hierarchical events

Massachusetts State Registry

2-year mortality (propensity adjusted) in 1298 matched pairs (2596 pts) with STEMI at 21 hospitals between 4/03–9/04



Drug-Eluting Stent					
No. at risk	1298	1289	1250	1227	1213
Cum. incidence (%)	0.7	3.7	5.5	6.5	8.5
Bare-Metal Stent					
No. at risk	1298	1292	1223	1194	1173
Cum. incidence (%)	0.5	5.8	8.0	9.6	11.6

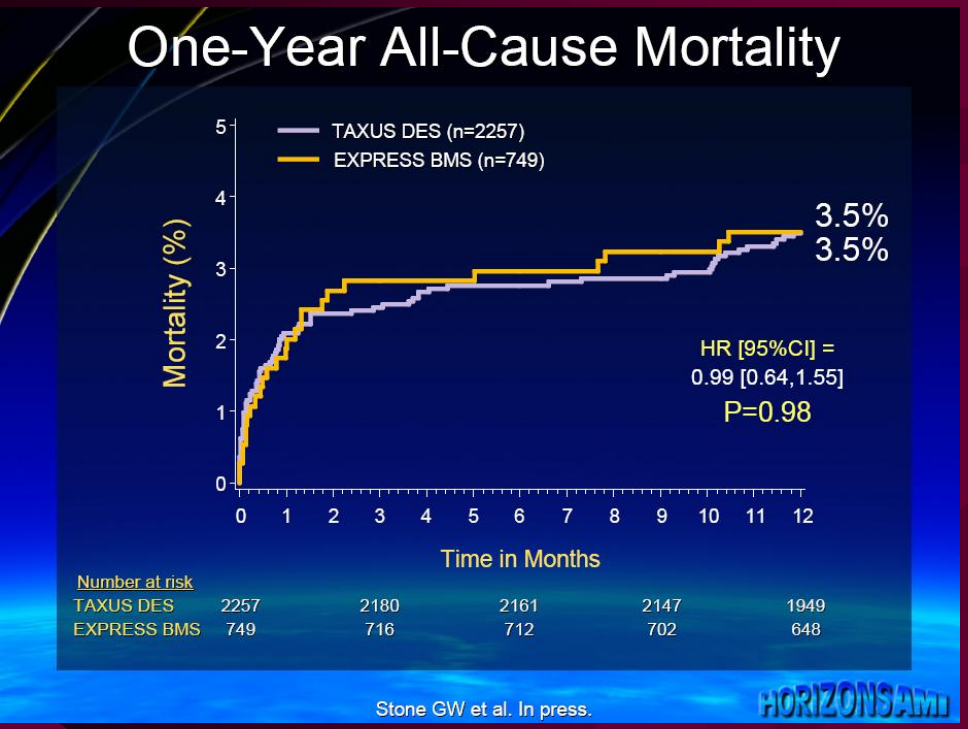
11 DES vs. BMS RCTs in AMI (n=3,607)

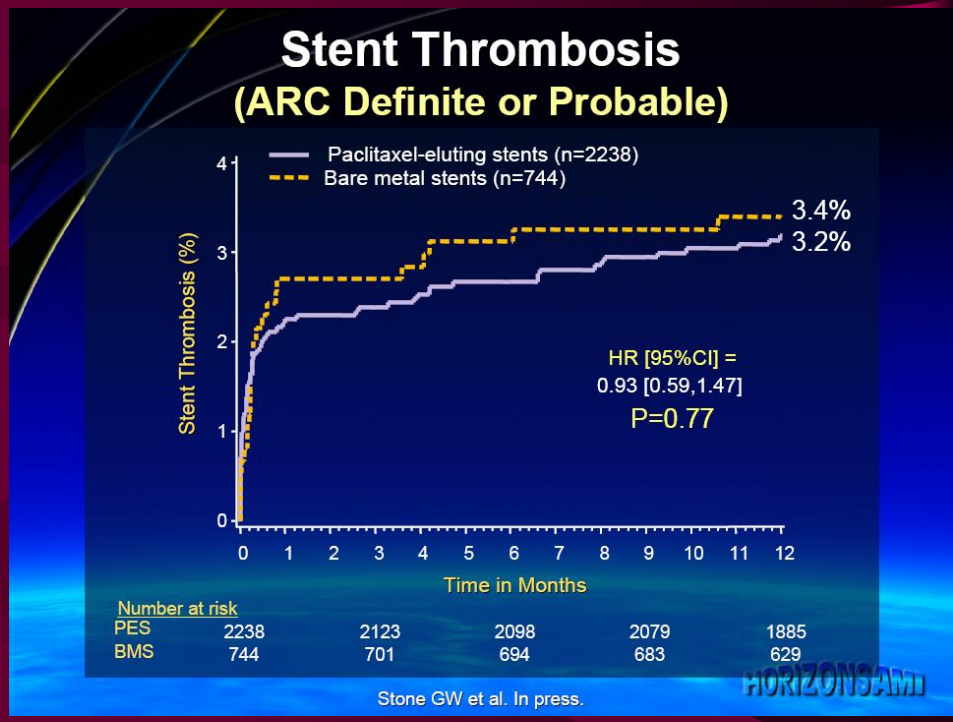
Death at 12 Months

Study	DES n/N	BMS n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
DiLorenzo et al	7/180	6/90		10.20	0.57 [0.18, 1.74]
BASKET-AMI	6/143	6/74		10.05	0.50 [0.15, 1.60]
DEDICATION	16/313	8/313		10.07	2.05 [0.87, 4.87]
Diaz de la Llera et al	3/60	2/54		2.65	1.37 [0.22, 8.52]
HAAMU-STENT	8/82	4/82		4.79	2.11 [0.61, 7.30]
MISSION	2/158	4/152		5.34	0.47 [0.09, 2.63]
PASSION	16/310	20/309		25.19	0.79 [0.40, 1.55]
SELECTION	1/40	3/40		3.88	0.32 [0.03, 3.18]
SESAMI	3/160	6/160		7.81	0.49 [0.12, 2.00]
STRATEGY	7/87	8/88		9.70	0.88 [0.30, 2.53]
TYPHOON	8/355	8/357		10.34	1.01 [0.37, 2.71]
Total (95% CI)	77/1888	75/1719		100.00	0.91 [0.66, 1.27] P=0.59
	4.1%	4.4%			

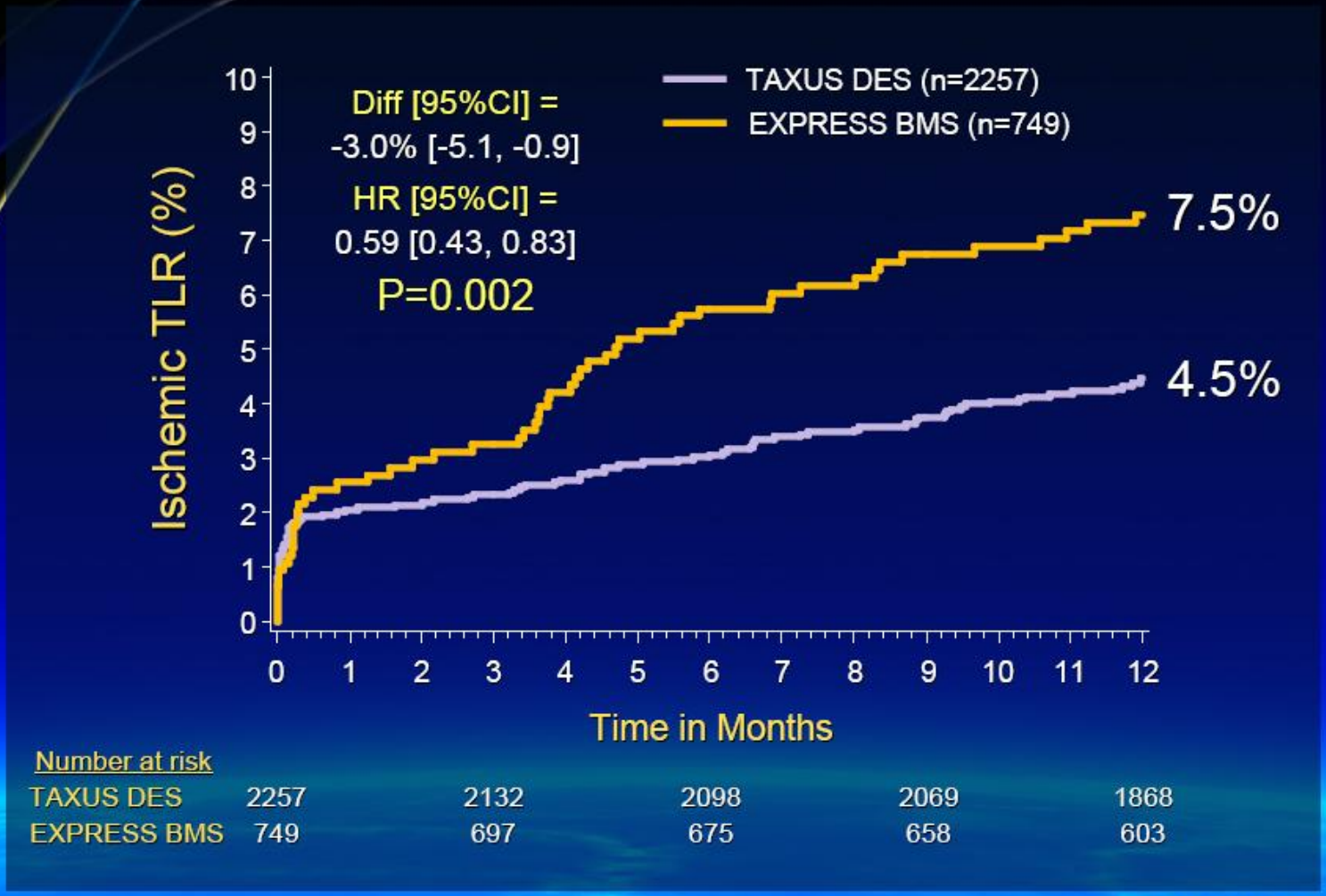
Test for heterogeneity: $I^2 = 0\%$

HORIZONS-AMI





Primary Efficacy Endpoint: Ischemic TLR



Stone GW et al. In press.

HORIZONS-AMI

Stent Selection in STEMI

- In pts with STEMI undergoing primary PCI, use of DES rather than BMS results in:
  - Comparable rates of stent thrombosis, reinfarction and death through 1 year
    - Registries were wrong regarding reduced death!
  - Significant reductions in TLR, TVR and angiographic late loss and restenosis, in all lesions except for those at low risk for restenosis
- Longer term follow-up is required to comprehensively assess the late safety and efficacy profile of DES in STEMI

HORIZONS AMI

Thank you!