SIRIUS 6 Year Follow-Up

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

Angioplasty Summit 2009 – TCT Asia Pacific
April 22-24, 2009; Seoul, Korea

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

Presenter Disclosure Information for Angioplasty Summit 2009

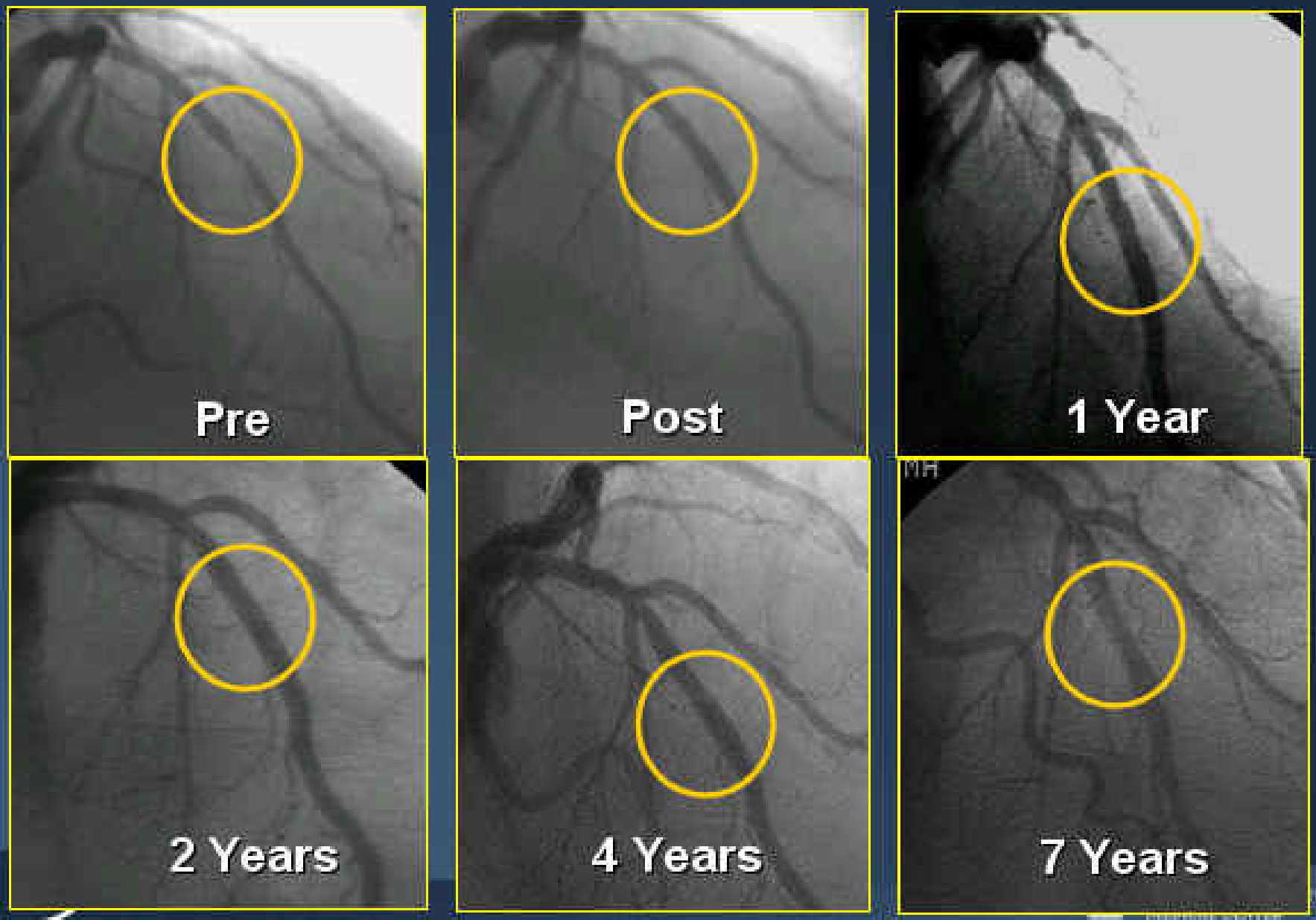
Martin B. Leon, M.D.

Scientific Advisory Board or Equity:
Abbott, Boston Scientific, Cordis, and Medtronic

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

CYPHER™ São Paulo: 7 Years FU



CARDIOVASCULAR RESEARCH FOUNDATION

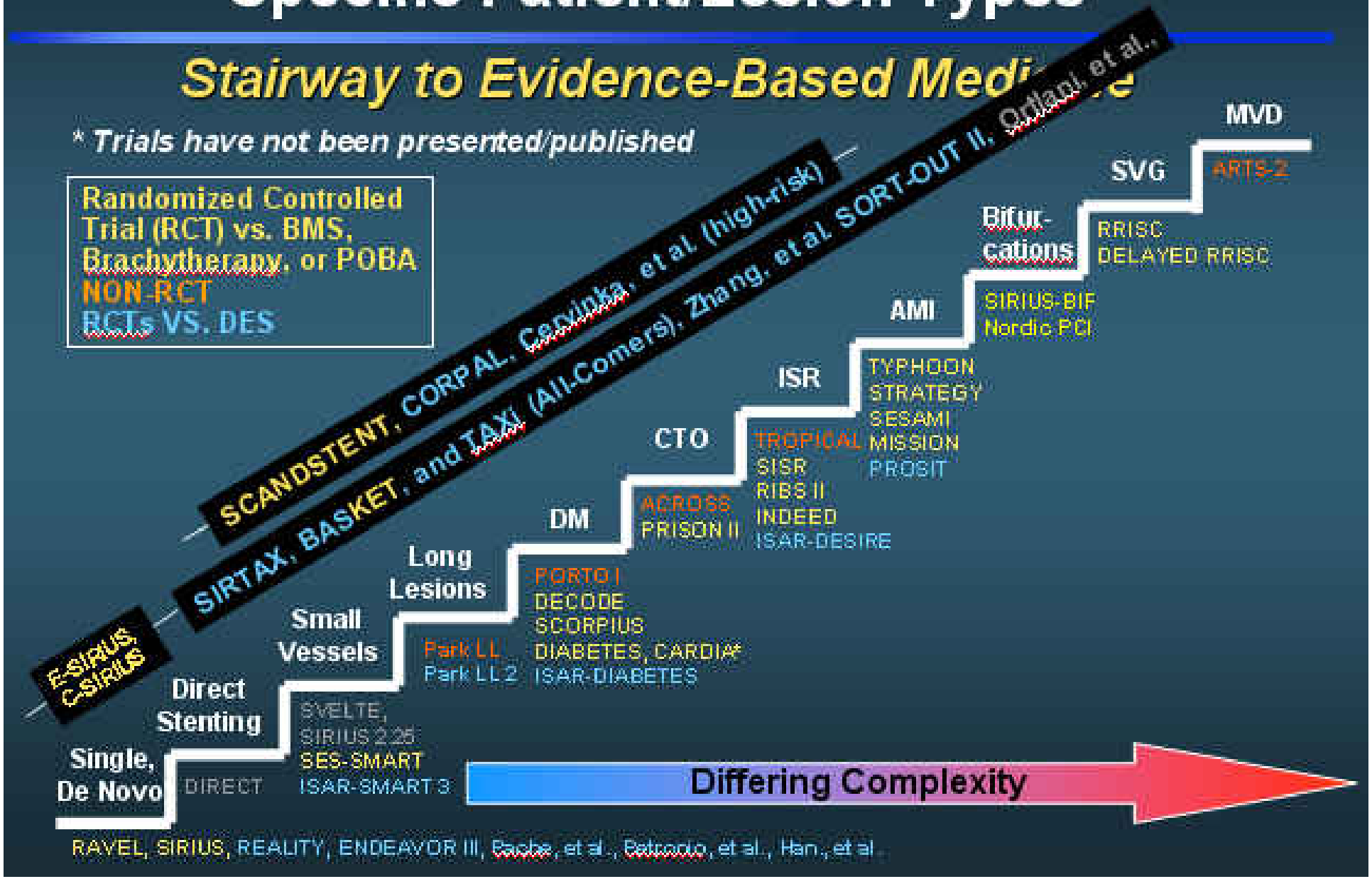
NewYork-Presbyterian

Sirolimus-Eluting Stent

Important Background

- The sirolimus-eluting stent has been studied under more clinical circumstances and in more patients than any other cardiovascular device in history!
- This device has stood the "test of time" and has been implanted in more patients than any other DES worldwide
- Apart from some baffling safety considerations (very late stent thrombosis), the clinical outcomes have been consistent and without equal!
- Late safety and efficacy data are essential to complete the overall clinical profile

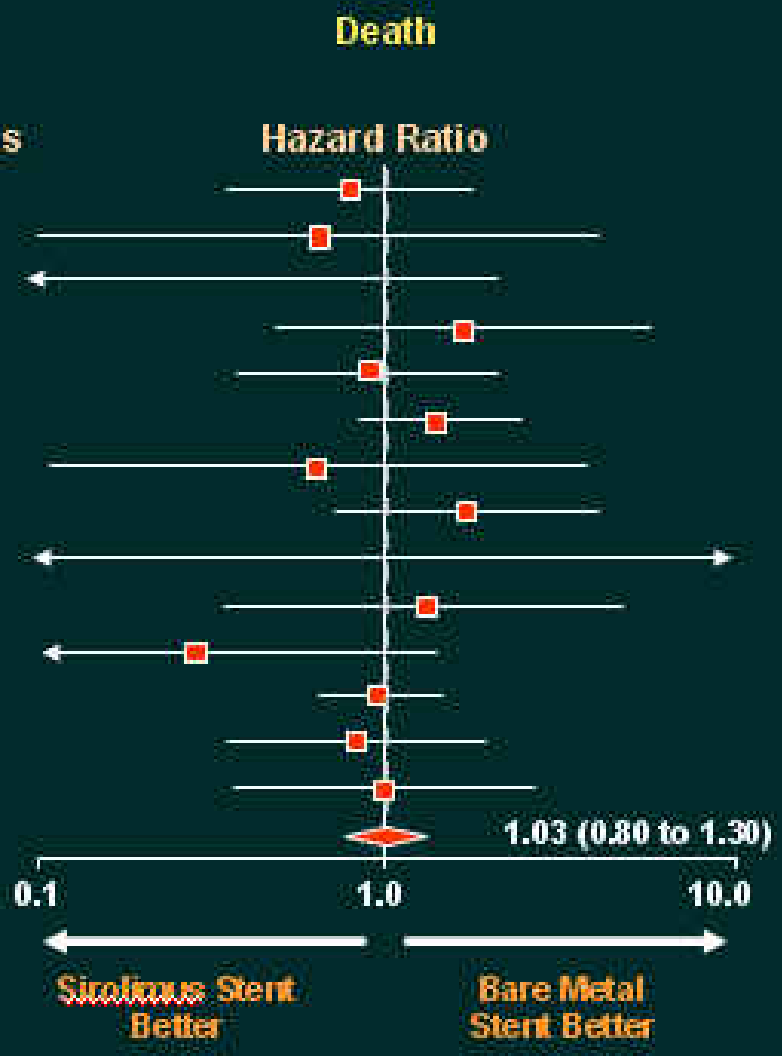
Dedicated Trials with CYPHER® Stent in Specific Patient/Lesion Types



14 Randomized Trials: SES vs. BMS

Death

Trial	Sirolimus Stent No. of events/total	Bare Metal Stent no. of patients
BASKET	10/264	13/281
C-SIRIUS	2/50	3/50
DECODE	0/54	2/29
DIABETES	7/80	5/80
E-SIRIUS	10/175	11/177
Pache et al.	29/250	24/250
PRISON II	2/100	3/100
RAVEL	14/120	8/118
SCANDSTENT	1/163	1/159
SCORPIUS	5/95	4/98
SESAMI	3/160	7/160
SIRIUS	45/533	46/525
STRATEGY	10/87	12/88
TYPHOON	8/355	8/357
OVERALL	146/2486	147/2472



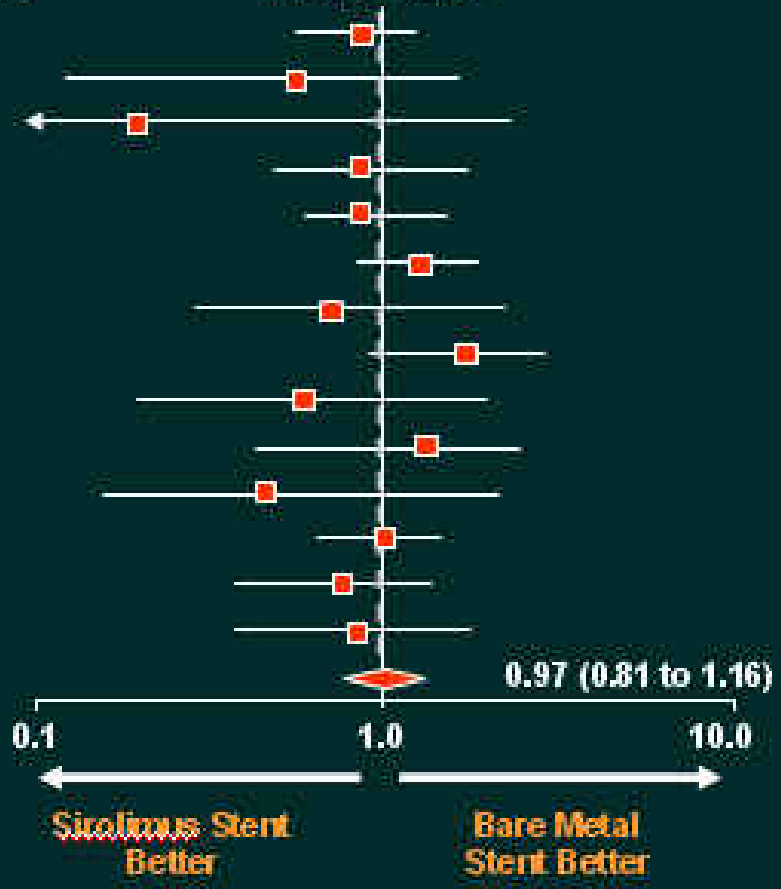
P (heterogeneity) = 0.75
I^2 = 0%
P (overall effect) = 0.80

Kastrati et al. *NEJM* 2007; 356: 1030-9

14 Randomized Trials: SES vs. BMS

Death or MI

Trial	Sirolimus Stent Stent No. of events/total	Bare Metal Stent No. of patients
BASKET	23/264	27/281
C-SIRIUS	4/50	7/50
DECODE	1/54	2/29
DIABETES	10/80	12/80
E-SIRIUS	19/175	22/177
Pache et al.	38/250	35/250
PRISON II	5/100	6/100
RAVEL	22/120	12/118
SCANDSTENT	4/163	7/159
SCORPIUS	10/95	9/98
SESAMI	6/160	10/160
SIRIUS	74/533	72/525
STRATEGY	14/87	18/88
TYPHOON	11/355	13/357
OVERALL	241/2486	252/2472



P (heterogeneity) = 0.80
I2 = 0%
P (overall effect) = 0.76

Cardiovascular Research Foundation

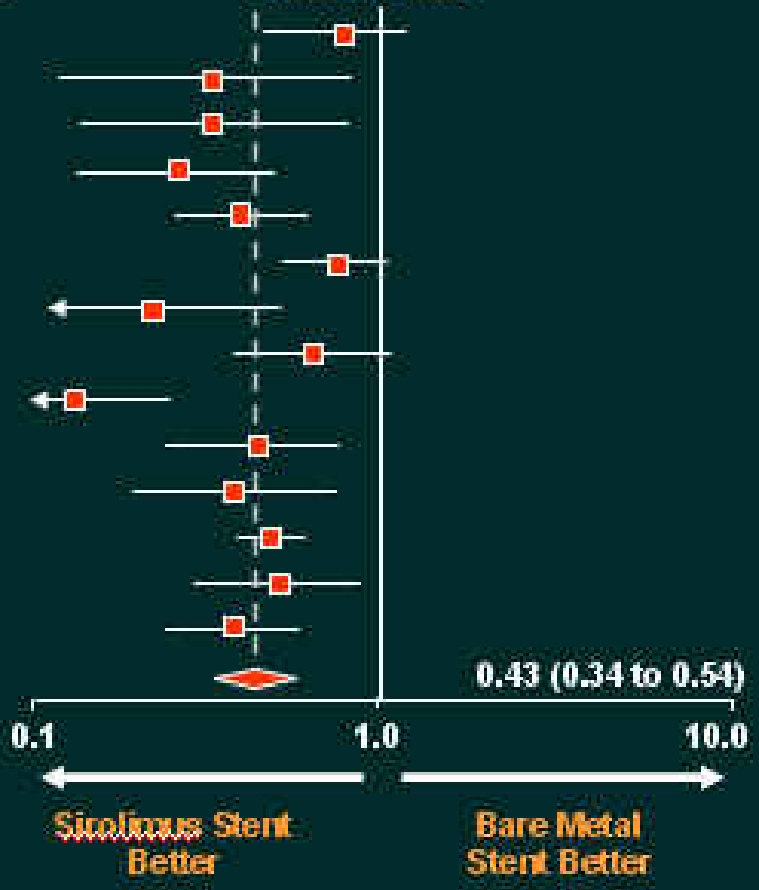
Kastrati et al. *NEJM* 2007; 356: 1030-9

Columbia University Medical Center
NewYork-Presbyterian

14 Randomized Trials: SES vs. BMS

Death, MI, or Re-Intervention

Trial	Sirolimus Stent Stent No. of events/total	Bare Metal Stent no. of patients
BASKET	32/264	41/281
C-SIRIUS	5/50	14/50
DECODE	8/54	11/29
DIABETES	10/80	33/80
E-SIRIUS	26/175	58/177
Pache et al.	59/250	73/250
PRISON II	6/100	25/100
RAVEL	20/120	28/118
SCANDSTENT	7/163	51/159
SCORPIUS	15/95	32/98
SESAMI	11/160	26/160
SIRIUS	91/533	164/525
STRATEGY	17/87	31/88
TYPHOON	24/355	62/357
OVERALL	331/2486	649/2472



P (heterogeneity) = 0.75
I2 = 0%
P (overall effect) = 0.80

CARDIOVASCULAR RESEARCH FOUNDATION

Kastrati et al. *NEJM* 2007; 356: 1030-9

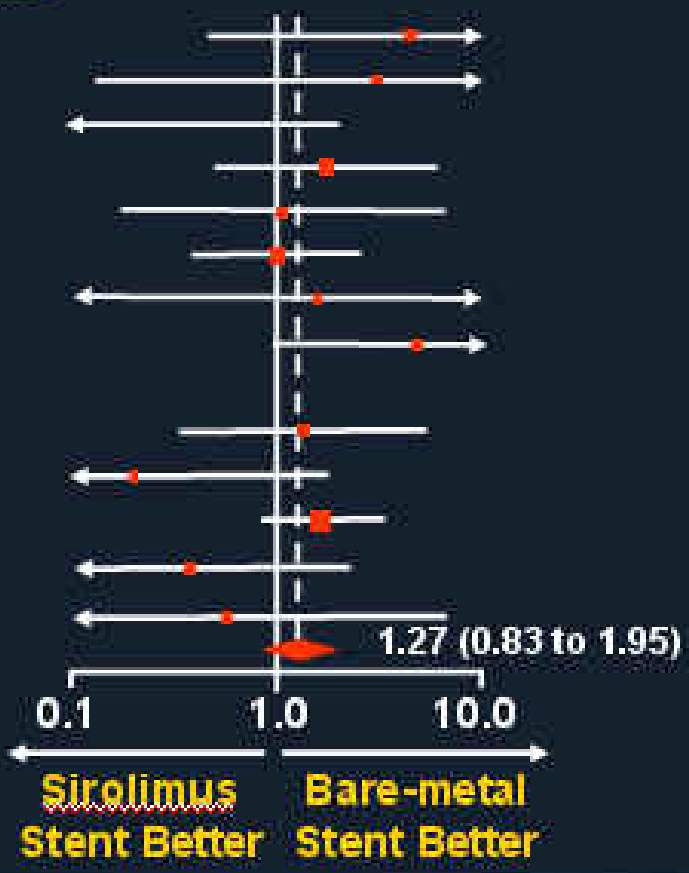
COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

14 Randomized Trials: SES vs. BMS

DIABETICS - *Death*

Trial	Sirolimus Stent No. of events/total no. of patients	Bare-Metal Stent No. of events/total no. of patients
BASKET	3/41	1/60
C-SIRIUS	1/12	0/12
DECODE	0/54	2/29
DIABETES	7/80	5/80
E-SIRIUS	2/33	3/48
Pache et al.	9/72	12/82
PRISON II	1/11	1/16
RAVEL	6/19	2/25
SCANDSTENT	0/29	0/29
SCORPIUS	5/95	4/98
SESAMI	2/28	6/37
SIRIUS	20/131	15/148
STRATEGY	2/15	3/11
TYPHOON	1/55	2/61
Overall	59/675	56/736

P (heterogeneity)=0.37
I^2=7%
P (overall effect)=0.26



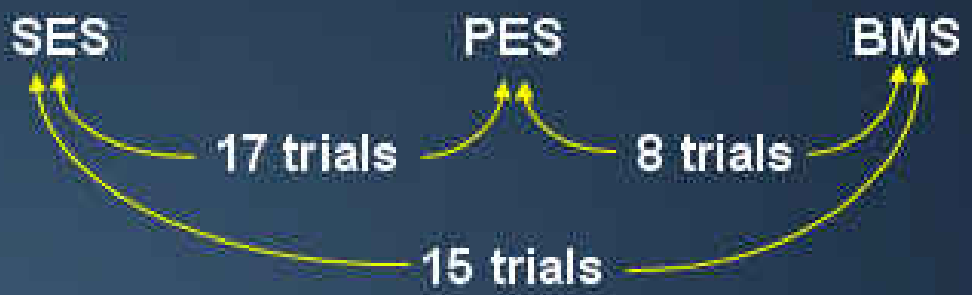
Kastrati et al, *N Eng J Med* 2007;356:1030-9

Collaborative Network Meta-analysis

Stettler C et al. Lancet 2007;370:937-48

38 trials; 18,023 patients

sirolimus-eluting, paclitaxel-eluting, bare metal stents



Description of the methodology

"An extension of multivariable Bayesian hierarchical random effects models for mixed multiple treatment comparisons"

"A random-walk model based on piece-wise constant hazards"

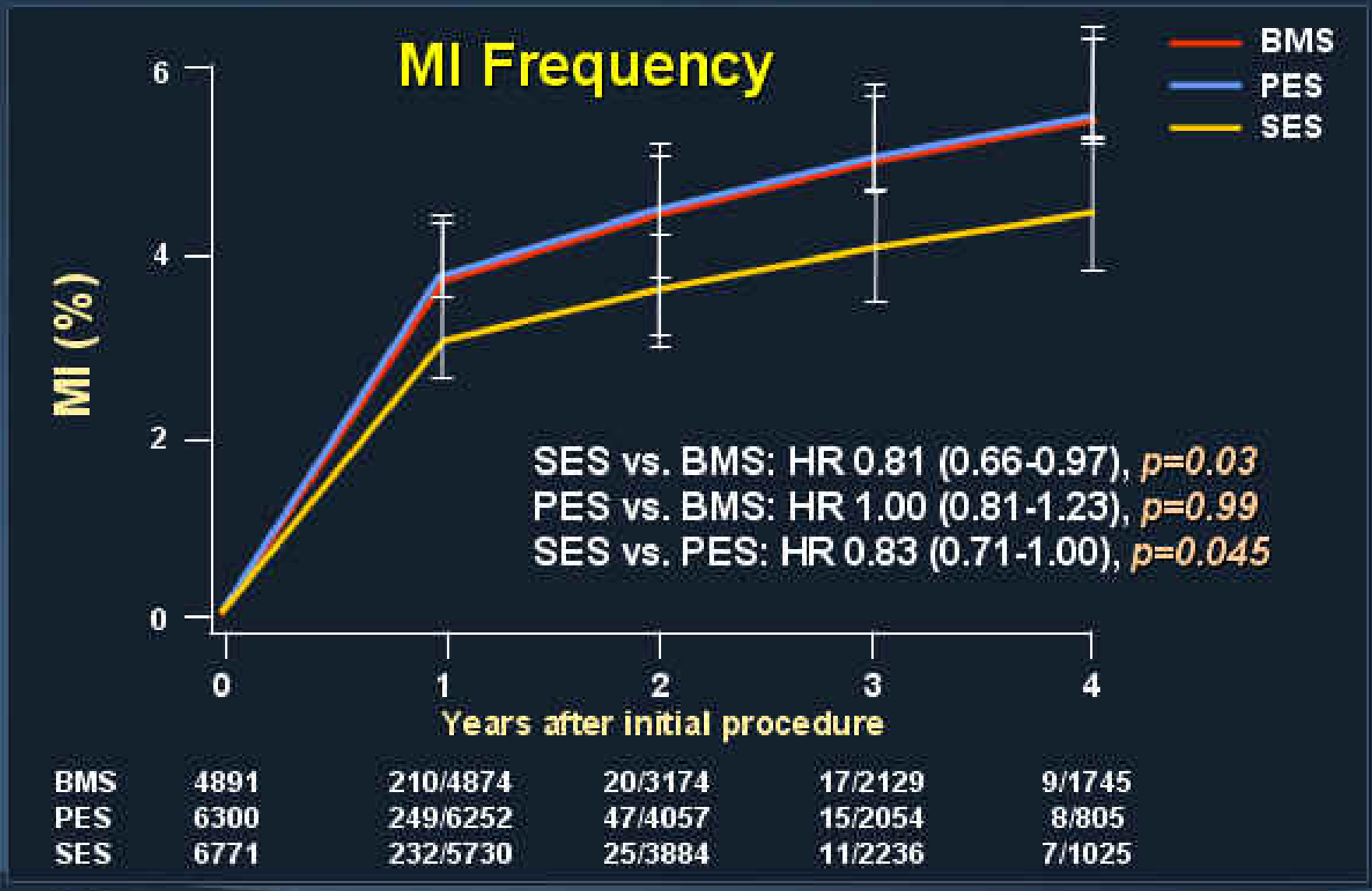
"Random effects at the level of trials, time periods and comparisons"

Network meta-analysis: 38 trials, 18,023 pts

BMS	4921	109/4904	48/3340	31/2264	44/1875
PES	6331	138/6283	78/4263	32/2187	15/869
SES	6771	139/6730	72/4041	38/2340	24/10810

Stettler C et al. Lancet 2007;370:937-48

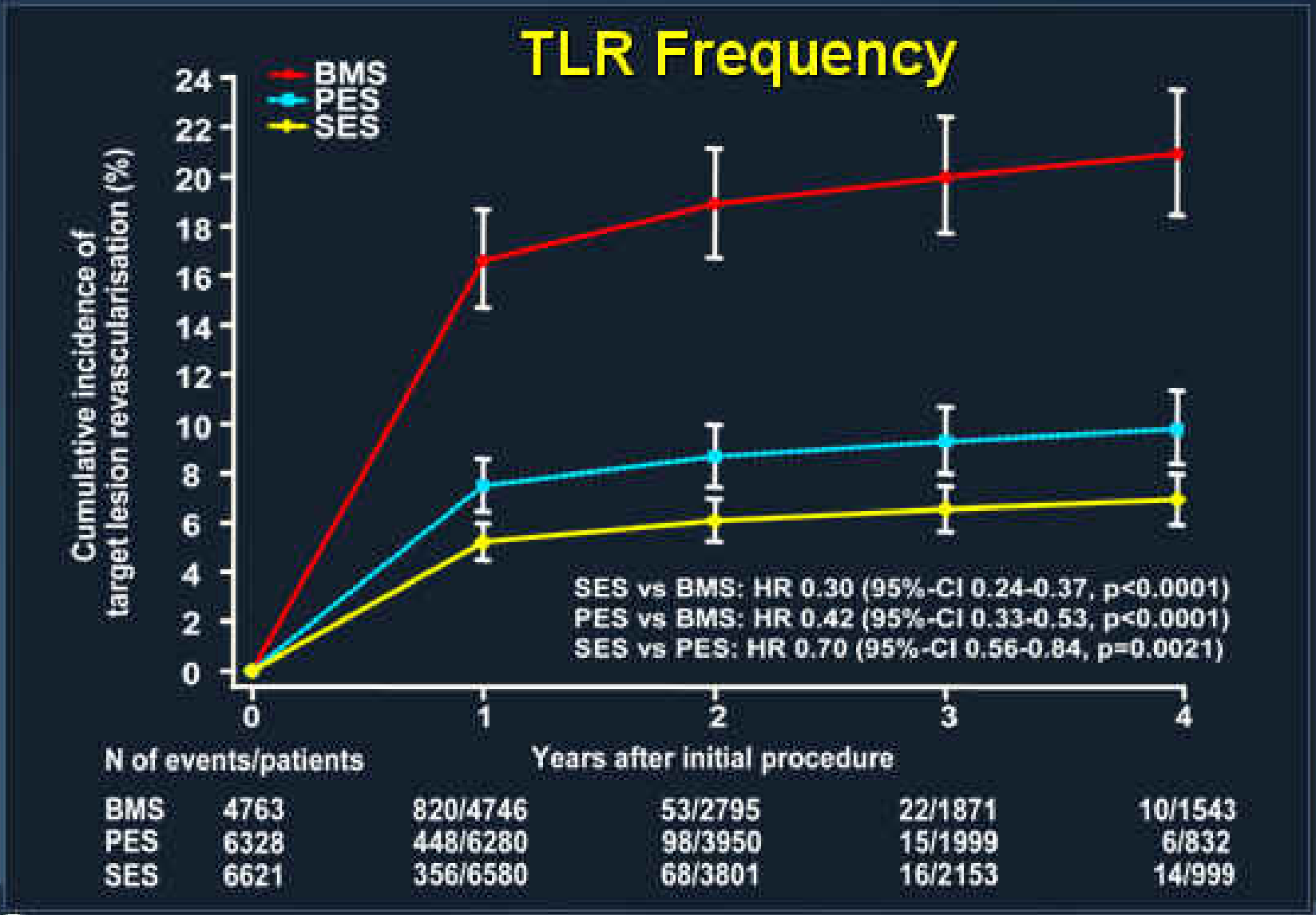
Network meta-analysis: 38 trials, 18,023 pts



BMS	4891	210/4874	20/3174	17/2129	9/1745
PES	6300	249/6252	47/4057	15/2054	8/805
SES	6771	232/5730	25/3884	11/2236	7/1025

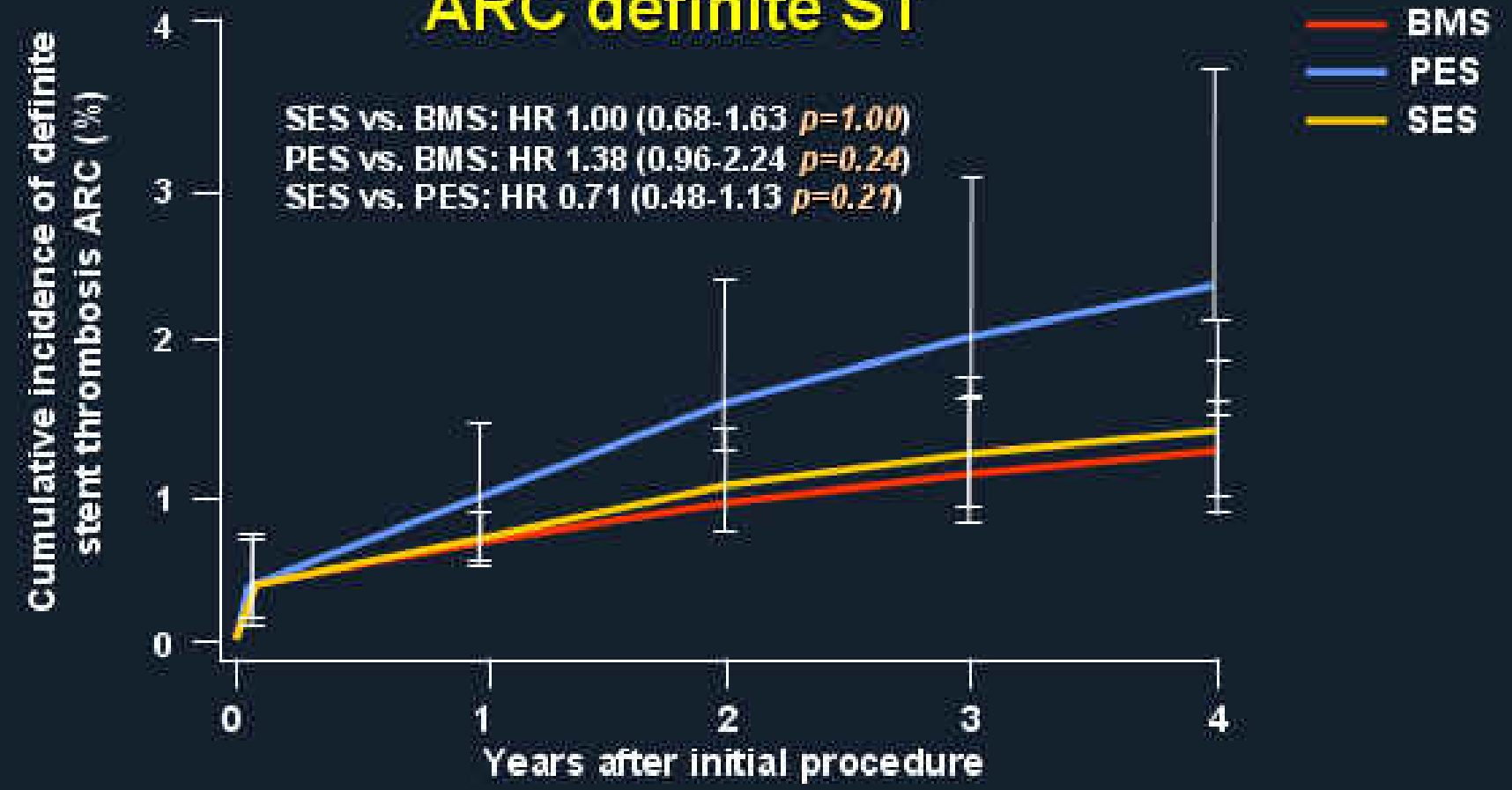
Stettler C et al. Lancet 2007;370:937-48

Network meta-analysis: 38 trials, 18,023 pts



Stettler C et al. Lancet 2007;370:937-48

Network meta-analysis: 38 trials, 18,023 pts



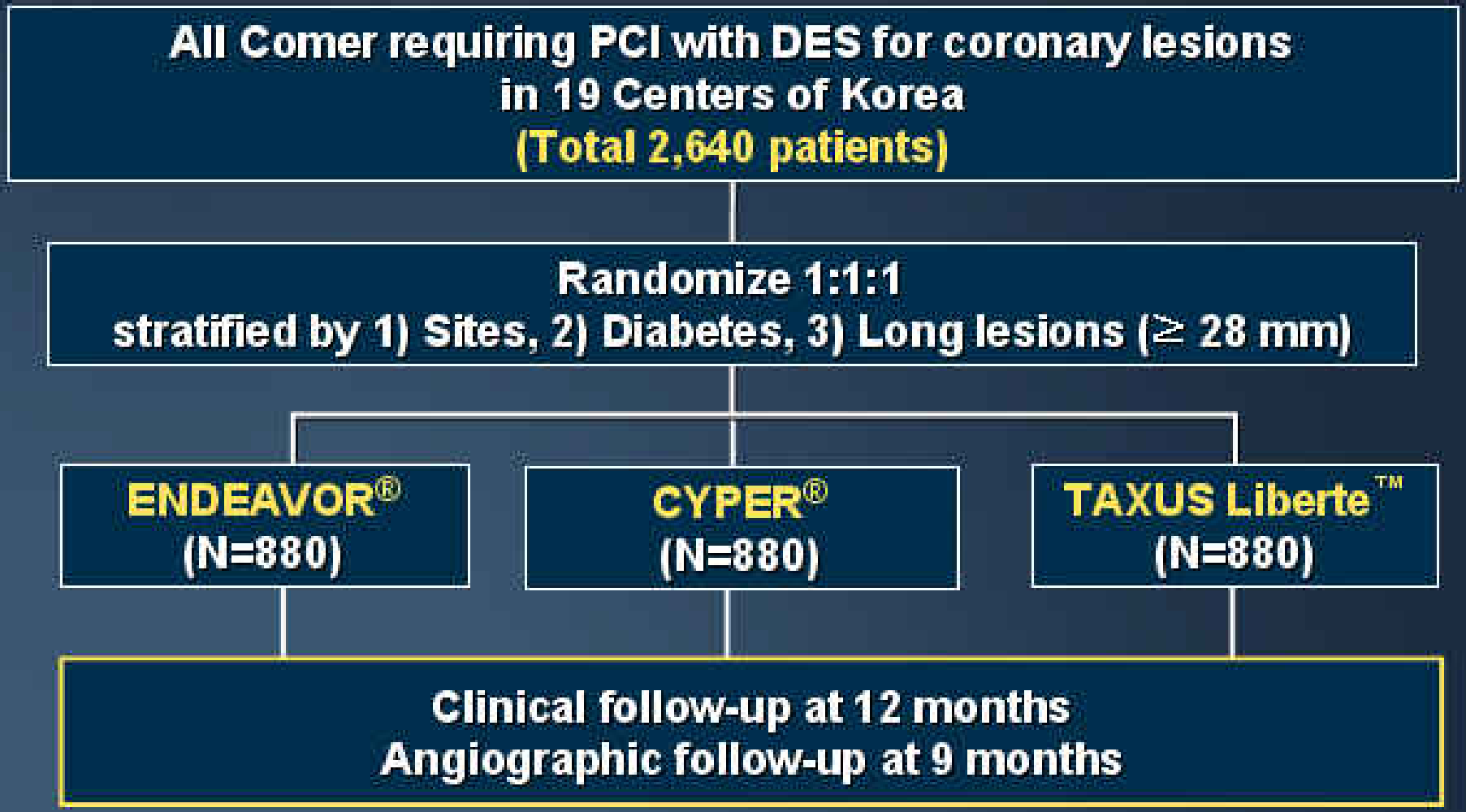
BMS	4003	42/4000	4/3048	3/1928	1/1806
PES	4327	46/4321	20/3711	5/1853	1/762
SES	4643	52/4642	9/3804	3/2257	2/1070

Stettler C, et al. *Lancet.* 2007;370:937-48

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

ZEST - Study Design



Intention-to-Treat Analyses

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

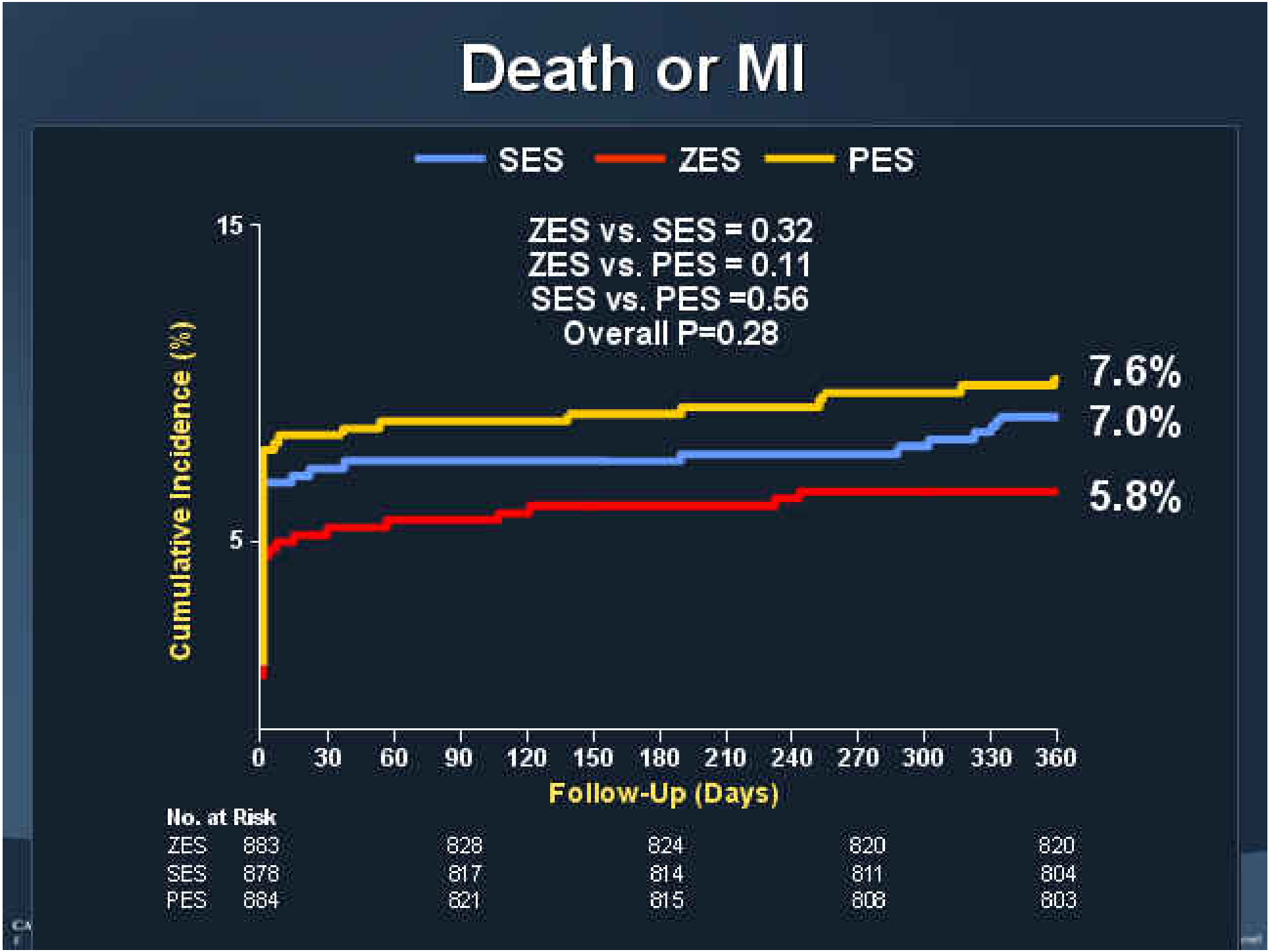
Death, MI, Ischemia-driven TVR

Primary End Point at 12 month

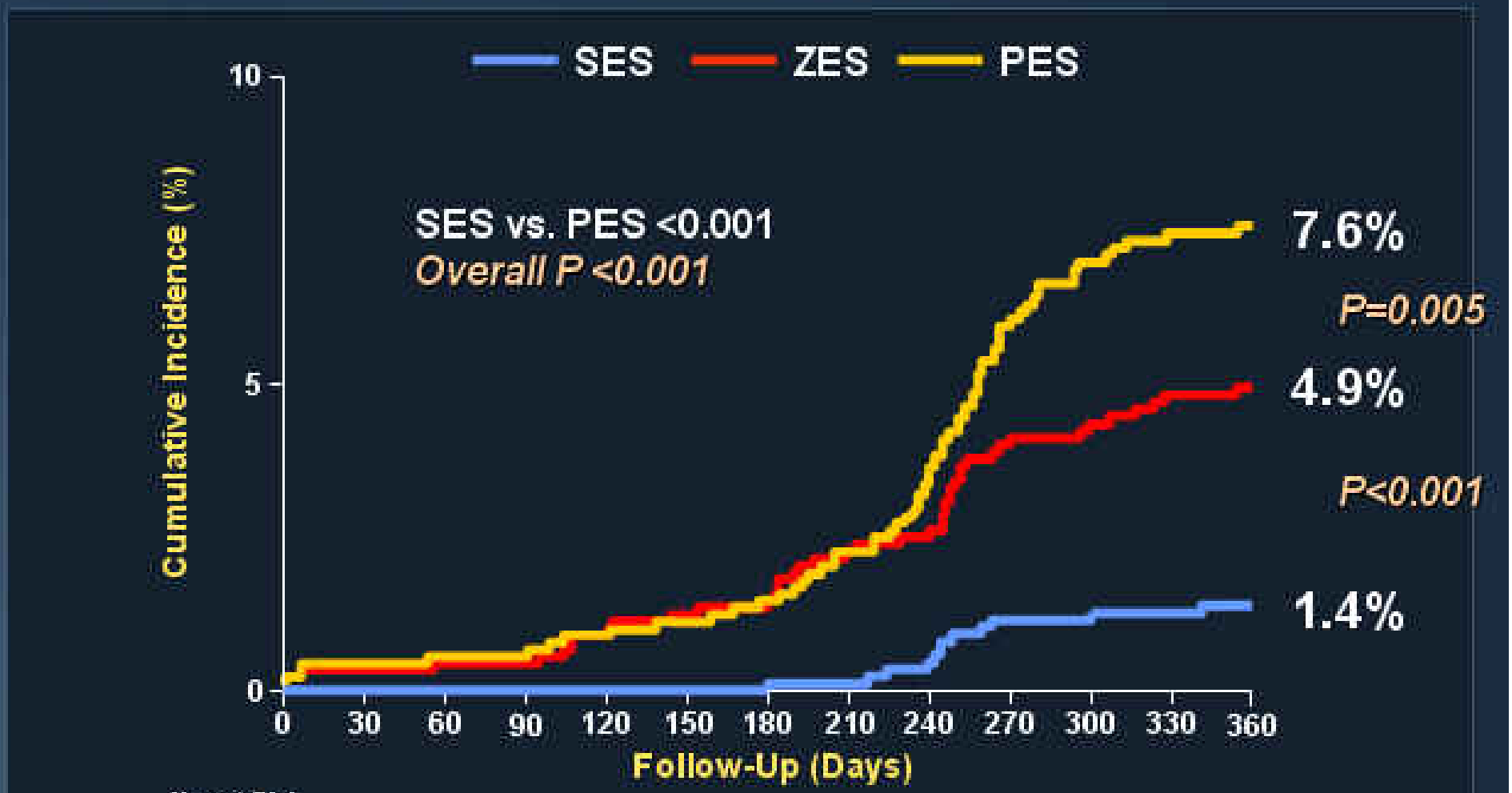
CARDIOVASCULAR RESEARCH FOUNDATION

NewYork-Presbyterian

Death or MI


SES
ZES
PES
ZES vs. SES = 0.32
ZES vs. PES = 0.11
SES vs. PES =0.56
Overall P=0.28
15
5
Cumulative Incidence (%)
7.6%
7.0%
5.8%
0
30
60
90
120
150
180
210
240
270
300
330
360
Follow-Up (Days)
No. at Risk
ZES 883 828 824 820 820
SES 878 817 814 811 804
PES 884 821 815 808 803

Ischemic Driven TLR

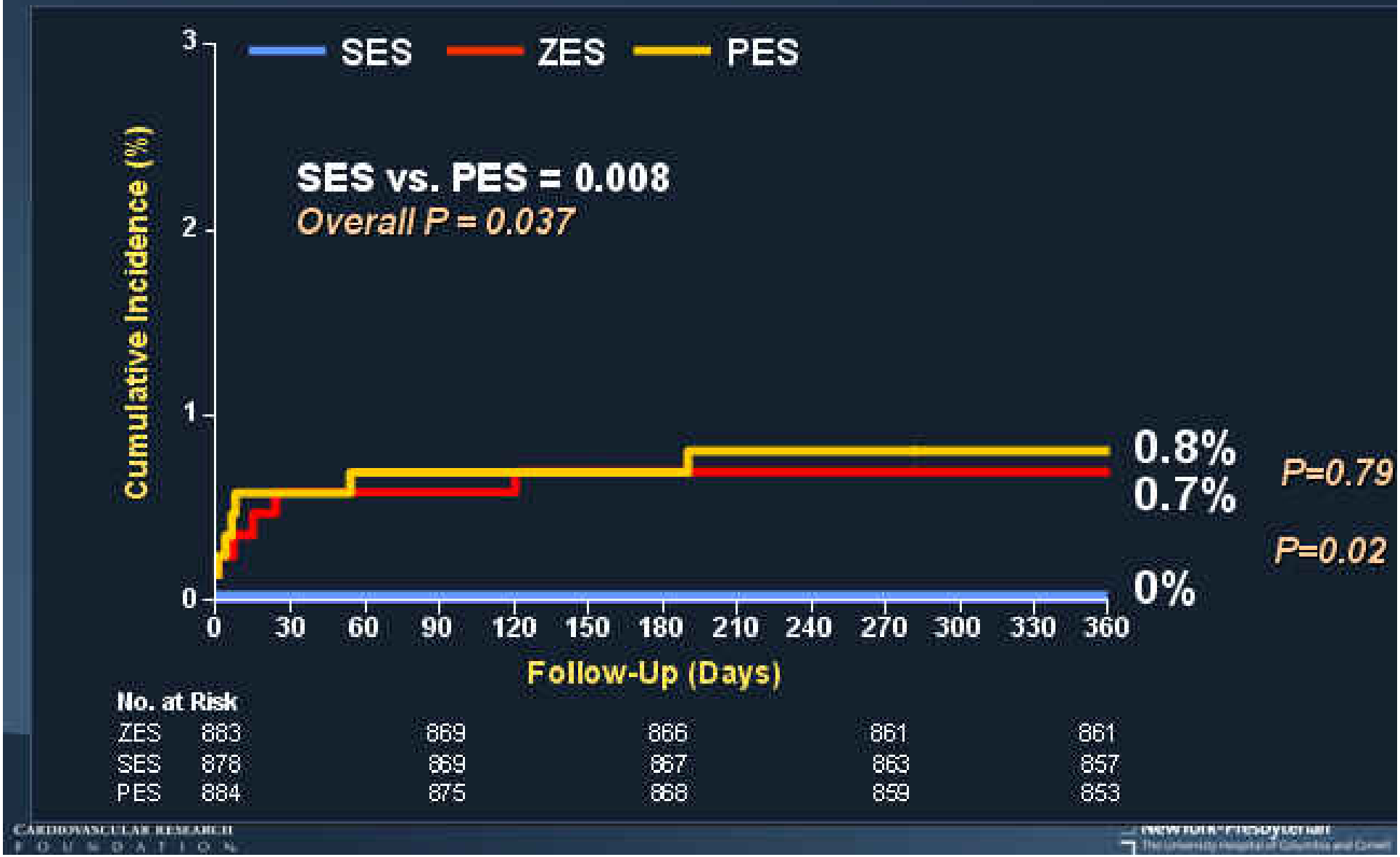


No. at Risk

ZES	883	868	857	829	822
SES	878	869	866	853	845
PES	884	875	861	813	794

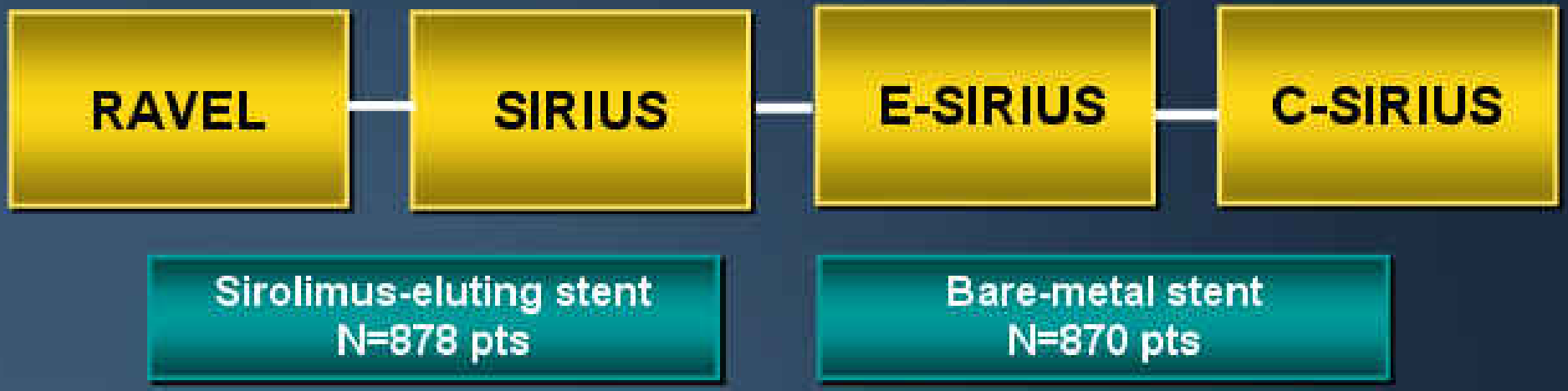
Stent Thrombosis

ARC Definite or Probable Criteria



Patient-level Pooled Analysis from 4 SES vs. BMS trials

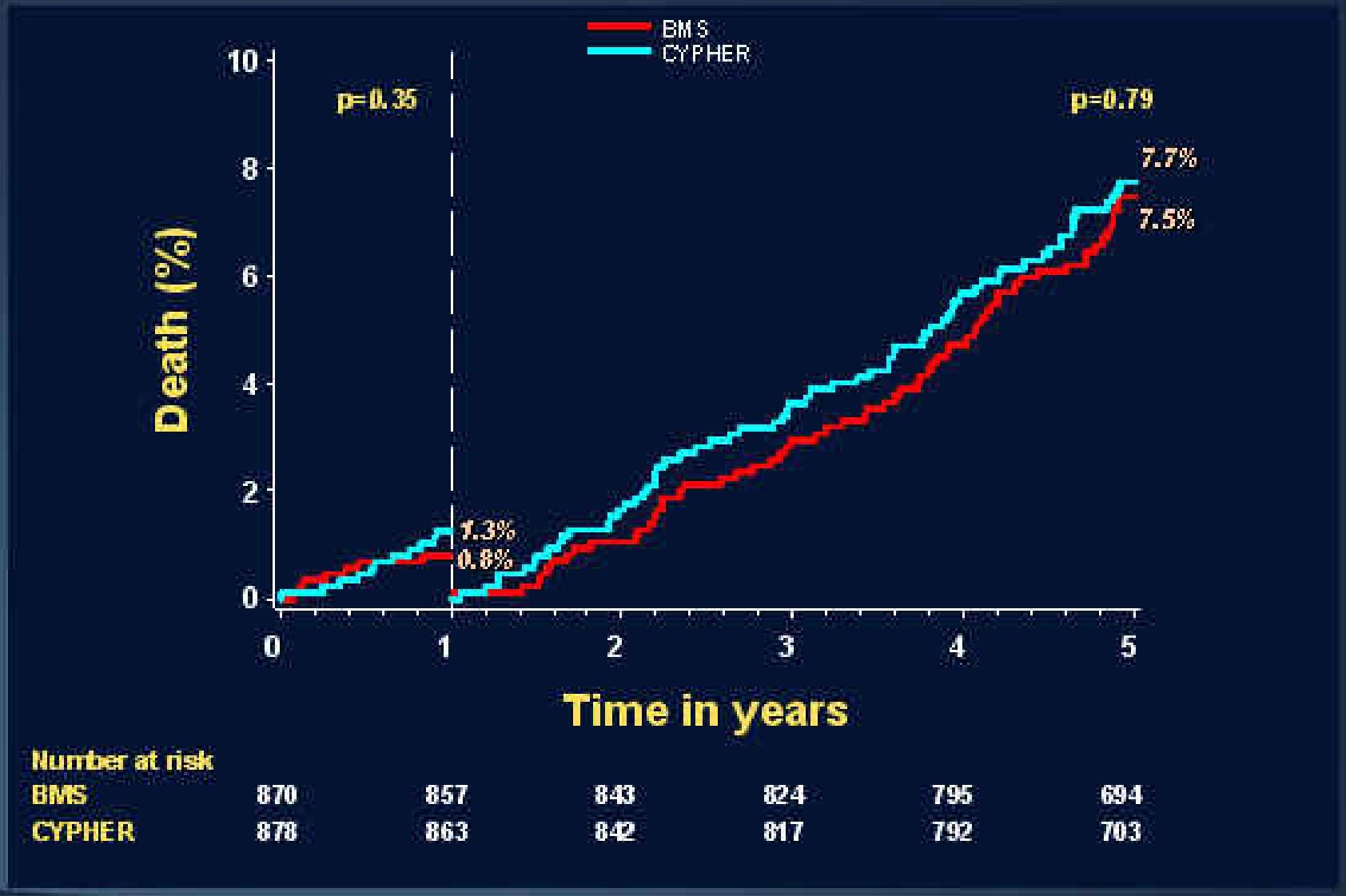
1,748 patients with stable or unstable angina or inducible ischemia treated at 115 international centers between August 2000 and April 2002



Completeness of 5-year follow-up: 87%

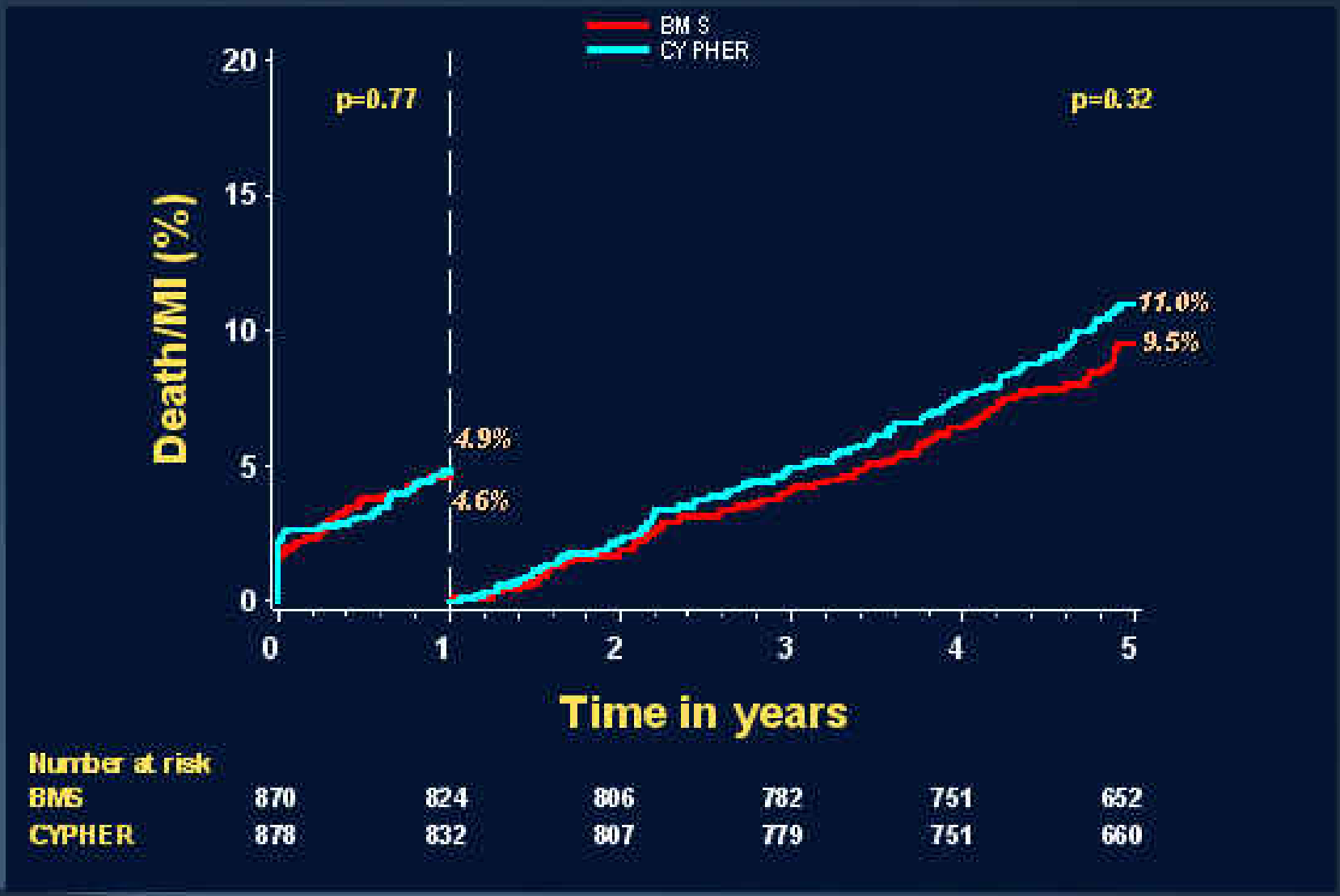
Caixeta A. et al, *JACC 2009;* in press

Landmark Analysis of All-cause Death: 4 SES vs. BMS Trials



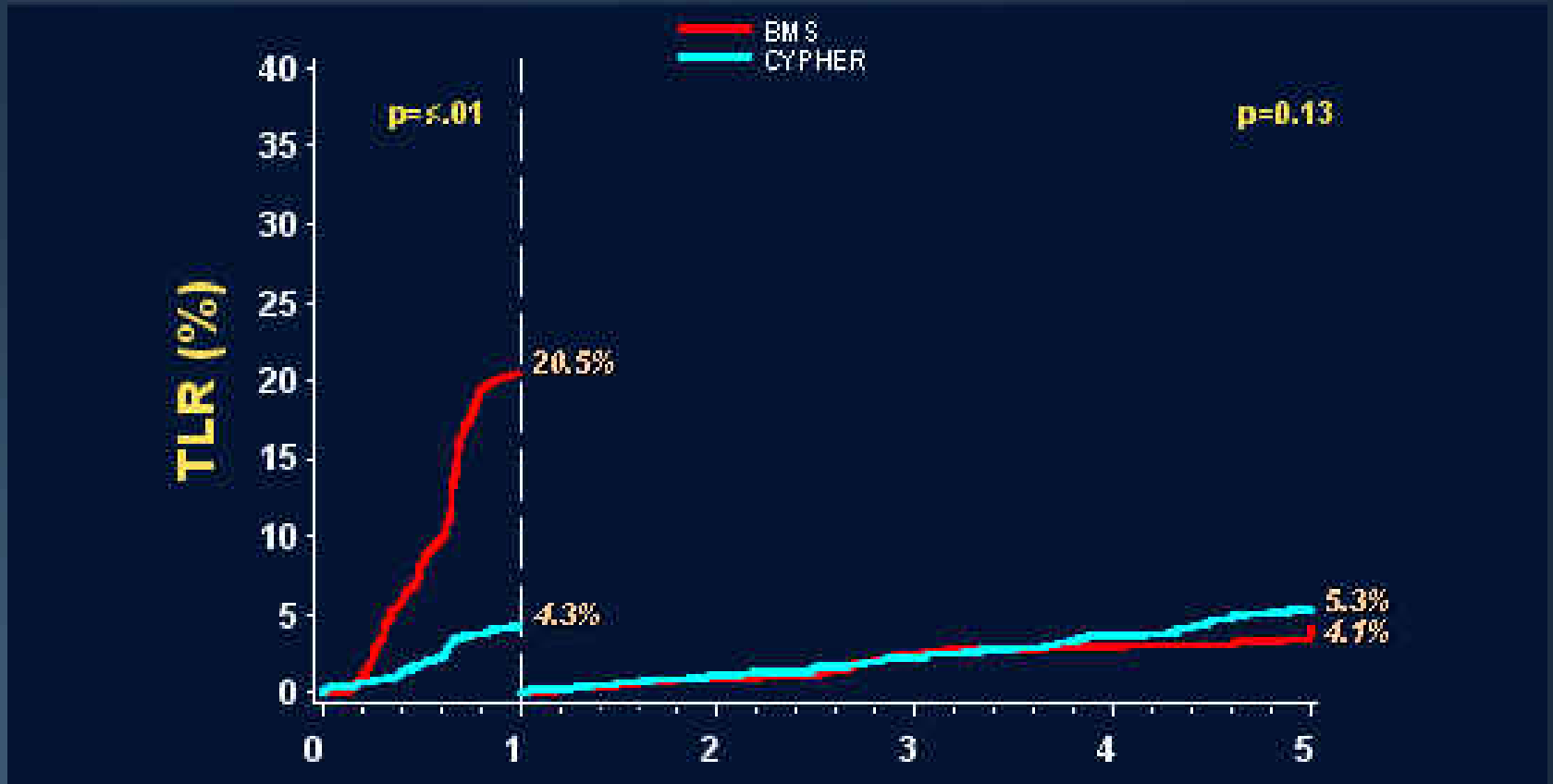
Caixeta A. et al, *JACC 2009*; in press

Landmark Analysis of Death or Myocardial Infarction: SES vs. BMS Trials



Caixeta A. et al, *JACC 2009*; in press

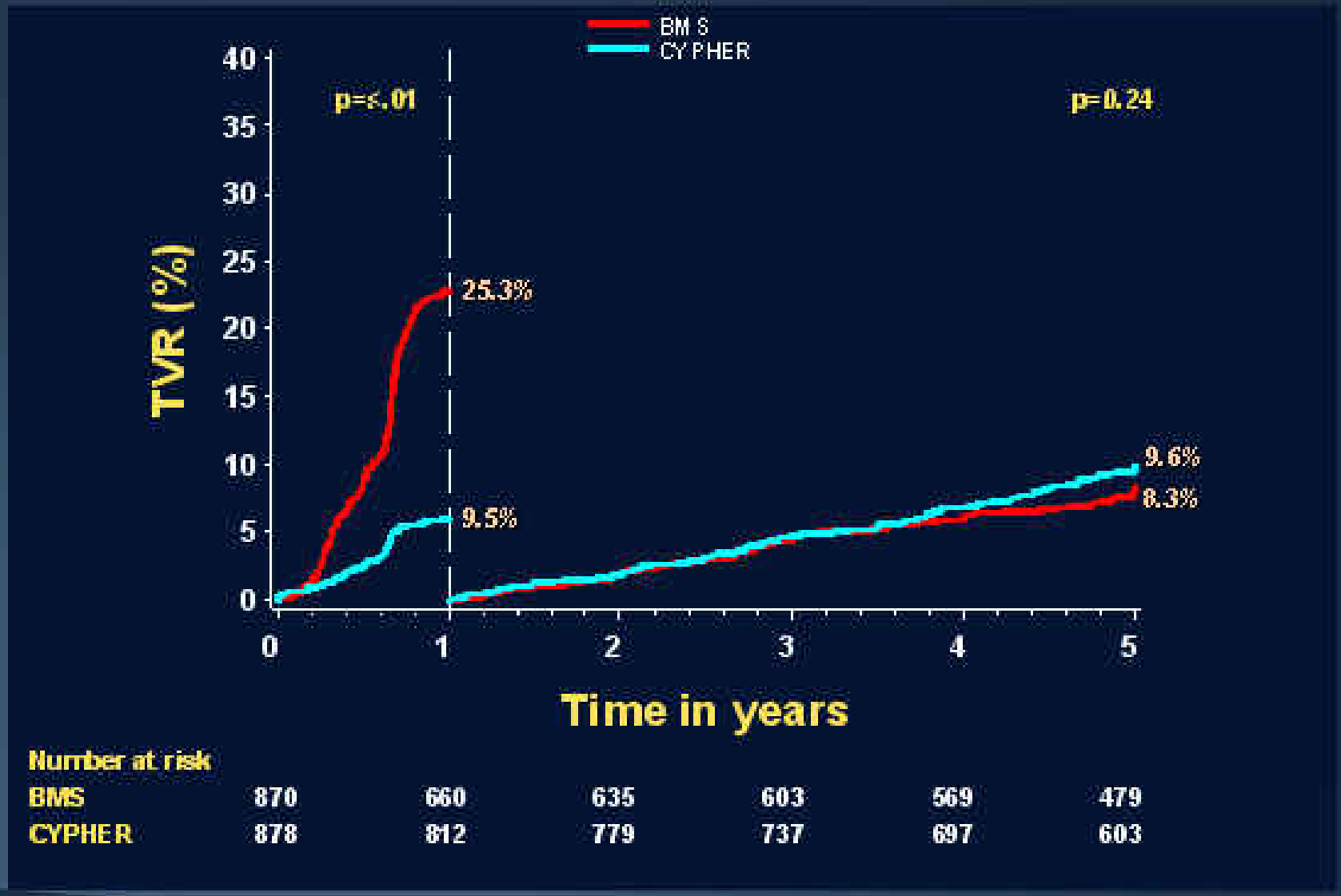
Landmark Analysis of Target Lesion Revascularization: 4 SES vs. BMS trials



Number at risk						
BMS	870	680	659	632	603	518
CYPHER	878	827	797	766	732	645

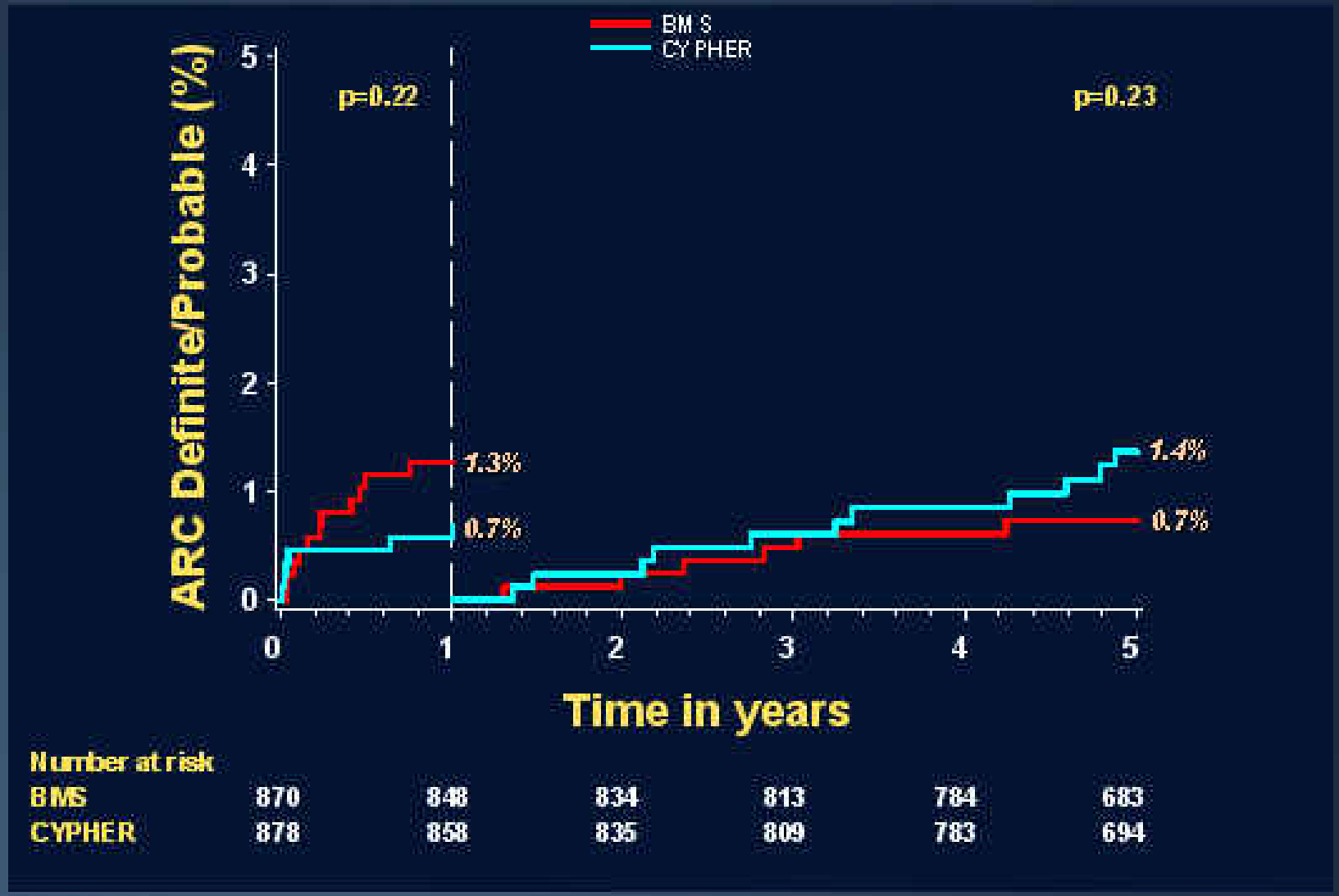
Caixeta A. et al, *JACC 2009*; in press

Landmark Analysis of Target Vessel Revascularization: 4 SES vs. BMS trials



Caixeta A. et al, *JACC 2009*; in press

Landmark Analysis of Definite/Probable (ARC) Stent Thrombosis: 4 SES vs. BMS trials



Caixeta A. et al, *JACC 2009*; in press

SIRIUS - Study Design

n = 1058

***De Novo* Coronary Lesions**

Diameter: 2.5 - 3.5 mm

Length: 15 - 30 mm

Sirolimus-eluting Bx VELOCITY™ n = 533

Control Bx VELOCITY™ n = 525

Primary Endpoint: **Target vessel failure (TVF) defined as cardiac death, MI or TVR (F/U 9 mos)**

Angiographic Substudy: **First 850 pts (F/U 8 mos)**

IVUS Substudy: **250 pts at selected sites (F/U 8 mos)**

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

NewYork-Presbyterian

SIRIUS - Patient Demographics

	Sirolimus (%) (n=533)	Control (%) (n=525)
Mean age (years)	62.1	62.4
Male	72.6	69.7
Prior MI	28.2	32.9
Prior PCI	26.3	23.1
Diabetes Mellitus	24.6	28.2
Hyperlipidemia	72.6	74.6
Hypertension	67.6	67.8
Current Smoker	17.7	22.4

SIRIUS - Clinical Events @ 9 months

	Sirolimus (n=533)	Control (n=525)	p-value
Death	0.9% (5)	0.6% (3)	0.73
MI (all)	2.8% (15)	3.6% (19)	0.49
Q-wave	0.8% (4)	0.8% (4)	1.00
Non Q-wave	2.1% (11)	2.9% (15)	0.43
TLR (all)	*4.1% (22)*	*16.6% (87)*	*<0.0001*
TVR (all)	*6.4% (34)*	*18.9% (99)*	*<0.0001*
TVR (non-TL)	3.4% (18)	4.8% (25)	0.28
MACE	*7.1% (38)*	*19.2% (101)*	*<0.0001*
TVF (1° endpoint)	*8.8% (47)*	*21.0% (110)*	*<0.0001*

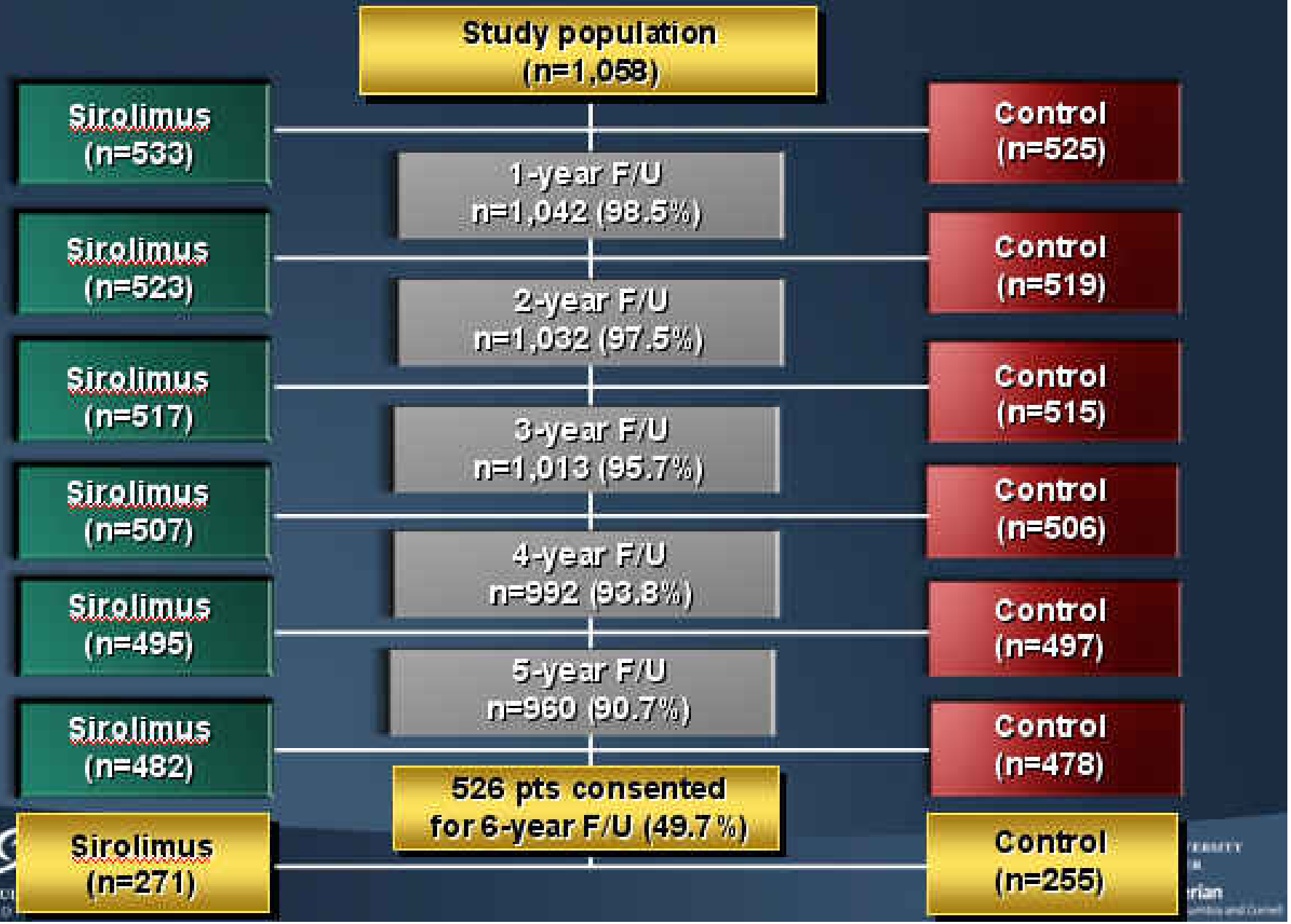
SIRIUS - Clinical Events @ 5 Years

	Sirolimus (n=533)	Control (n=525)	p-value
Death	8.4% (45)	8.4% (44)	1.00
MI (all)	6.2% (33)	6.5% (34)	0.90
Q-wave	1.5% (8)	1.1% (6)	0.79
Non Q-wave	4.9% (26)	5.3% (28)	0.78
TLR (all)	*9.4% (50)*	*24.2% (127)*	*<0.001*
TVR (all)	*16.5% (88)*	*30.5% (160)*	*<0.001*
TVR (non-TL)	10.3% (55)	13.0% (68)	0.21
MACE	*20.3% (108)*	*33.5% (176)*	*<0.0001*
TVF	*22.5% (120)*	*34.7% (182)*	*<0.0001*

SIRIUS - Protocol Amendment

- On December 7, 2006, a protocol amendment was issued extending the follow-up period for an additional 3 years for a total of 8 years
- At 6 years post-procedure, 527 patients were re-consented and assessed for angina status, all adverse events, concomitant medications, and any repeat revascularization since the previous contact

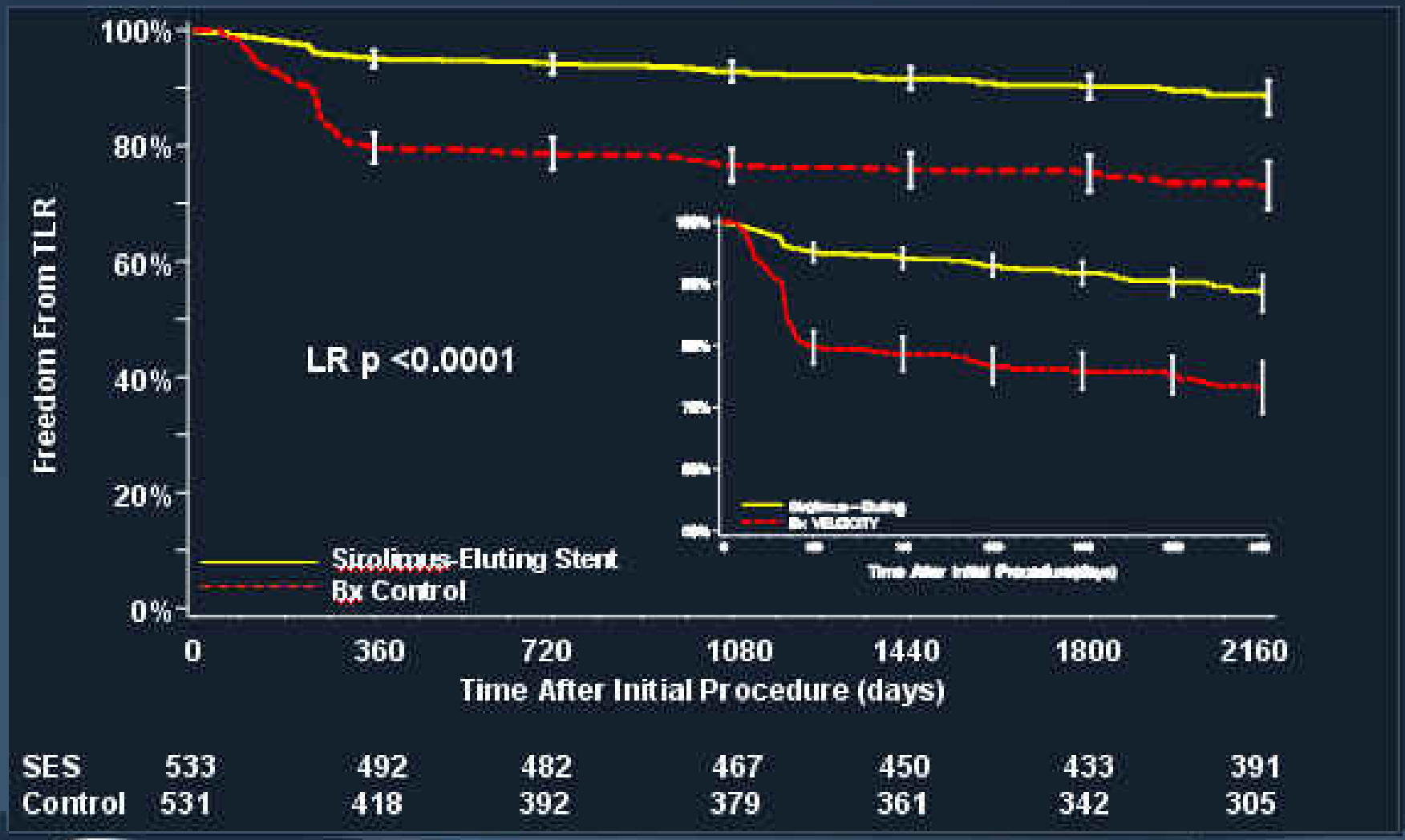
SIRIUS - Patient Flow (Clinical)



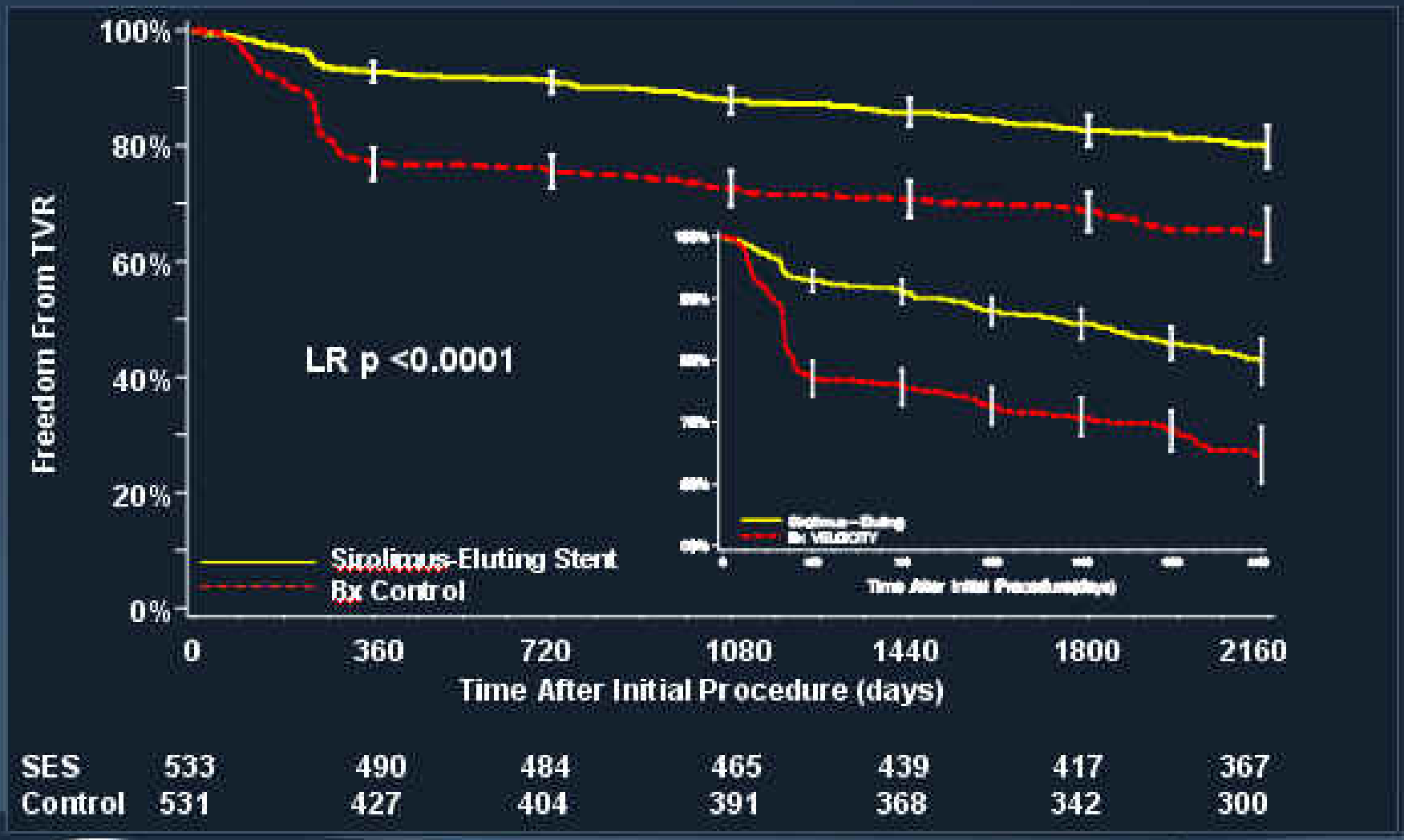
SIRIUS - Clinical Events @ 6 Years

	Sirolimus (n=533)	Control (n=525)	p-value
Death	8.9% (46)	9.4% (46)	0.974
MI (all)	6.4% (33)	7.0% (35)	0.774
Q-wave	1.9% (9)	1.2% (6)	0.452
Non Q-wave	5.1% (26)	5.9% (29)	0.655
Death or MI	14.4% (75)	14.7% (73)	0.917
TLR	*11.9% (55)*	*27.9% (134)*	*<0.001*
TVR (all)	*20.3% (96)*	*35.7% (172)*	*<0.001*
TVR (non-TL)	13.5% (62)	16.2% (75)	0.187
MACE	*22.6% (114)*	*37.2% (186)*	*<0.001*
TVF	*26.1% (128)*	*39.9% (195)*	*<0.001*

SIRIUS - Survival-Free Target Lesion Revascularization



SIRIUS - Survival-Free Target Vessel Revascularization



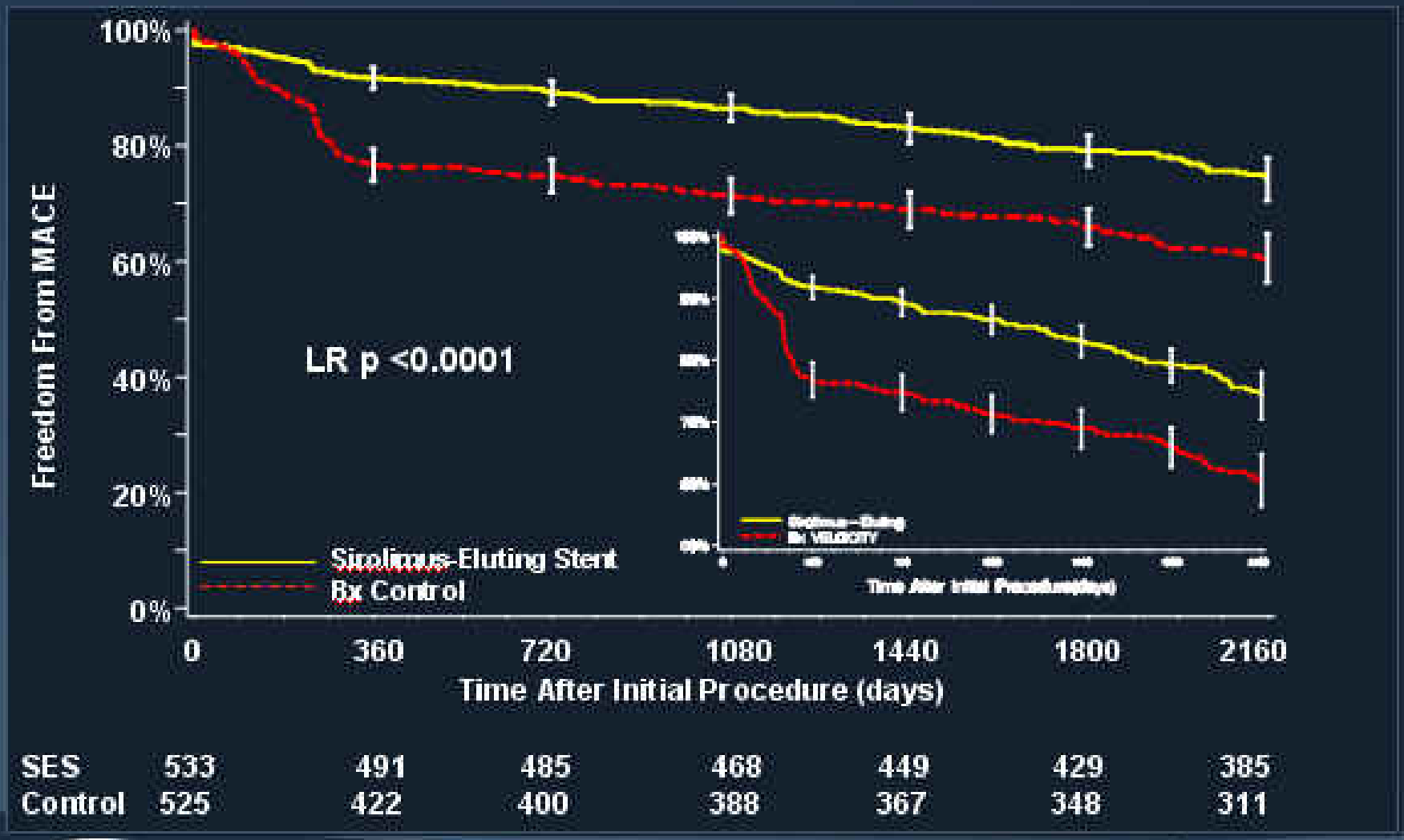
SES	533	490	484	465	439	417	367
Control	531	427	404	391	368	342	300

SIRIUS - Survival-Free Target Vessel Failure

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

SIRIUS - Survival-Free Major Adverse Cardiac Events



CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

Stent Thrombosis Definitions

Protocol Definition
Early (Acute + Subacute) ≤ 30 Days
Acute – within 24 hours
Subacute – 24 hours to 30 days
- Angiographic documentation of target vessel occlusion or any death or MI occurring within 30 days that is not clearly related to causes other than stent occlusion
Late > 30 Days
- MI occurring >30 days after the index procedure and attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion of the target site and freedom from an interim revascularization of the target vessel

ARC Definition
Definite
- Acute coronary syndrome, AND EITHER - Angiographic confirmation of thrombus or occlusion, OR - Pathologic confirmation of acute thrombosis
Probable
- Unexplained death within 30 days, OR - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
Possible
- Unexplained death after 30 days

SIRIUS - Stent Thrombosis @ 6 Years

	Early (0-30d)		Late (31-360d)		Very Late (361-2160d)		Overall (0-2160d)		p-value (Overall)
	SES	CS	SES	CS	SES	CS	SES	CS	
Protocol	0.2	0.2	0.2	0.6	0.8	0.0	1.2	0.8	0.536
ARC Definitions									
Definite/Prob.	0.2	0.4	0.2	0.8	0.8	1.0	1.2	2.1	0.304
Any ARC	0.2	0.4	0.4	1.0	3.4	3.6	3.9	5.0	0.622

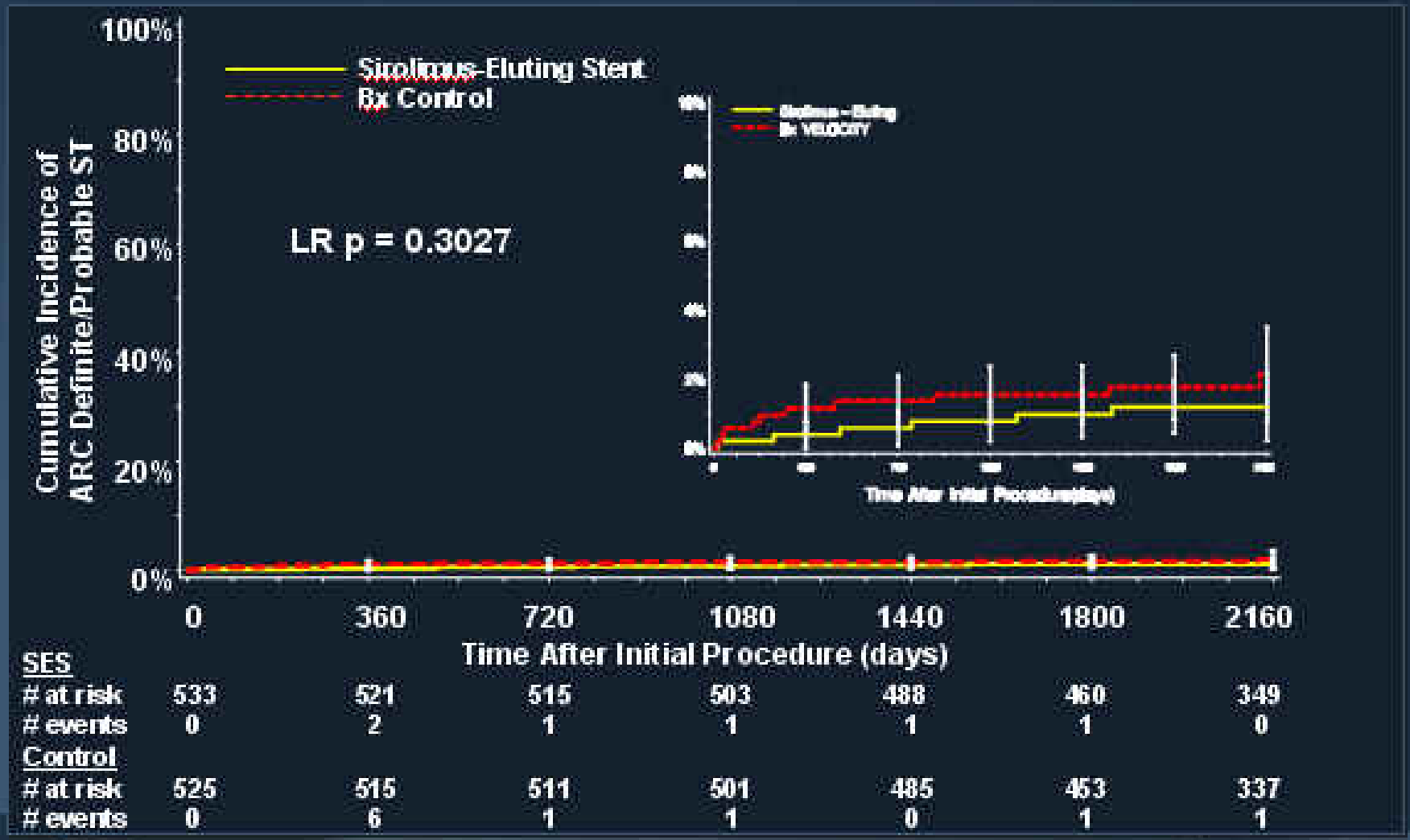
SIRIUS - Cumulative Incidence of Protocol Defined Stent Thrombosis

SES							
# at risk	533	521	515	503	488	460	349
# events	0	2	1	1	1	1	0
Control							
# at risk	525	516	512	503	487	455	338
# events	0	4	0	0	0	0	0

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

SIRIUS - Cumulative Incidence of ARC Definite/Probable ST



SES							
# at risk	533	521	515	503	488	460	349
# events	0	2	1	1	1	1	0
Control							
# at risk	525	515	511	501	485	453	337
# events	0	6	1	1	0	1	1

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

SIRIUS - Limitations

- **6-year clinical** follow-up was completed on only 50% of the originally enrolled patients

- While Kaplan-Meier analysis partially adjusts for this, the possibility of bias cannot be ruled out as patients who did receive follow-up were not a random subset of the original cohort

SIRIUS - Conclusions

- *The 6-year results of the SIRIUS trial demonstrate that the treatment benefit and safety of the Sirolimus-Eluting Stent are preserved in longer-term follow up*
- There is no evidence of late "catch-up restenosis"
- The highly significant differences ($p<0.001$) between Sirolimus-Eluting and control stents for all clinical endpoints were sustained at 6-year follow-up
- Furthermore, the cumulative event rates of death, MI and stent thrombosis (both protocol and ARC definitions) show no significant differences between Sirolimus-Eluting and control stents

“Vintage” Wines

A "Vintage" Stent

2003 was a very good year...

...and now with 6 year follow-up outcomes

SIRIUS - de novo
Coronary Lesions

Diameter: 2.5 - 3.5 mm
Length: 15 - 30 mm