In Stent Restenosis: The Last Achilles' Hill to Still Conquer

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David R. Holmes, M.D.
Mayo Clinic
Rochester, MN

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Presenter Disclosure Information

David R. Holmes, Jr., M.D.

In Stent Restenosis:
The Last Achilles' Hill to Still Conquer

The following relationships exist related to this presentation:

No relationships to disclose

Bare Metal Stents

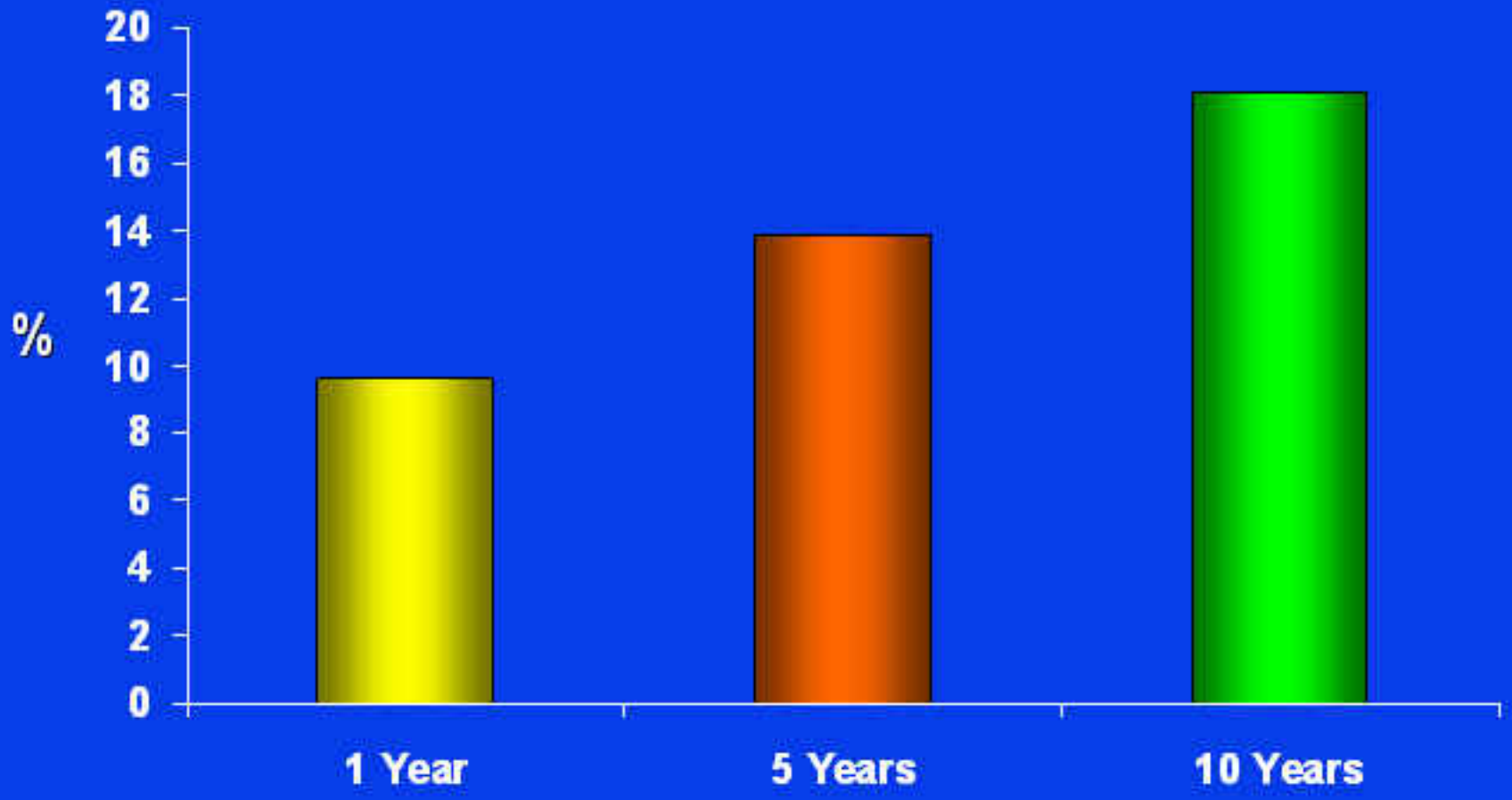
- Revolutionized PCI
- Initially developed to treat AC/TC and were very successful
- Tested for prevention of restenosis and were also very successful
- Became predicate devices
- Did not eliminate restenosis and in fact, NIH was even increased vs conventional PTCA
- Restenosis of BMS, not benign

Stent Thrombosis & Restenosis
Bare Metal Stents

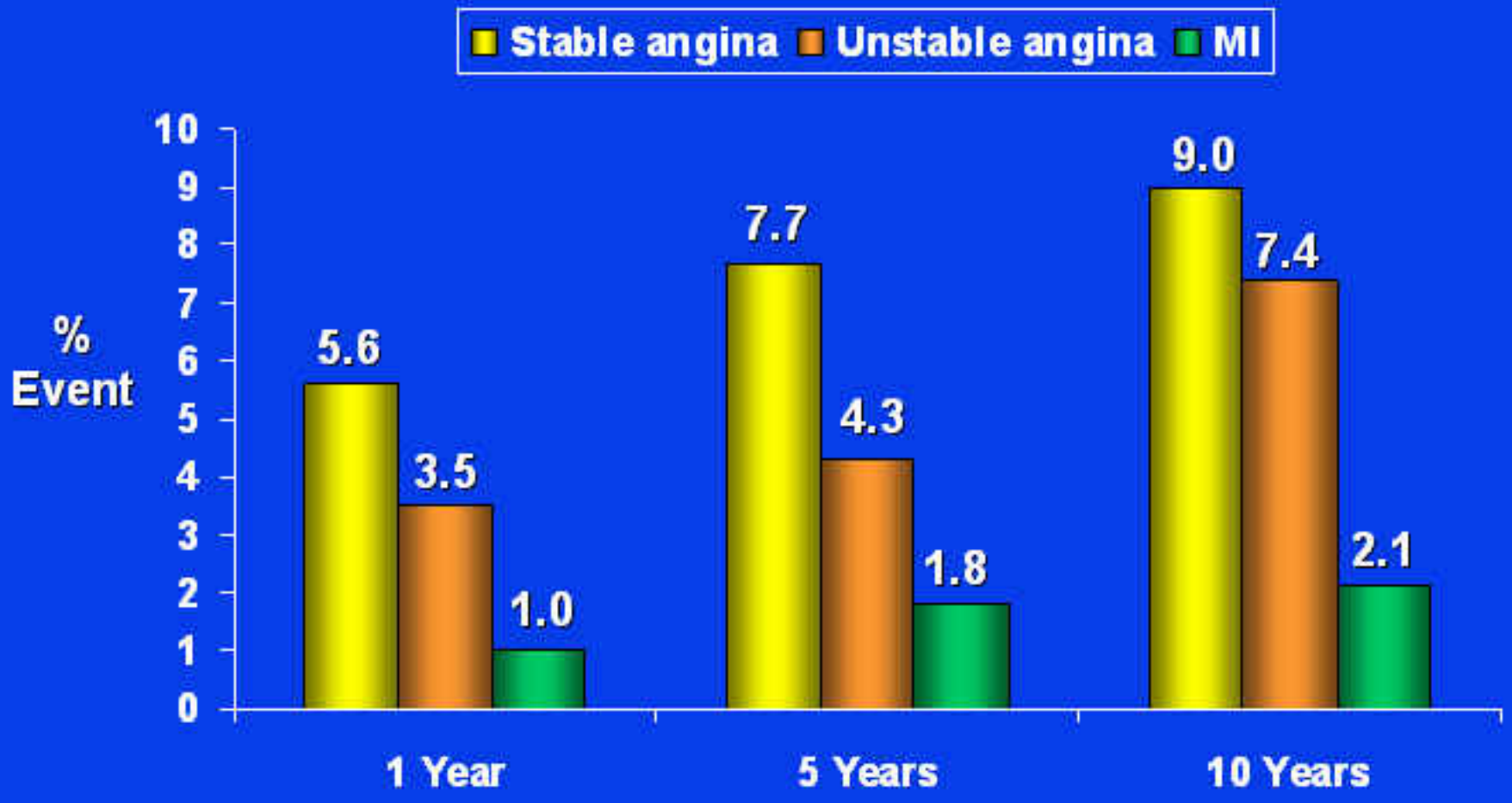
- Single center study
- 4503 patients with ≥1 BMS between 1994 and 2000, receiving dual antiplatelet therapy
- Mean follow-up 7.9 years (IQR 6.7-9.1 yrs)
- Stent thrombosis defined as per ARC
- Clinical restenosis:
  - Symptoms or abnormal functional testing attributed to stenotic lesion in the index treated segment

Doyle B et al; Circ 116:2391-98, 2007

Restenosis During Follow-up



Restenosis During Follow-Up



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Doyle B et al; Circ 116:2391-98, 2007

Ten Year Outcome of BMS

- Definite/probable BMS ST occurs in 2.0% of patients
- Myocardial infarction from BMS restenosis occurs in 2.1%
- With BMS, either ST or restenosis are associated with increased mortality

DES for In-Stent Restenosis of BMS
Meta-Analysis

- 4 randomized trials
  - SES or PES vs PTCA or VBT
- 1,230 patients with BMS – In-stent restenosis
- Primary outcome: TLR

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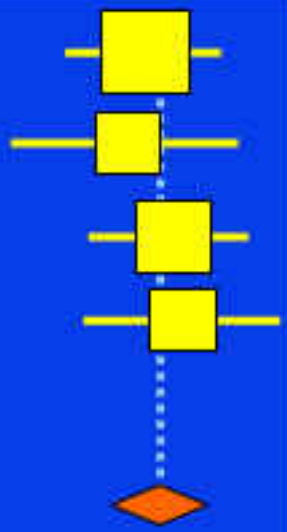
Dibra A et al: JACC 49:616, 2007

TLR

Study	DES (no.)	Conventional (no.)	Odds ratio (95% CI)
ISAR-DESIRE	27/200	33/100	0.32 (0.18, 0.57)
RIBS II	8/76	22/74	0.28 (0.11, 0.67)
SISR	22/259	24/125	0.39 (0.21, 0.73)
TAXUS-V ISR	12/195	27/201	0.42 (0.21, 0.86)
Total	69/730	106/500	
Overall (fixed effects)			0.35 (0.25, 0.49)



Test for heterogeneity: X^2=0.76 (df=3) P=0.86
Test for overall effect: z=6.04 P<0.001

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Favors DES Favors coventional

Dibra A et al: JACC 49:616, 2007

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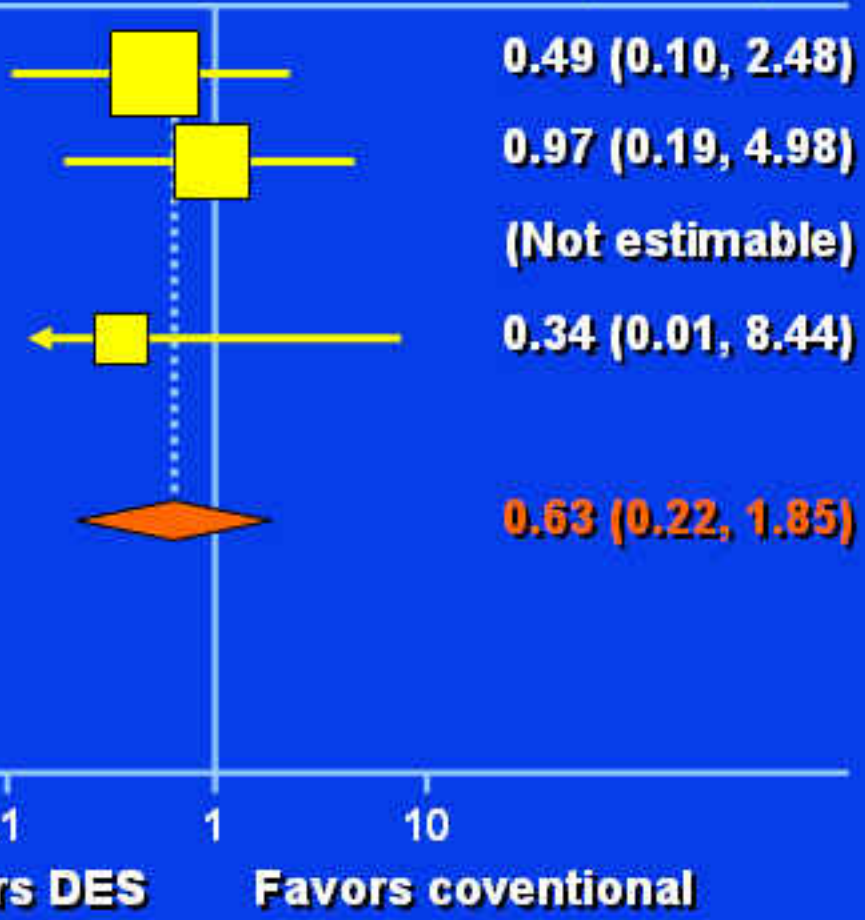
CP130853O-1

Mortality

Study	DES (no.)	Conventional (no.)	Odds ratio	Odds ratio (95% CI)
ISAR-DESIRE	3/200	3/100		0.49 (0.10, 2.48)
RIBS II	3/76	3/74		0.97 (0.19, 4.98)
SISR	0/259	0/125		(Not estimable)
TAXUS-V ISR	0/195	1/201		0.34 (0.01, 8.44)
Total	6/730	7/500		
Overall (fixed effects)				0.63 (0.22, 1.85)

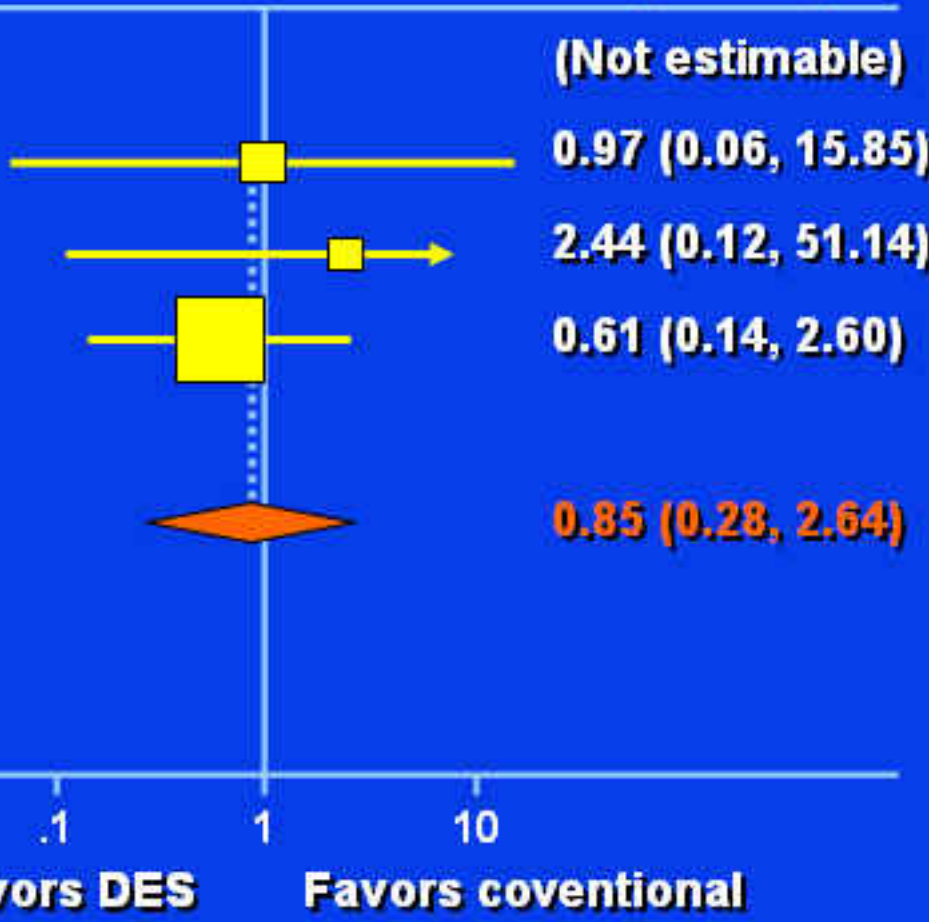


Test for heterogeneity: X^2=0.50 (df=2) P=0.78
Test for overall effect: z=0.83 P=0.41

Dibra A et al: JACC 49:616, 2007

Stent Thrombosis

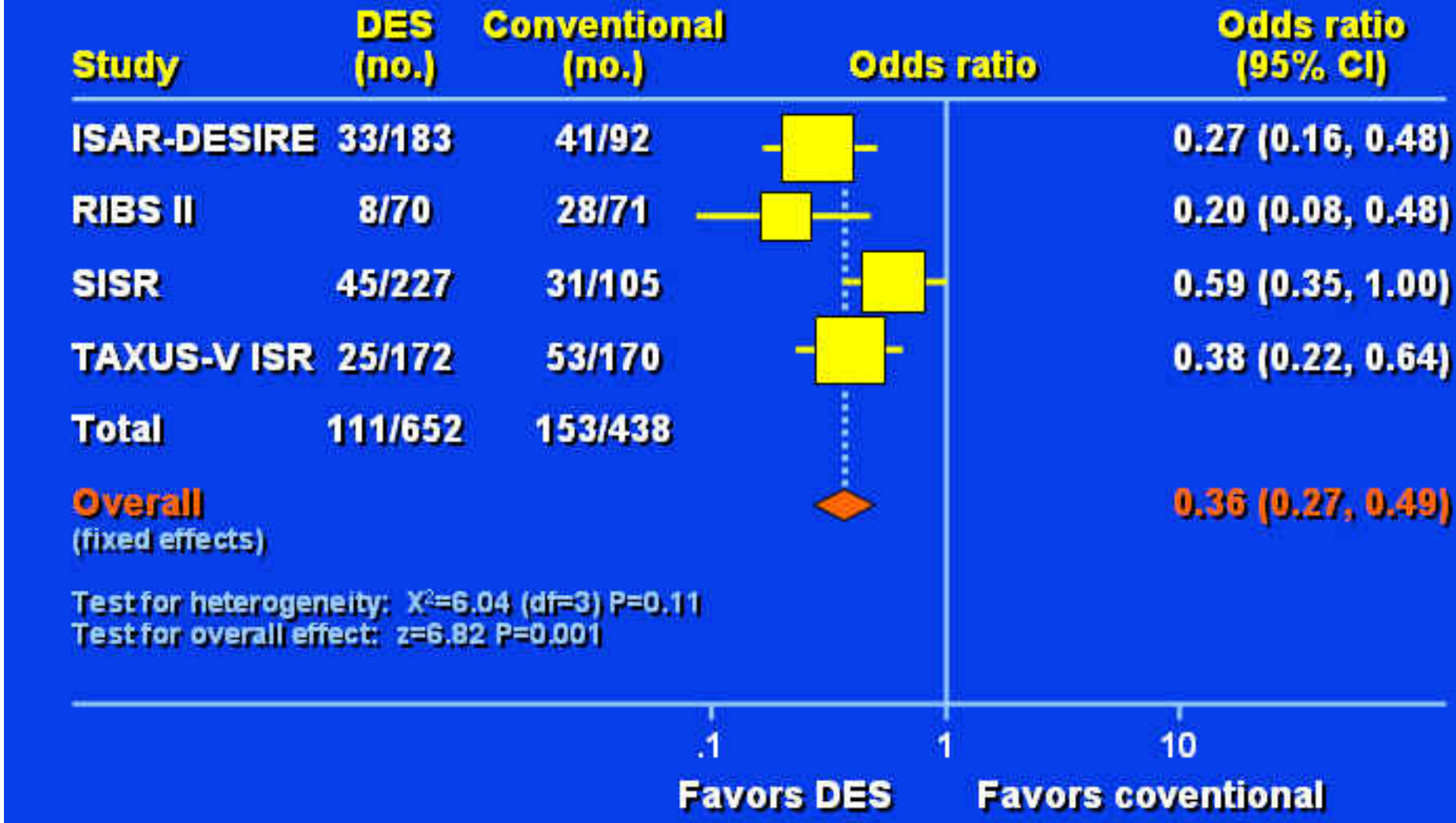
Study	DES (no.)	Conventional (no.)	Odds ratio (95% CI)
ISAR-DESIRE	0/200	0/100	(Not estimable)
RIBS II	1/76	1/74	0.97 (0.06, 15.85)
SISR	2/259	0/125	2.44 (0.12, 51.14)
TAXUS-V ISR	3/195	5/201	0.61 (0.14, 2.60)
Total	6/730	6/500	
Overall (fixed effects)			0.85 (0.28, 2.64)



Test for heterogeneity: X^2=0.67 (df=2) P=0.72
Test for overall effect: z=0.27 P=0.79

Dibra A et al: JACC 49:616, 2007

Angiographic Restenosis



Dibra A et al: JACC 49:616, 2007

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Vascular Brachytherapy

Issues

System

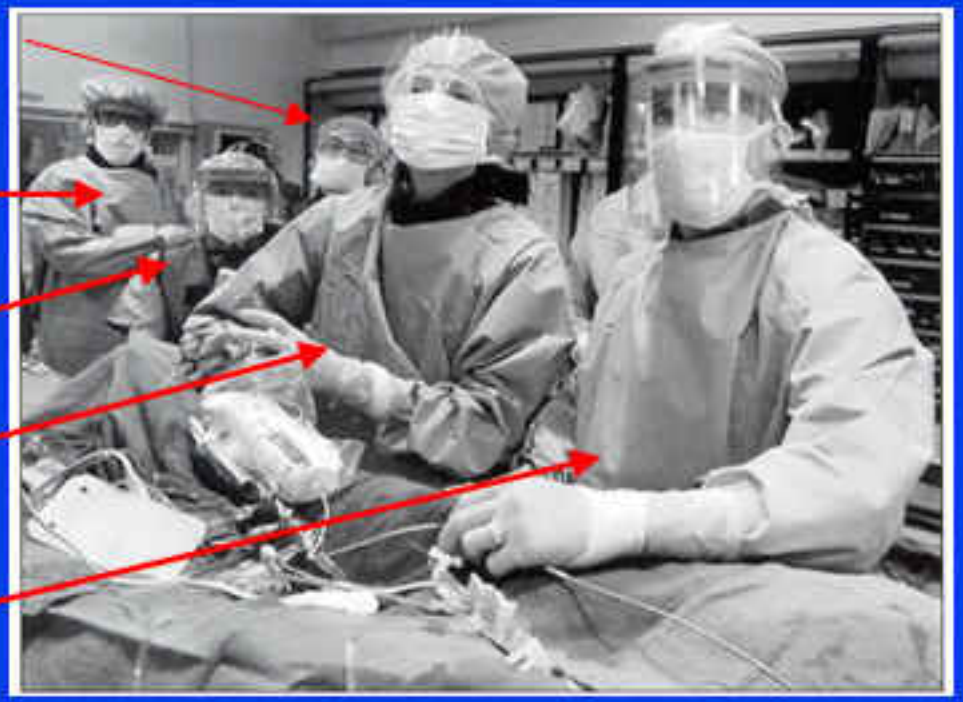
Radiation safety officer

Some other guy

Radiation technician

Radiation oncologist

Cardiologist

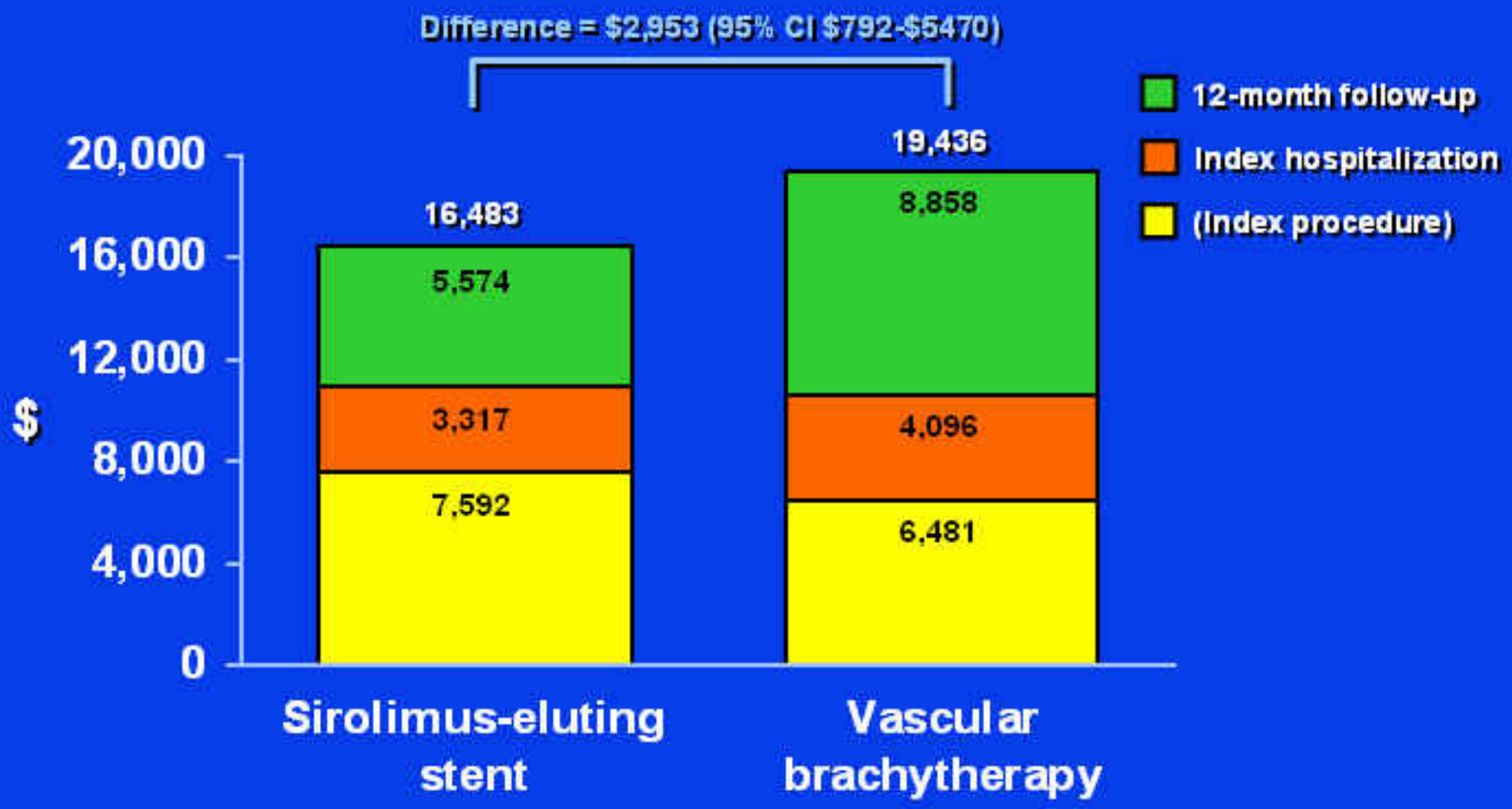


Cost Effectiveness
SES vs VBT
SISR Trial

Primary endpoint: Cost per repeat revascularization avoided

Reynolds MR et al: Am Heart J 2007; 154:1221-27

12-Month Costs per Treatment Received



Reynolds MR et al: Am Heart J 154:1221, 2007

William Heberden

- New drugs and new medicines always work miracles for awhile.

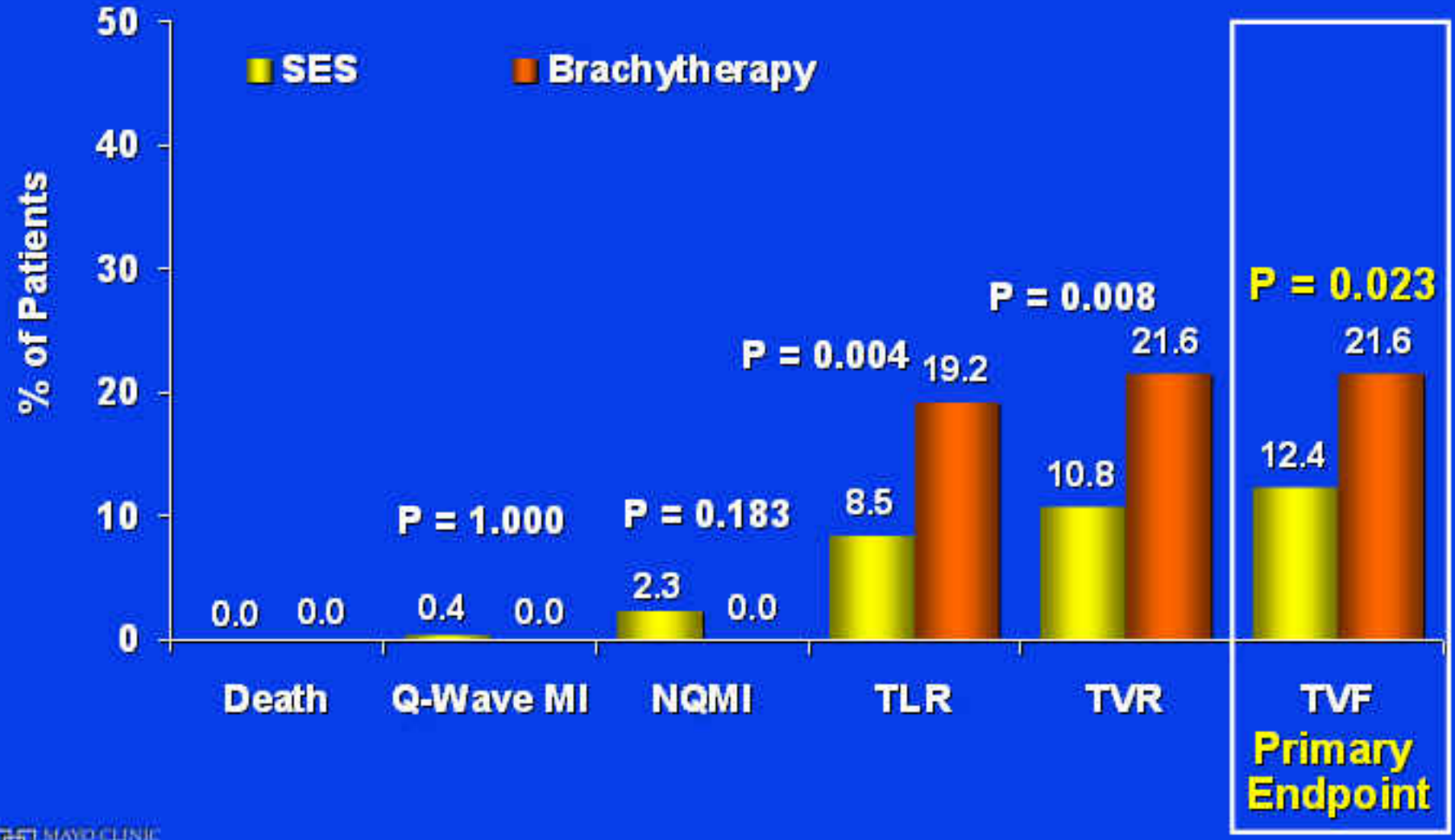
Background

- Treatment of restenosis in a bare-metal stent (BMS) has been problematic and characterized by high recurrence rates
- Vascular brachytherapy (VBT) was found to improve early outcomes although late catch-up events were observed
- In the SISR trial, the sirolimus-eluting stent was found to be both non-inferior and superior to VBT at 9 months for the primary endpoint of TVF predominantly due to a reduction in TVR

Background
Questions Remain

- Will the problems of late thrombosis and late catch-up seen with vascular brachytherapy for in-stent restenosis be seen with DES in this setting?

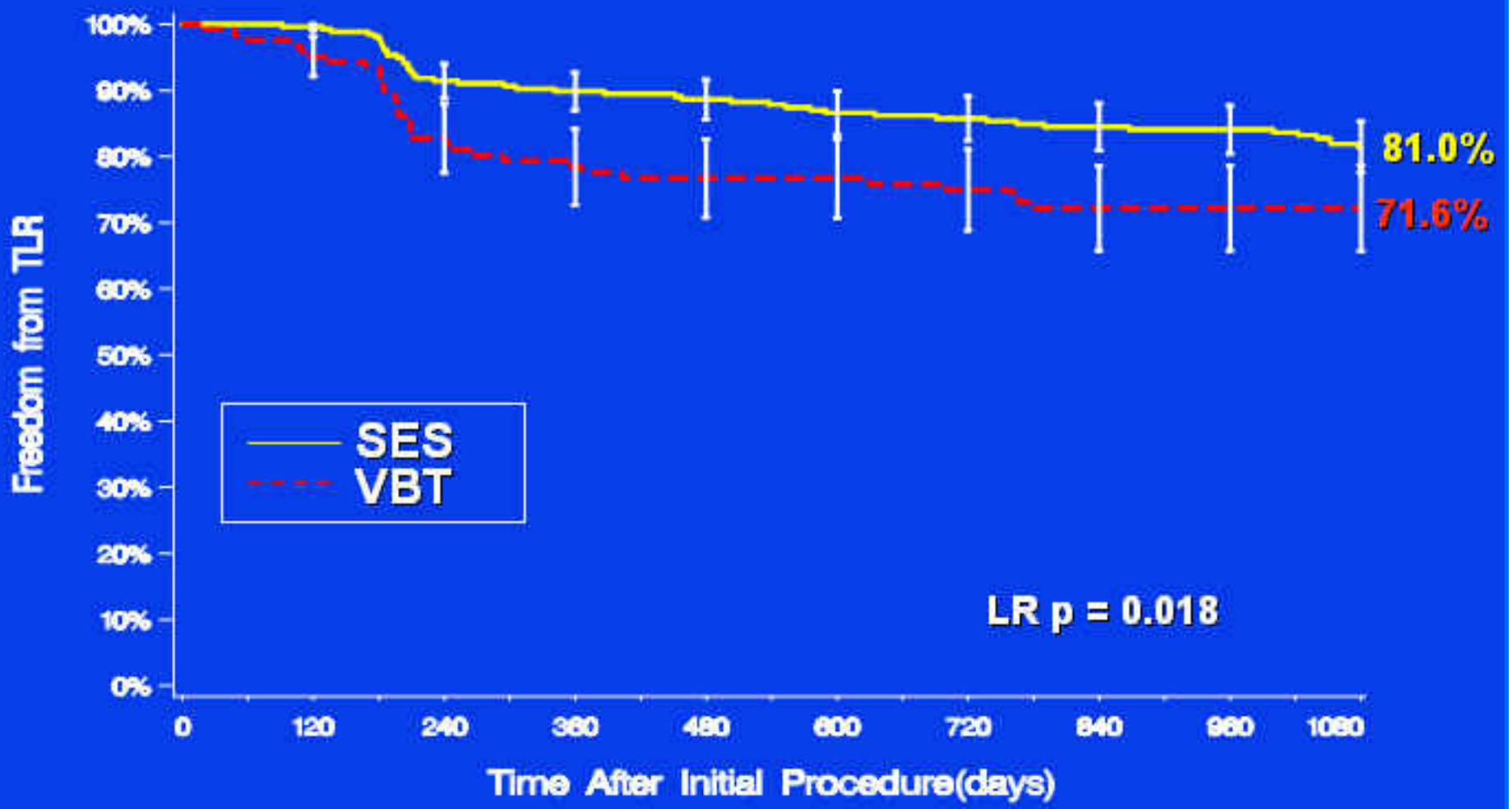
Clinical Outcomes Through 9-Months



Death or MI to 1080 Days

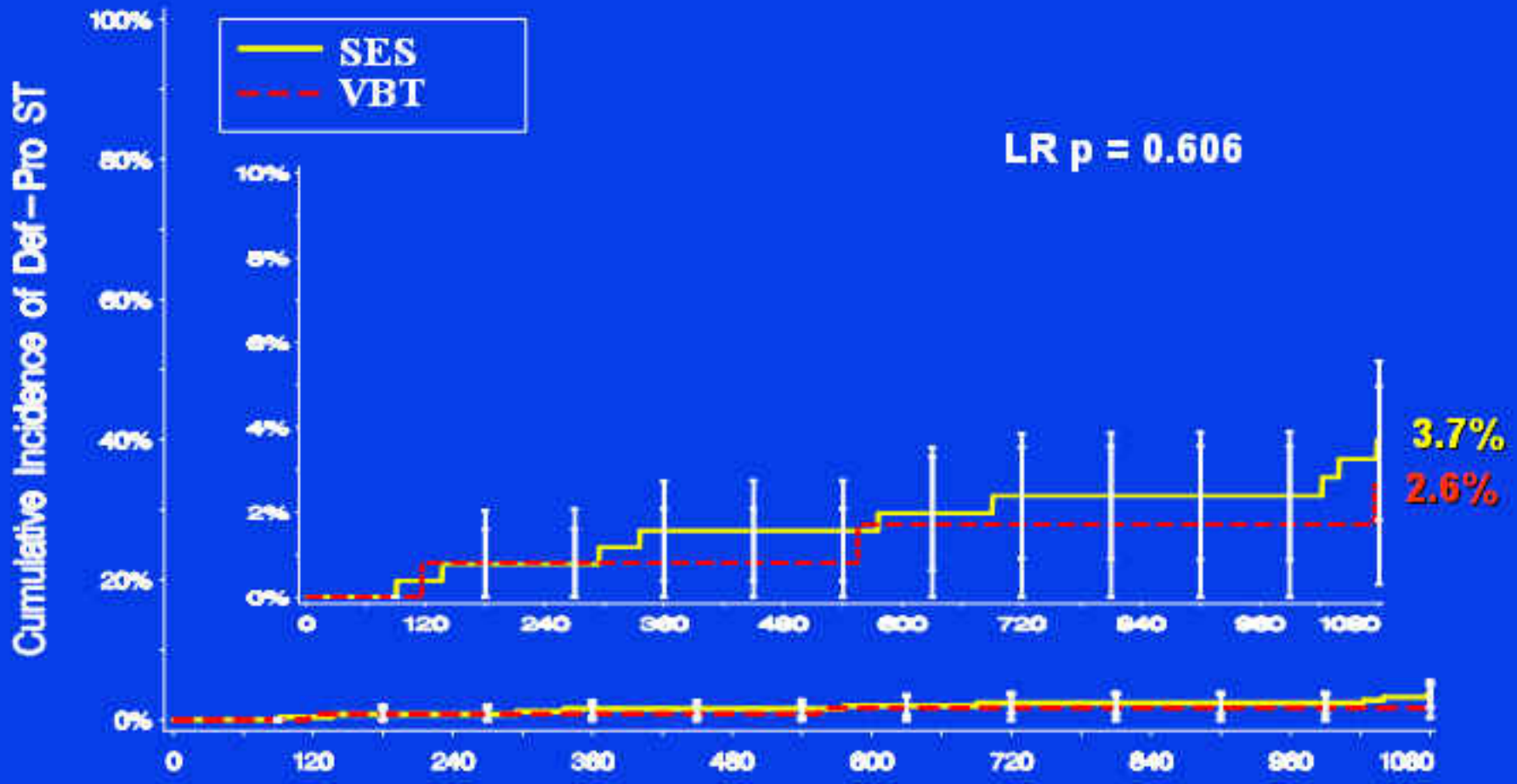
	VBT 125 patients	SES 259 patients	p-value
Death	2.4	3.9	0.560
Cardiac	0.8	1.5	1.000
Non-Cardiac	1.6	2.3	1.000
MI (Q- or non-Q wave)	3.2	6.2	0.327
All Q-Wave MI	0.0	1.5	0.309
Target Vessel Q-wave MI	0.0	1.5	0.309
Non-Target Vessel Q-wave MI	0.0	0.0	--
All Non-Q Wave MI	3.2	5.4	0.444
Target Vessel Non-Q wave MI	3.2	5.0	0.598
Non-Target Vessel Non Q MI	0.0	0.4	1.000
All Target Vessel MI	3.2	5.8	0.325
All Non-Target Vessel MI	0.0	0.4	1.000

Survival Free from TLR to 1080 Days



TLR: Target Lesion Revascularization defined as any "clinically-driven" repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel

Cumulative Incidence of Definite/Probable ARC Thrombosis to 1080 Days



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Conclusions

- At 3 years of follow up, survival free from TLR (SES 81.0%; VBT 71.6%, p=0.018) and TVR (SES 78.2%; VBT 68.8%, p=0.022) continues to demonstrate a significant improvement with SES as compared with VBT
- Although 3-year target vessel failure (SES 75.1%; VBT 67.9%, p=0.067) and MACE (SES 75.5%; VBT 70.5%, p=0.186) rates were both improved with SES, this did not reach statistical significance, likely reflecting in part progression of disease and trial design
- Stent thrombosis rates were not significantly different in the frequency of ARC Definite & Probable stent thrombosis (SES 3.7%; VBT 2.6%, p=0.606)
- Both treatment modalities studied in this trial demonstrated no new safety issues

SISR
3-Year Follow-Up
Conclusions

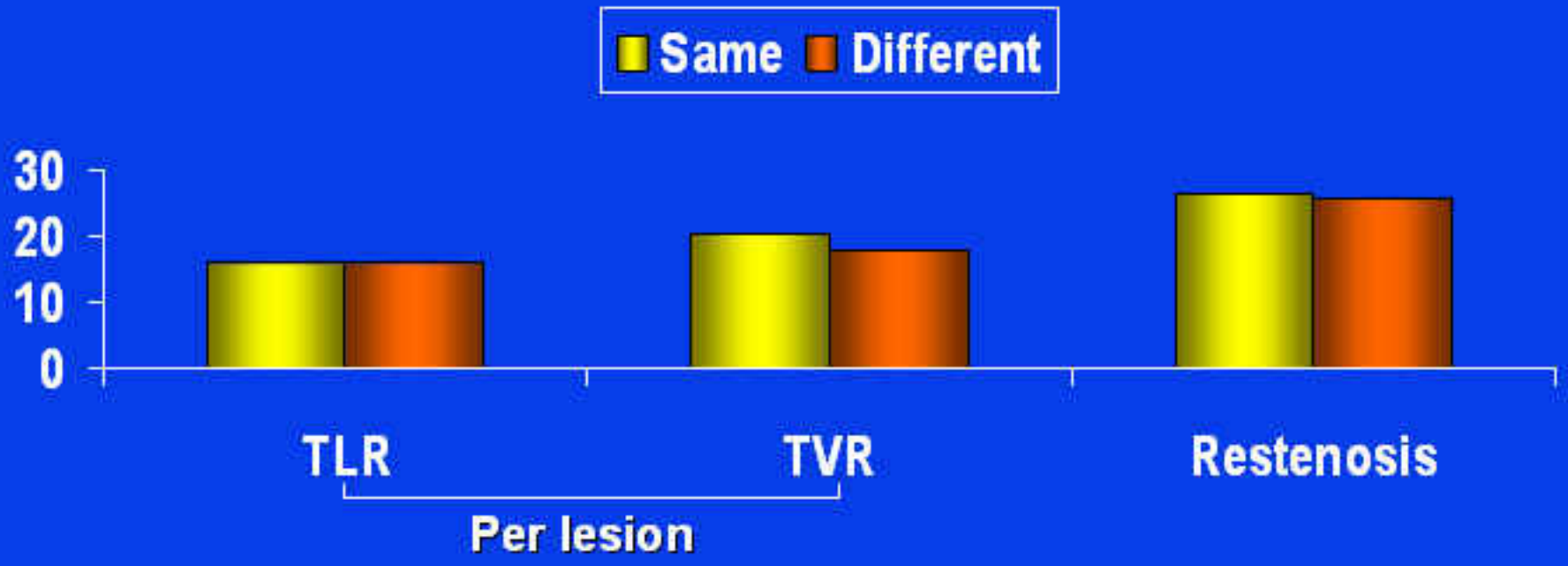
- Sirolimus-eluting stents remain superior in achieving the goal of decreasing need for subsequent revascularization

What can we say

- In-stent restenosis is not benign
- The best way to treat restenosis is to prevent it
- An ounce of prevention is worth a pound of cure
- Focus attempts to optimize the INITIAL results

In-Stent Restenosis of DES
What next?

- Single center observational study
- 201 restenotic lesions in 174 patients



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Cosgrave J et al: Am Heart J 2007; 153:354-9

German Cypher Registry
ISR of BMS
Presentation

ACS	36.5%
Unstable angina	24.6%
NSTEMI	8.3%
STEMI	3.6%
Shock	1.2%

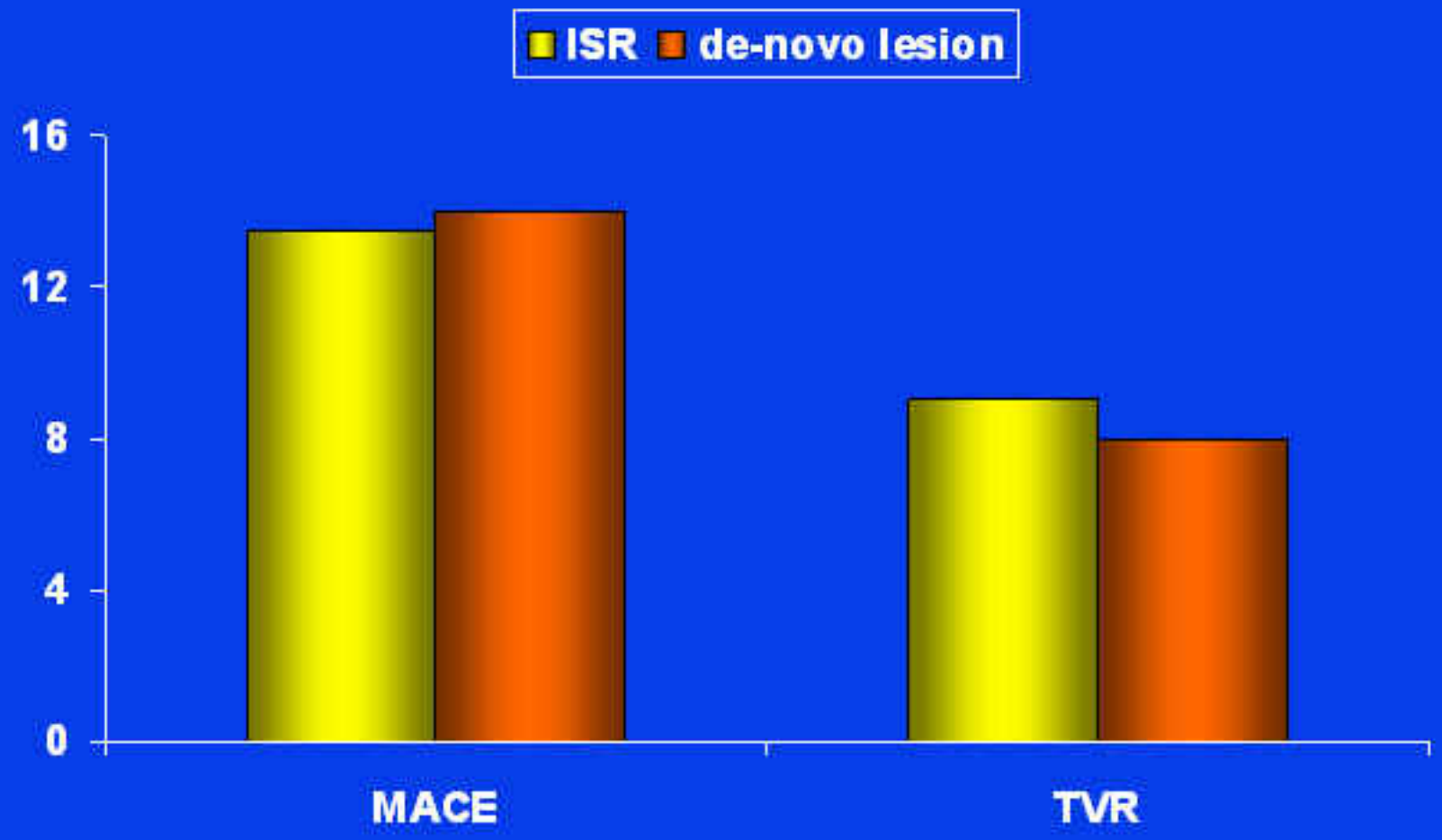
Mollmann H et al: Clin Res Cardiol 2008

In-Hospital Outcome

	Total (%)	In-stent restenosis (%)	De novo stenosis (%)	P	Odds ratio (95% CI)
MACE	2.6	2.1	2.8	NS	0.76 (0.52-1.13)
Mortality	0.4	0.1	0.5	NS	0.28 (0.07-1.17)
MI	1.1	0.8	1.3	NS	0.63 (0.34-1.17)
Revasc	1.5	1.6	1.4	NS	1.13 (0.71-1.80)
CABG	0.3	0.1	0.4	NS	0.35 (0.08-1.50)
PCI	1.1	1.5	1.0	NS	1.41 (0.86-2.33)
SAT	0.3	0.7	0.2	<0.05	3.11 (1.06-9.07)

Mollmann H et al: Clin Res Cardiol 2008

MACE



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Mollmann H et al: Clin Res Cardiol 2008

Clinical Follow-up
6 Months

	Total (%)	In-stent restenosis (%)	De novo stenosis (%)	P	Odds ratio (95% CI)
MACE	14.1	13.8	14.2	NS	0.97 (0.82-1.14)
Mortality	1.5	1.4	1.6	NS	0.87 (0.54-1.41)
MI	1.2	1.9	1.0	<0.01	1.90 (1.20-3.01)
MACCE	14.5	14.4	14.5	NS	0.97 (0.82-1.14)
Revasc	12.6	12.3	12.7	NS	0.97 (0.81-1.15)
CABG	1.5	1.7	1.4	NS	1.27 (0.81-2.01)
PCI	11.3	10.7	11.4	NS	0.93 (0.77-1.12)

Mollmann H et al: Clin Res Cardiol 2008

Same vs Different DES

Variable	Same DES	Different DES	P
Focal DES restenosis	78	47	
DM	26.9% (21)	17% (8)	.28
Angio f/u lesions	71.4% (55)	78.3% (36)	.53
TLR (per lesion)	12.8% (10)	8.5% (4)	.57
TVR (per lesion)	19.2% (15)	12.8% (6)	.46
Restenosis	20% (11)	13.9% (5)	.58
Nonfocal DES restenosis	29	47	
DM	58.6% (17)	31.9% (15)	.03
Angio f/u lesions	60.7% (17)	63.8% (30)	.81
TLR (per lesion)	24.1% (7)	23.4% (11)	1.0
TVR (per lesion)	24.1% (7)	23.4% (11)	1.0
Restenosis	47.1% (8)	40% (12)	.76

Cosgrave J et al: Am Heart J 2007; 153:354-9

De Novo Restenotic Lesions Same vs Different DES

Variable	Same DES	Different DES	P
Focal DES restenosis	60	37	
DM	25% (15)	21.6% (8)	.81
Angio f/u lesions	70% (42)	77.8% (28)	.48
TLR (per lesion)	13.3% (8)	2.7% (1)	.15
TVR (per lesion)	20% (12)	8.1% (3)	.15
Restenosis	21.4% (9)	7.1% (2)	.18
Nonfocal DES restenosis	23	41	
DM	47.8% (11)	31.7% (13)	.28
Angio f/u lesions	59.1% (13)	63.4% (26)	.79
TLR (per lesion)	17.4% (4)	23.4% (8)	1.0
TVR (per lesion)	17.4% (4)	23.4% (8)	1.0
Restenosis	38.5% (5)	40% (9)	1.0

Cosgrave J et al: Am Heart J 2007; 153:354-9

Baseline Clinical and Angiographic Characteristics

	DES (n=730)	Conventional (n=500)
Age (yrs)	63.0	63.6
Male (%)	70.0	71.2
Diabetes (%)	34.4	29.2
LL (mm)	16.74	16.12
Diameter (mm)	2.65	2.61

Dibra A et al: JACC 49:616, 2007

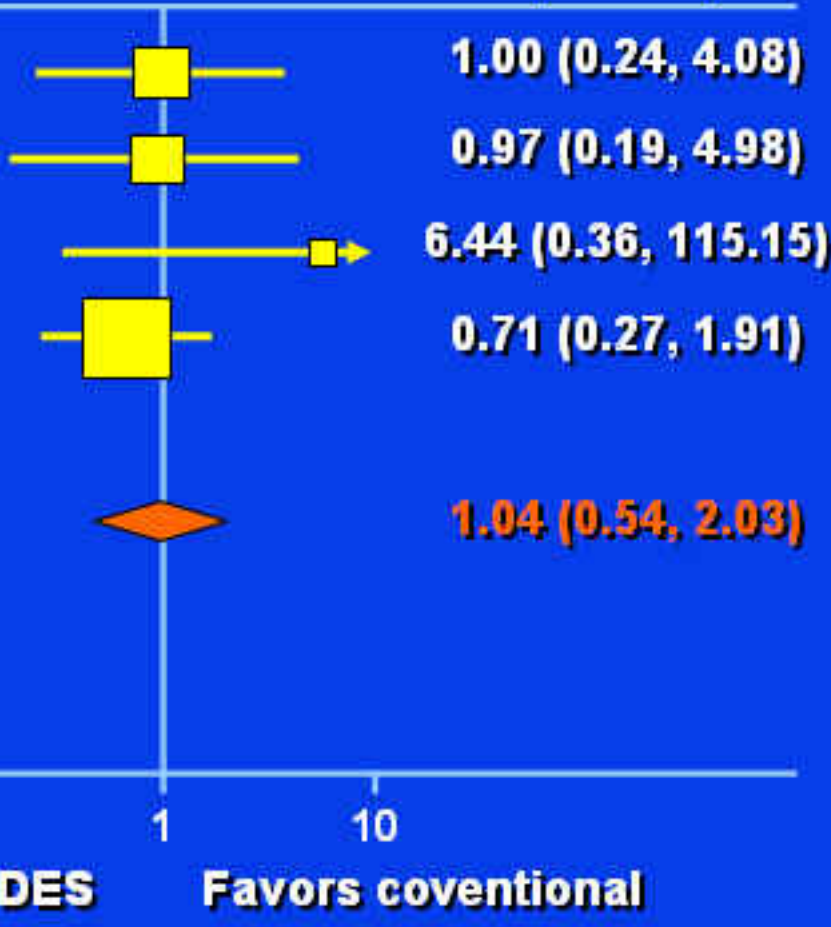
DES for In-Stent Restenosis of BMS

SISR	SES vs VBT	(384 pts)
TAXUS-V ISR	PES vs VBT	(396 pts)
RIBS-II	SES vs PTCA	(150 pts)
ISAR-DESIRE	SES, PES, PTCA	(300 pts)

Dibra A et al: JACC 49:616, 2007

Death or MI

Study	DES (no.)	Conventional (no.)	Odds ratio (95% CI)
ISAR-DESIRE	6/200	3/100	1.00 (0.24, 4.08)
RIBS II	3/76	3/74	0.97 (0.19, 4.98)
SISR	6/259	0/125	6.44 (0.36, 115.15)
TAXUS-V ISR	7/195	10/201	0.71 (0.27, 1.91)
Total	22/730	16/500	
Overall (fixed effects)			1.04 (0.54, 2.03)



Test for heterogeneity: X^2=2.12 (df=3) P=0.55
Test for overall effect: z=0.13 P=0.90

Dibra A et al: JACC 49:616, 2007

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CP1308530-4

In-Stent Restenosis

BMS

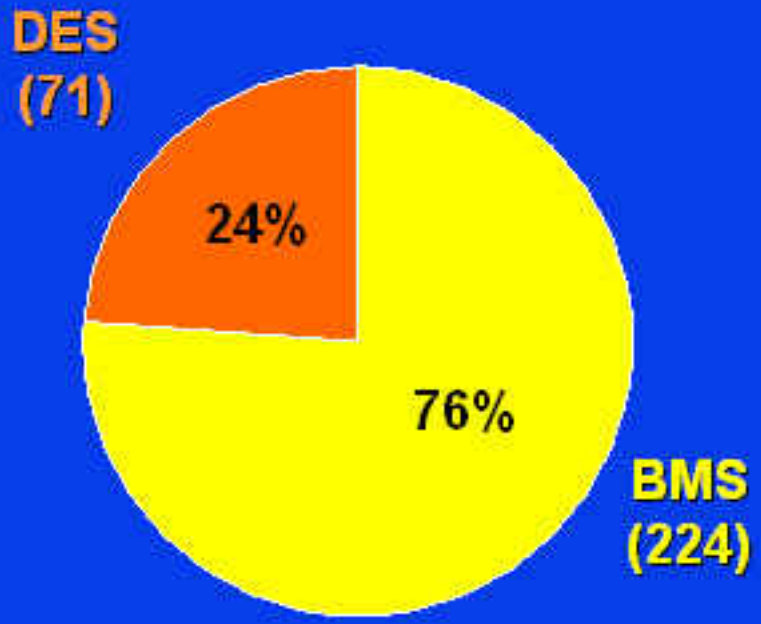
- Neointimal hyperplasia
- Under expansion
- Edge effects
- Stent fracture

DES

- Drug resistance
- Polymer toxicity
- Drug toxicity
- Under expansion
- Inflammation
- Geographic miss
- Other:
  - e.g. stent fracture

SES for In-Stent Restenosis

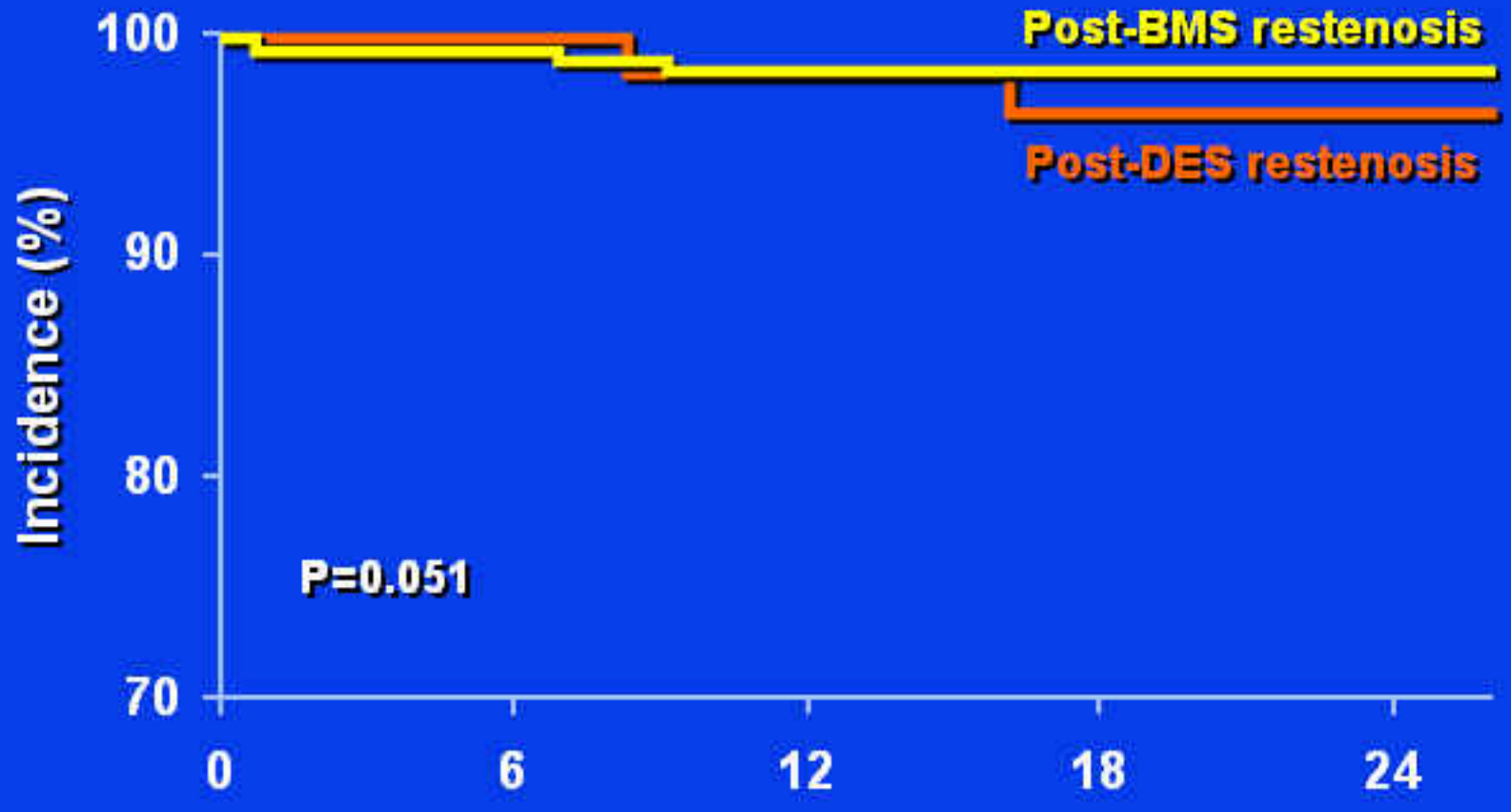
- Single center study
- 295 consecutive patients with ISR



- ISR of BMS
  - More complex lesions
  - 61% diffuse (vs (22%)

Lee CW et al, Cath & Cardiovasc Interven 71:594-598, 2008

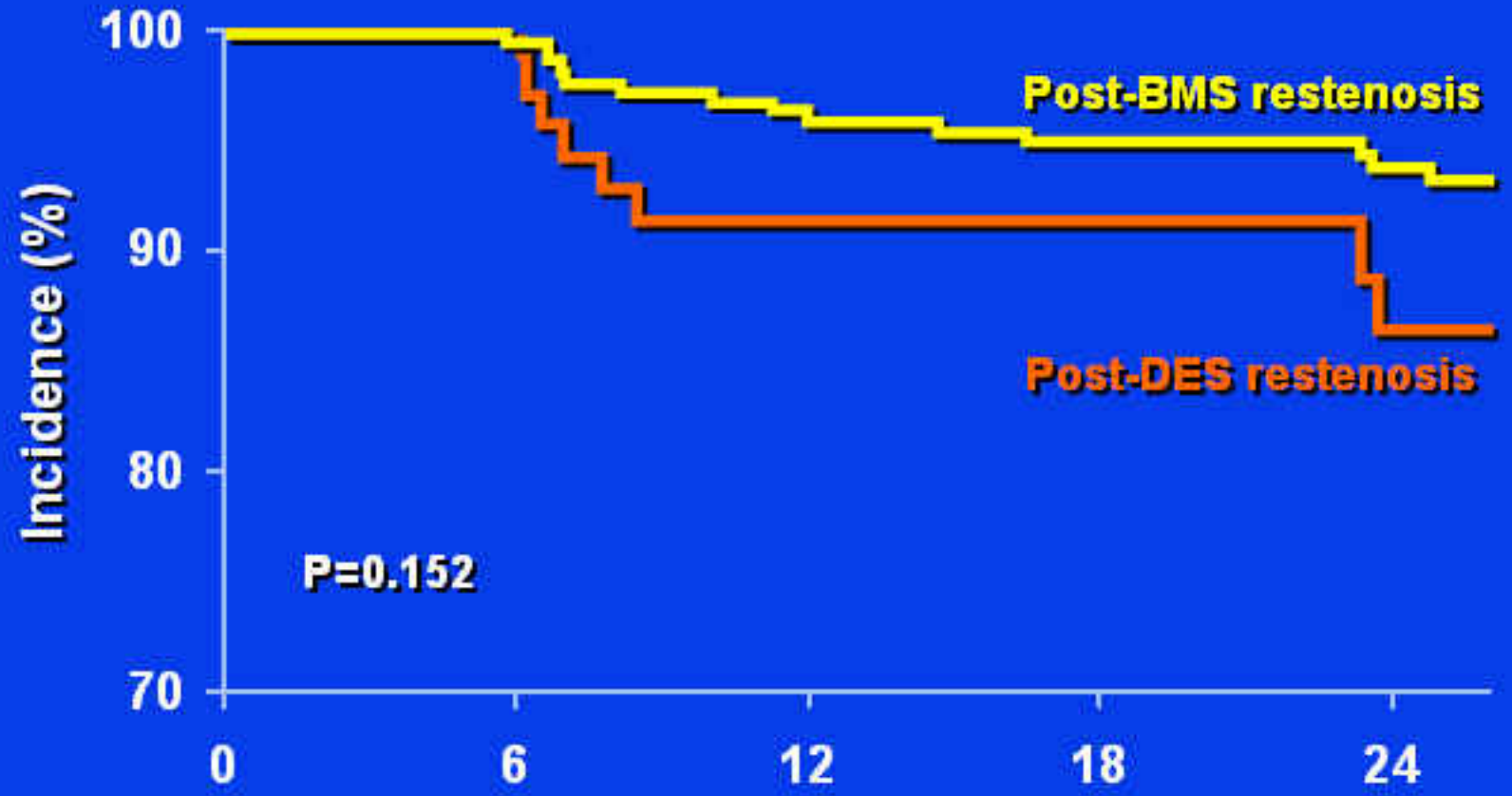
Incidence of Death or MI



No. at risk					
BMS	224	221	217	201	174
DES	71	69	68	47	38

Lee CW et al: Cath & Cardiovasc Interven 71:594, 2008

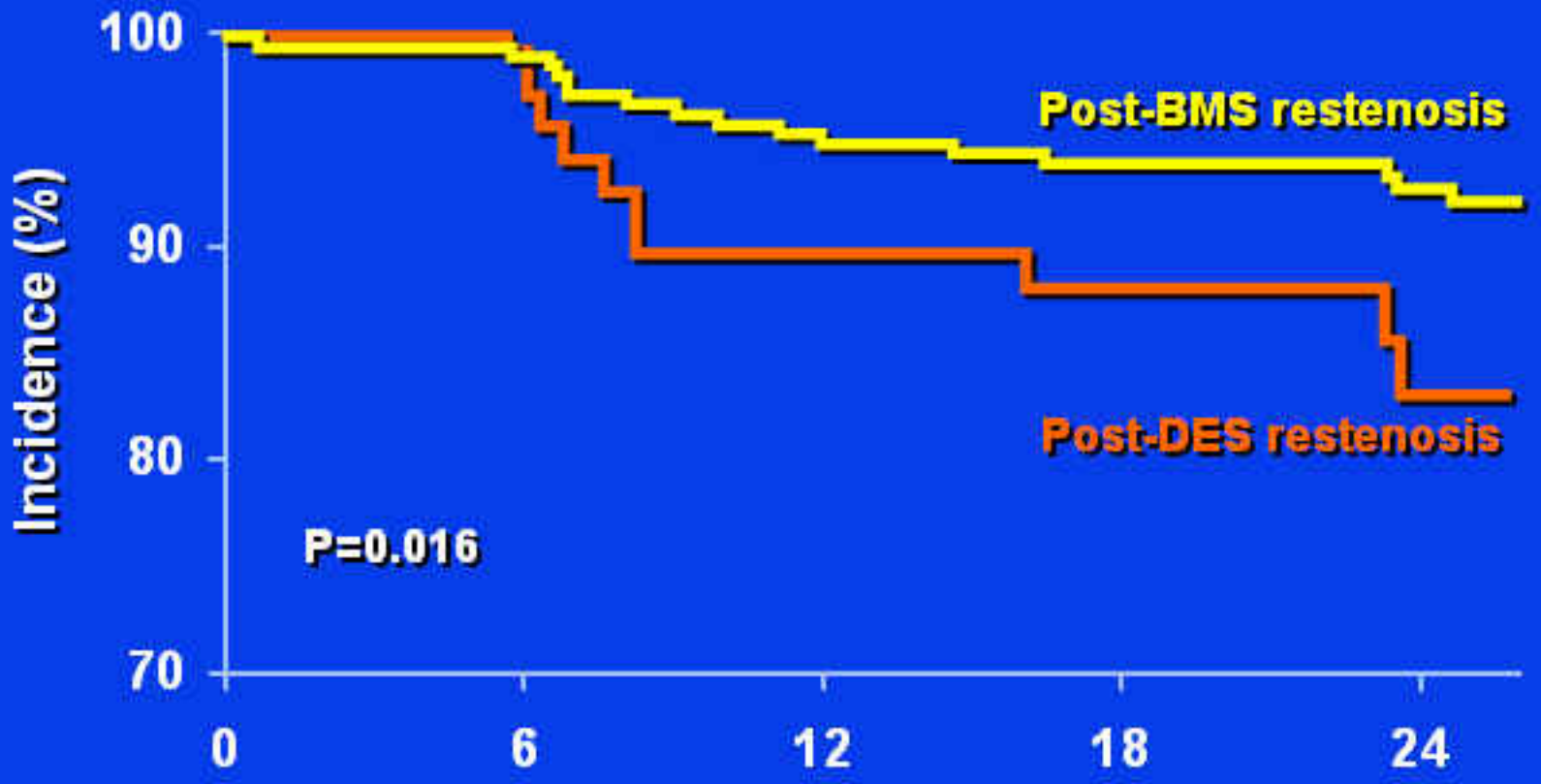
Incidence of TLR



No. at risk					
BMS	224	221	217	201	174
DES	71	69	68	47	38

Lee CW et al: Cath & Cardiovasc Interven 71:594, 2008

MACE Rate



No. at risk					
BMS	224	220	210	191	162
DES	71	69	62	44	34

With multivariate analysis, part DES associated with increased MACE

Lee CW et al: Cath & Cardiovasc Interven 71:594, 2008

The SISR Trial: Long-term Follow-up at 3 Years

A Multicenter, Randomized Study of the Sirolimus-Eluting Bx VELOCITY® Stent versus Intravascular Brachytherapy in the Treatment of Patients with In-Stent Restenotic Coronary Artery Lesions

David R. Holmes, MD
Mayo Clinic
Rochester, MN

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Presenter Disclosure Information

David R. Holmes, Jr., M.D.

"Three-Year Outcomes of Sirolimus-Eluting Stents for the Treatment of In-Stent Restenosis: The SISR Trial"

The following relationships exist related to this presentation:

No relationships to disclose

Study Design

Prospective, randomized, multicenter study (26 sites), of patients undergoing treatment of in-stent restenosis occurring post-implantation of a bare-metal stent
Lesion Length ≥ 15mm and ≤ 40mm; diameter ≥ 2.5mm to ≤ 3.5mm
(N=384)

Randomized 1:2

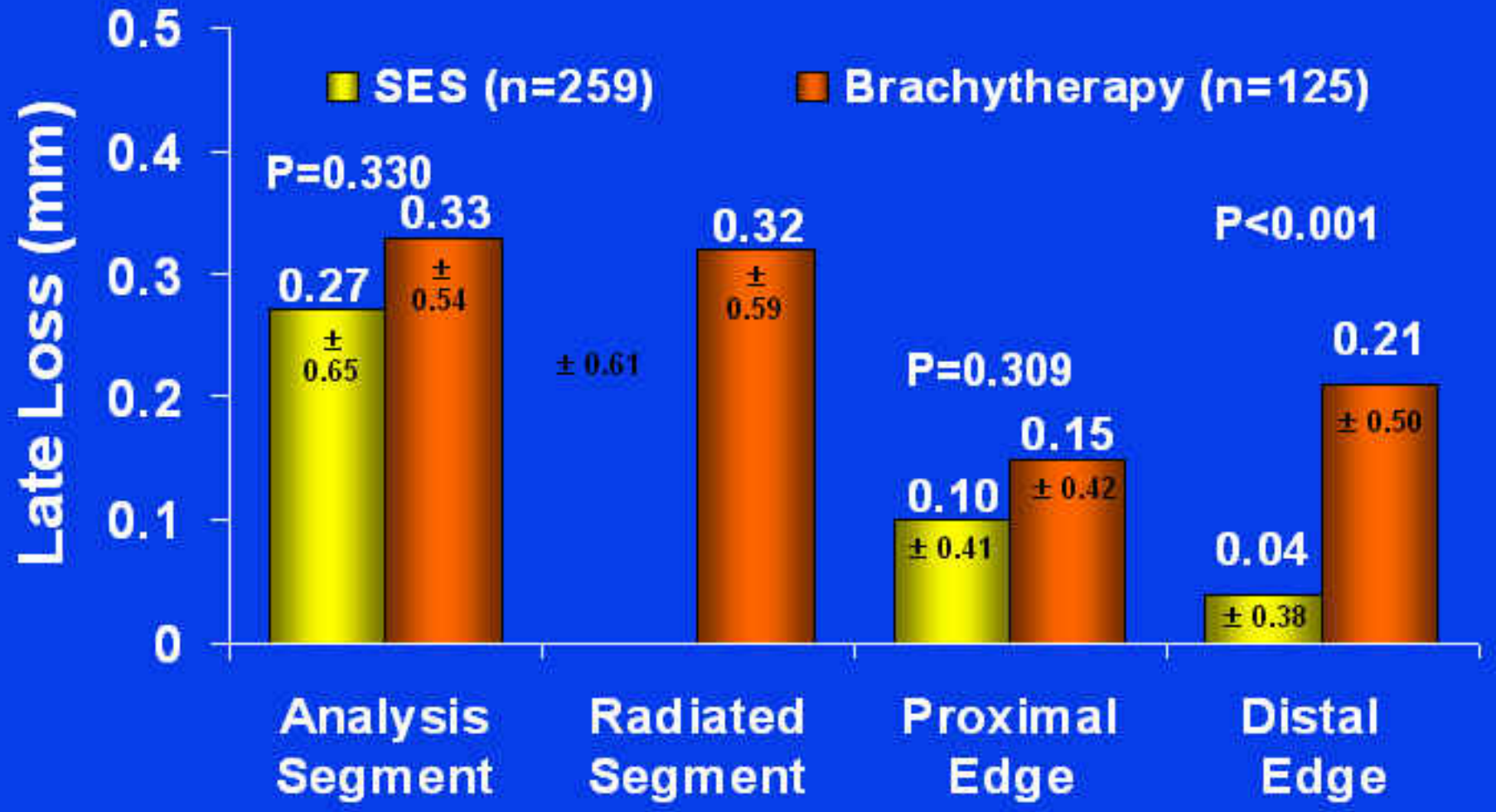
VBT with approved β or γ-source (n = 125)	Sirolimus-eluting Bx VELOCITY® stent (n = 259)
Clinical Compliance	Clinical Compliance
240 & 270 days: 93.6% (117/125)	240 & 270 days: 98.5% (255/259)
360 days: 92.0% (115/125)	360 days: 98.1% (254/259)
720 days: 91.2% (114/125)	720 days: 95.4% (247/259)
1080 days: 88.0% (110/125)	1080 days: 91.9% (238/259)

Angiographic follow-up at 6 months (129 pt. IVUS substudy)
Clinical follow-up will continue annually to 5 years

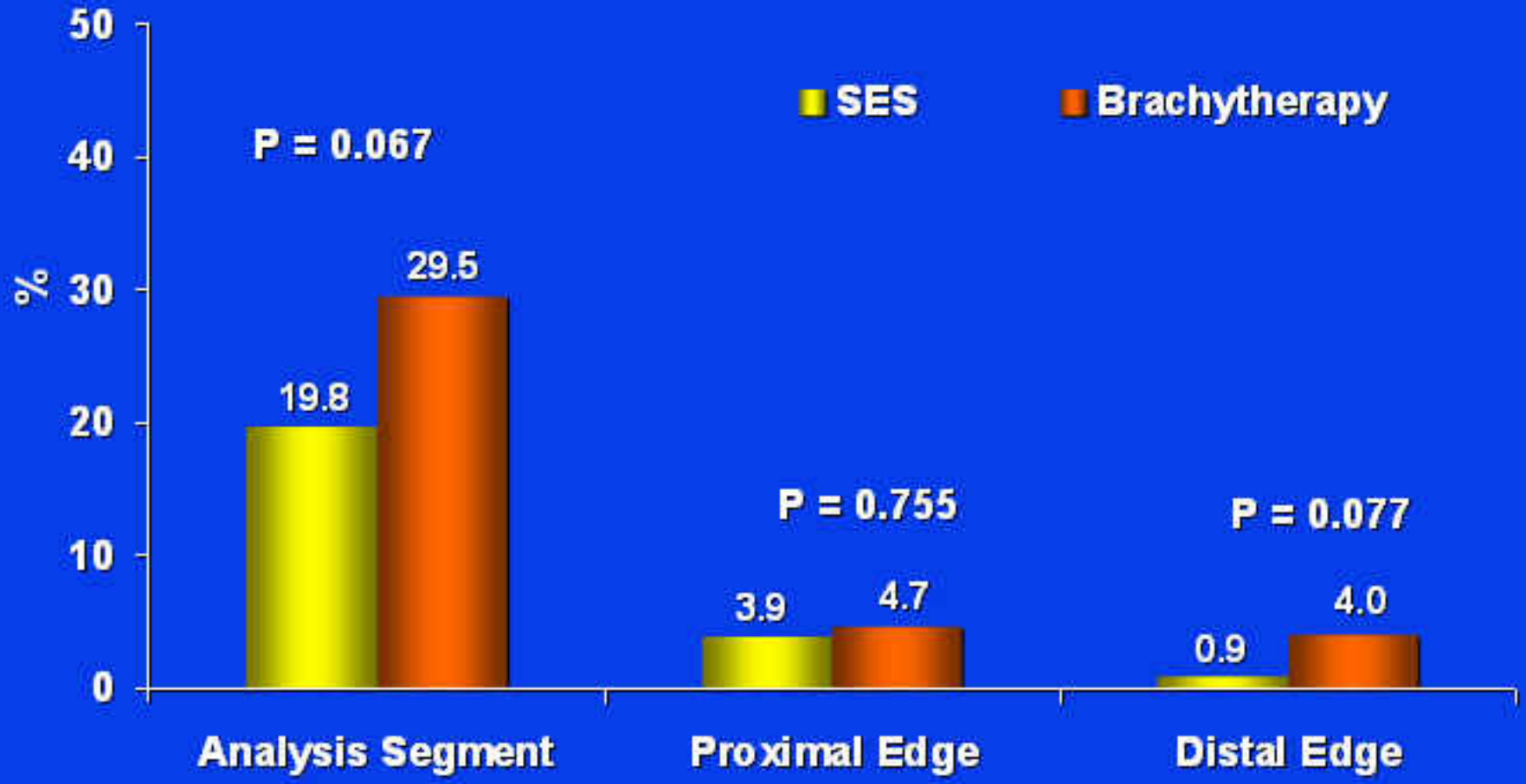
Baseline Demographics

	VBT 125 patients	SES 259 patients	p-value
Age (years)	63.5 ± 11.7	62.7 ± 10.7	0.49
Male (%)	65.6	68.2	0.64
Hypertension (%)	83.2	80.6	0.59
Hyperlipidemia (%)	88.8	91.5	0.46
Smoking (%)	66.4	66.9	>0.99
Diabetes (%)	29.6	33.3	0.49
Prior MI (%)	53.0	44.4	0.15
Prior CABG (%)	12.8	15.1	0.64
Congestive Heart Failure (%)	9.7	8.6	0.71
Unstable Angina (%)	50.9	46.9	0.55
Renal Insufficiency (%)	3.2	9.3	0.04
Ejection Fraction (%)	55.3 ± 8.5	56.8 ± 9.0	0.13

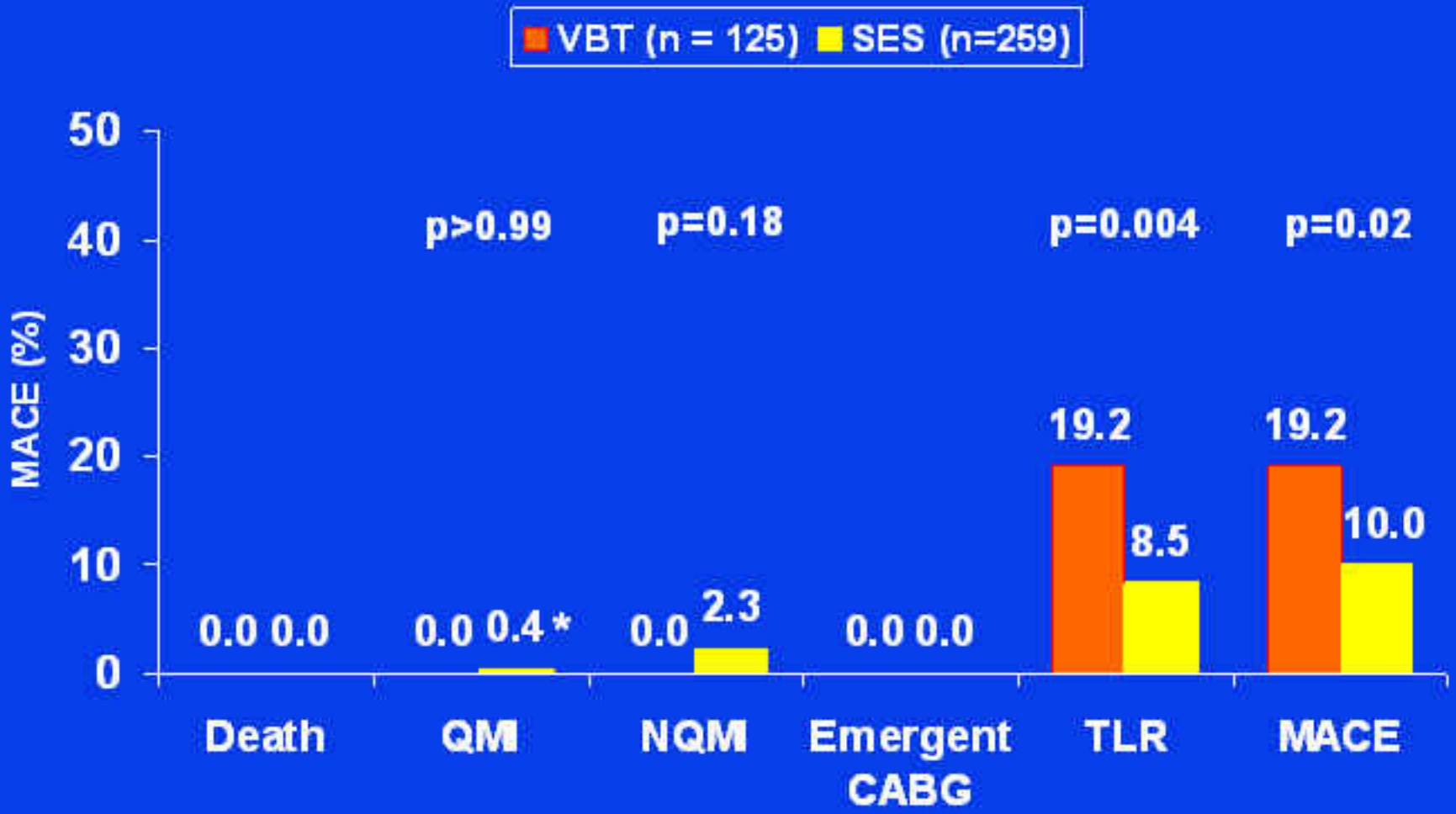
SISR: 6-month Late Loss



Binary Angiographic Restenosis at 6-Month Follow-Up



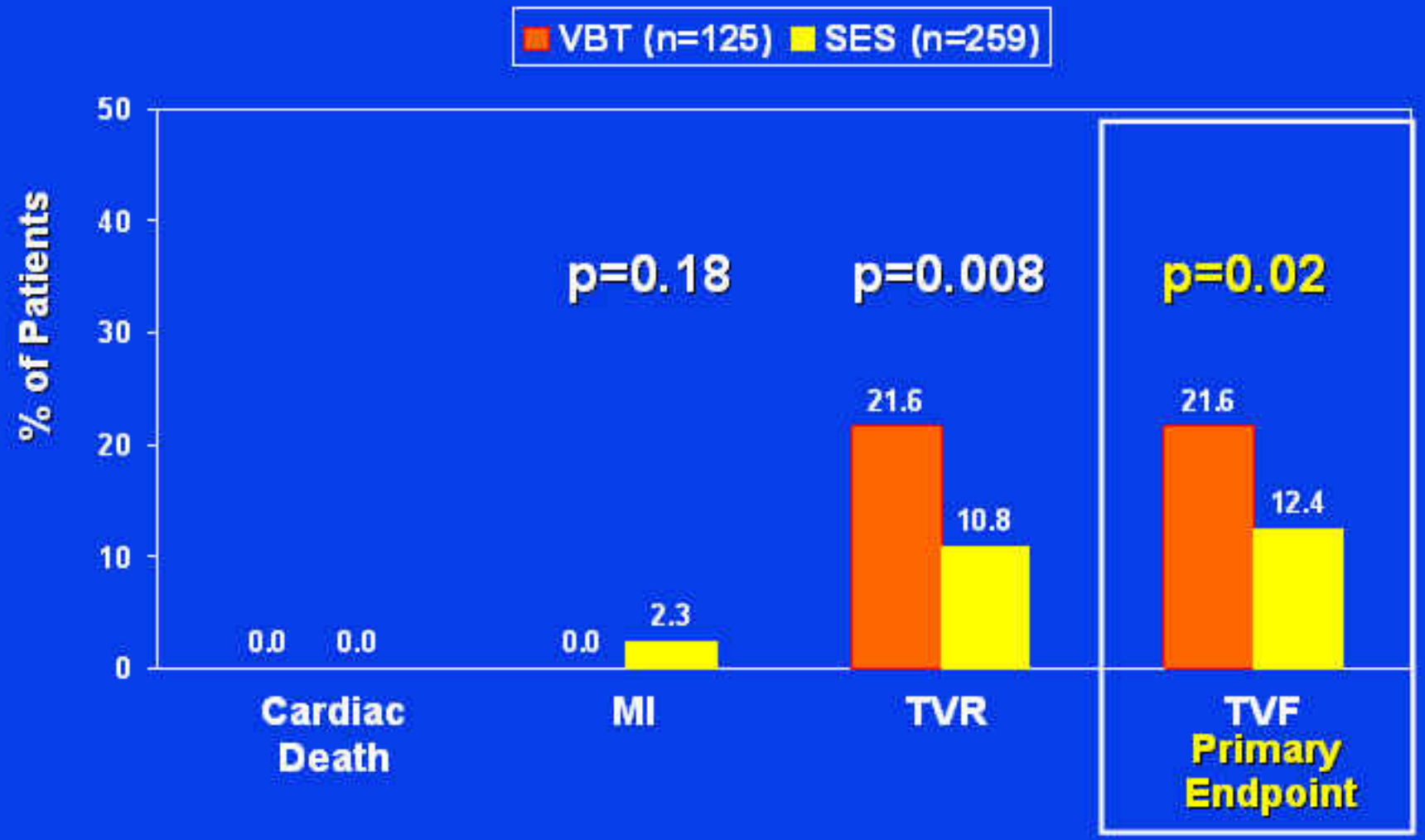
Major Adverse Events Through 270 Days



MACE: Major Adverse Cardiac Event defined as death, MI (Q- and non-Q), emergent bypass surgery, or target lesion revascularization

* One MI was classified as Q-wave and Non-Q-Wave

Primary Endpoint Through 270 Days



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Purpose

- Evaluate the 3-year outcome of patients treated in the multicenter SISR which randomized patients with in-stent restenosis of bare metal stents to either placement of a sirolimus-eluting stent (SES) or vascular brachytherapy (VBT)

Statistical Analysis

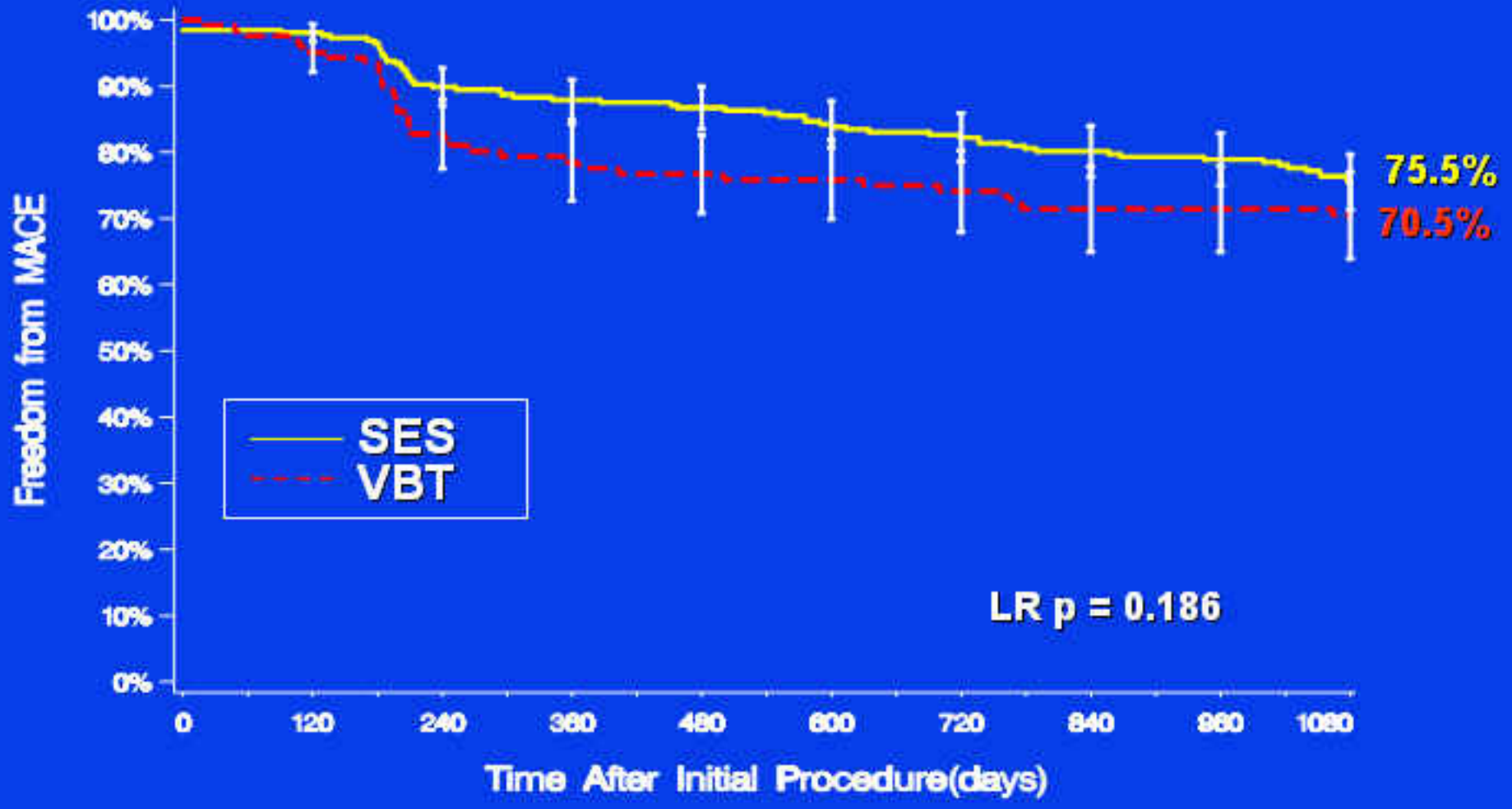
- SES demonstrated non-inferiority to VBT for safety and efficacy based on a significant reduction in target vessel failure (primary endpoint) at 9 months
- Superiority of SES to VBT was also established by significant reduction in target lesion revascularization due to an improvement in the analysis segment net gain
- Since the trial was neither powered nor designed for long-term follow-up, the focus of this longer-term follow up involved examination of pre-specified safety endpoints (death, MI and stent thrombosis) and of the efficacy endpoint (TLR) to determine whether any new safety issues emerged and whether the major benefit of SES, namely reduction in TLR, was maintained

3-Year Outcome

	VBT n=125		SES n=259		All Pts 384 Pts 384 Lesions		
	%	#	%	#	%	#	P
MACE*	28.0	35/125	23.6	61/259	25.0	96/384	0.379
Death	2.4	3/125	3.9	10/259	3.4	13/384	0.560
Cardiac	0.8	1/125	1.5	4/259	1.3	5/384	1.000
Non-Cardiac	1.6	2/125	2.3	6/259	2.1	8/384	1.000
TV Q-wave MI	0.0	0/125	1.5	4/259	1.0	4/384	0.309
TV non-Q wave MI	3.2	4/125	5.0	13/259	4.4	17/384	0.598
All target vessel MI	3.2	4/125	5.8	15/259	4.9	19/384	0.325
All non-target vessel MI	0.0	0/125	0.4	1/259	0.3	1/384	1.000

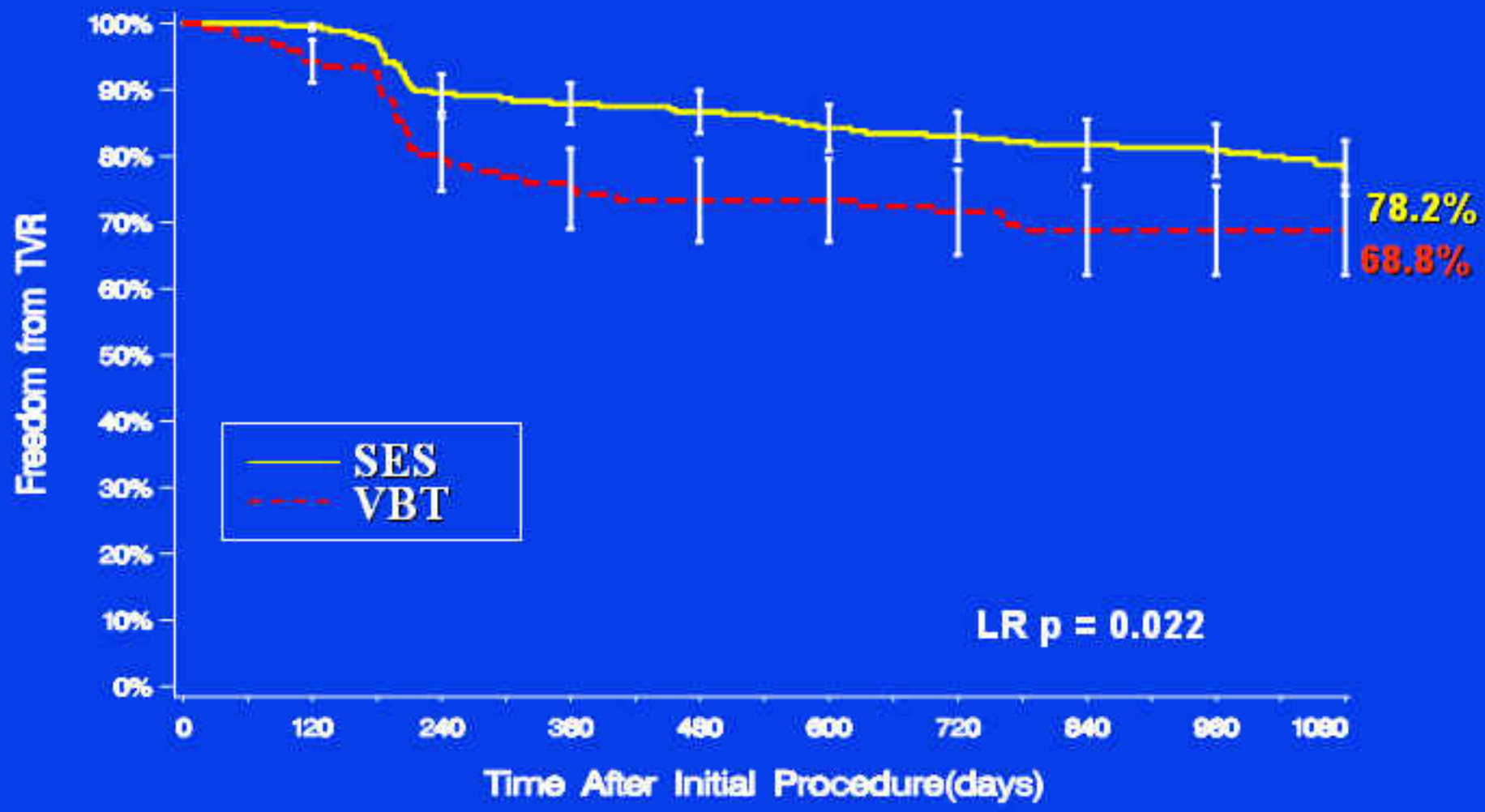
*death, Q/non-Q wave MI, EM CABG, TLR

Survival Free from MACE to 1080 Days



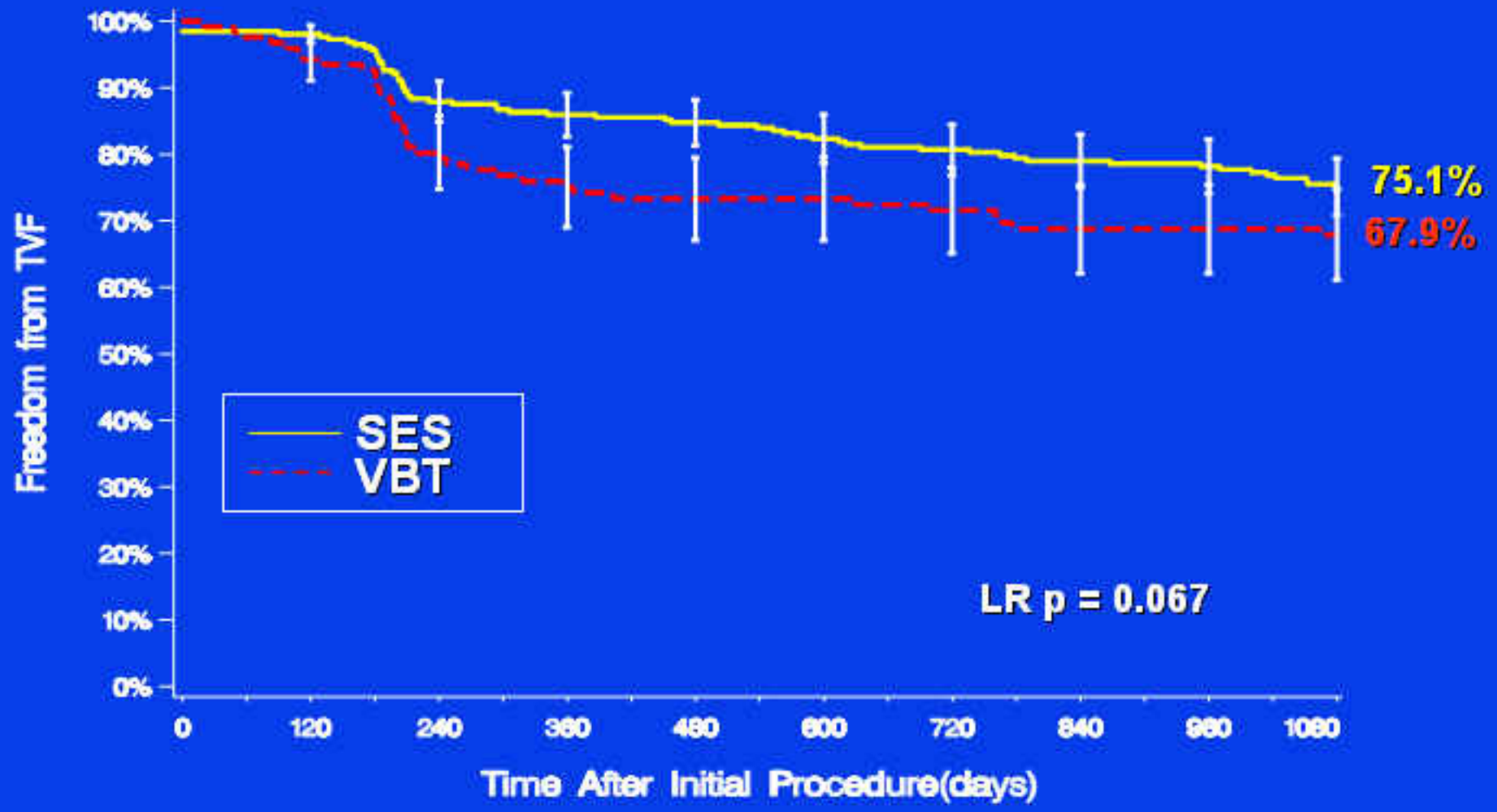
MACE: Major Adverse Cardiac Event defined as death, MI (Q- and non-Q), emergent bypass surgery, or target lesion revascularization

Survival Free from TVR to 1080 Days



TVR: Target Vessel Revascularization defined as any "clinically-driven" repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel

Survival Free from TVF to 1080 Days



TVF: Target Vessel Failure defined as target vessel revascularization, Q- or non-Q MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel

Anti platelet treatment

- VBT patients: ASA indefinitely, and Clopidogrel or Ticlopidine for 12 months if they received a new stent, or 6 months if no new stent placed.
- SES patients: ASA indefinitely, and Clopidogrel or Ticlopidine for at least 12 weeks.

Medication Use to 3 Years

Measure	VBT n=125 %	VBT n=125 #	SES n=259 %	SES n=259 #	All Pts 384 Pts 384 Lesions %	All Pts 384 Pts 384 Lesions #	P
Discharge							
ASA + Th*	87.2	109/125	87.9	226/257	87.7	335/382	0.869
Clopidogrel only	12.0	15/125	11.7	30/257	11.8	45/382	1.000
Ticlopidine only	0.8	1/125	0.0	0/257	0.3	1/382	0.327
6-month F/U							
ASA + Th*	75.0	87/116	70.1	176/251	71.7	263/367	0.384
ASA only	5.2	6/116	6.8	17/251	6.3	23/367	0.649
Clopidogrel only	15.5	18/116	21.9	55/251	19.9	73/367	0.163

*Th = thienopyridine

Medication Use to 3 Years

	VBT n=125		SES n=259		All Pts 384 Pts 384 Lesions		
Measure	%	#	%	#	%	#	P
12-month F/U							
ASA + Th*	55.7	64/115	52.0	127/244	53.2	191/359	0.571
ASA only	16.5	19/115	21.7	53/244	20.1	72/359	0.263
Clopidogrel only	20.0	23/115	19.7	48/244	19.8	71/359	1.000
3-year F/U							
ASA + Th*	57.8	63/109	56.1	128/228	56.7	191/337	0.815
ASA only	30.3	33/109	30.3	69/228	30.3	102/337	1.000
Clopidogrel only	3.7	4/109	5.3	12/228	4.7	16/337	0.597

*Th = thienopyridine

Stent Thrombosis Definitions

Protocol Definition
Early (Acute + Subacute) ≤ 30 Days
Thrombotic occlusion of the stented vessel observed at the time of a clinically-driven angiographic restudy
OR
Q-wave MI in territory of stented vessel
OR
Any death not attributed to a non-cardiac cause
Late > 30 Days
MI attributed to the target vessel, with angiographic documentation of thrombus or total occlusion of target site, and freedom from an interim revascularization of target vessel

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

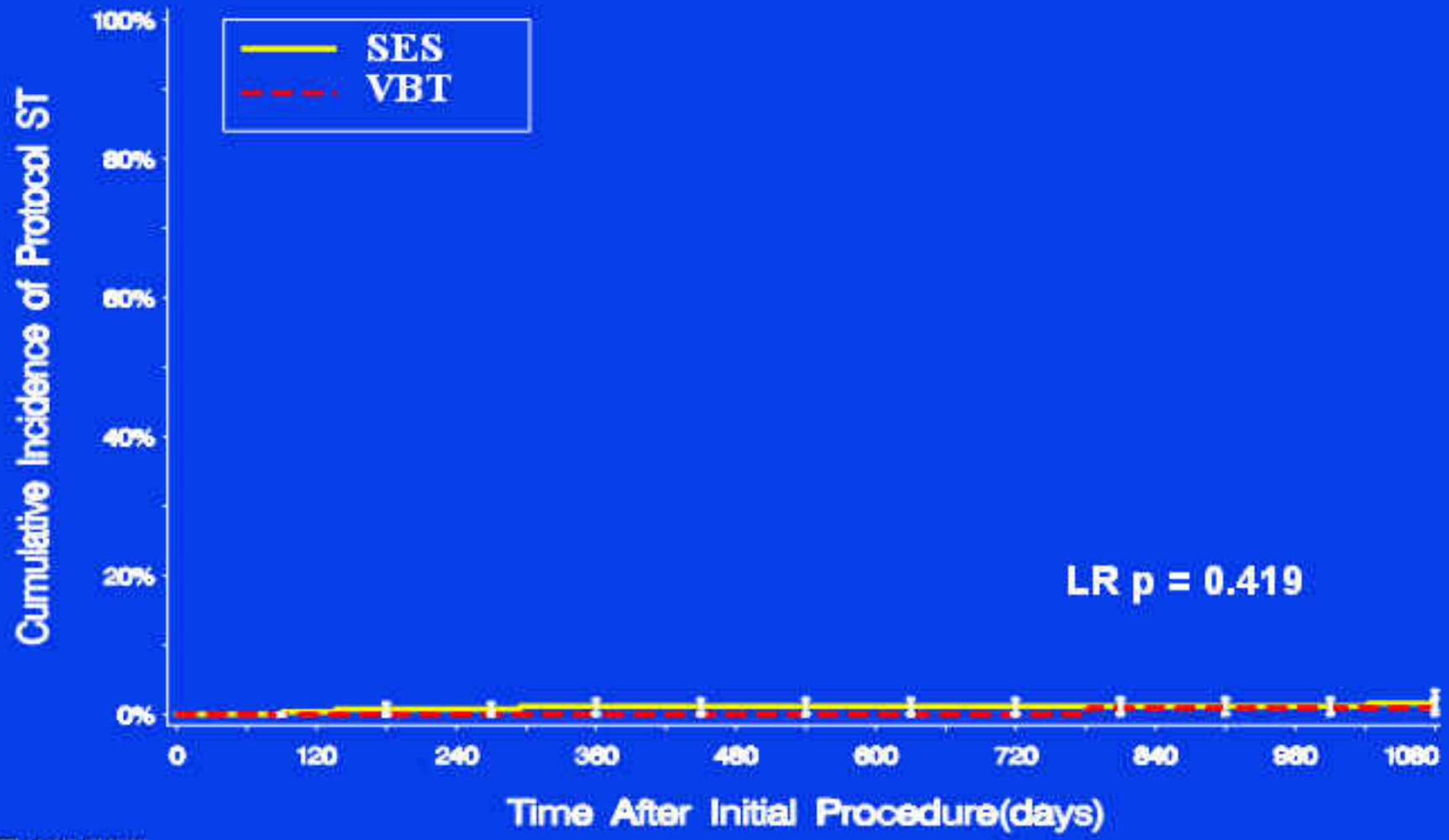
Note: Patients who have a TLR prior to a thrombosis are included by this set of definitions.

Protocol Medication Usage to 1080 Days

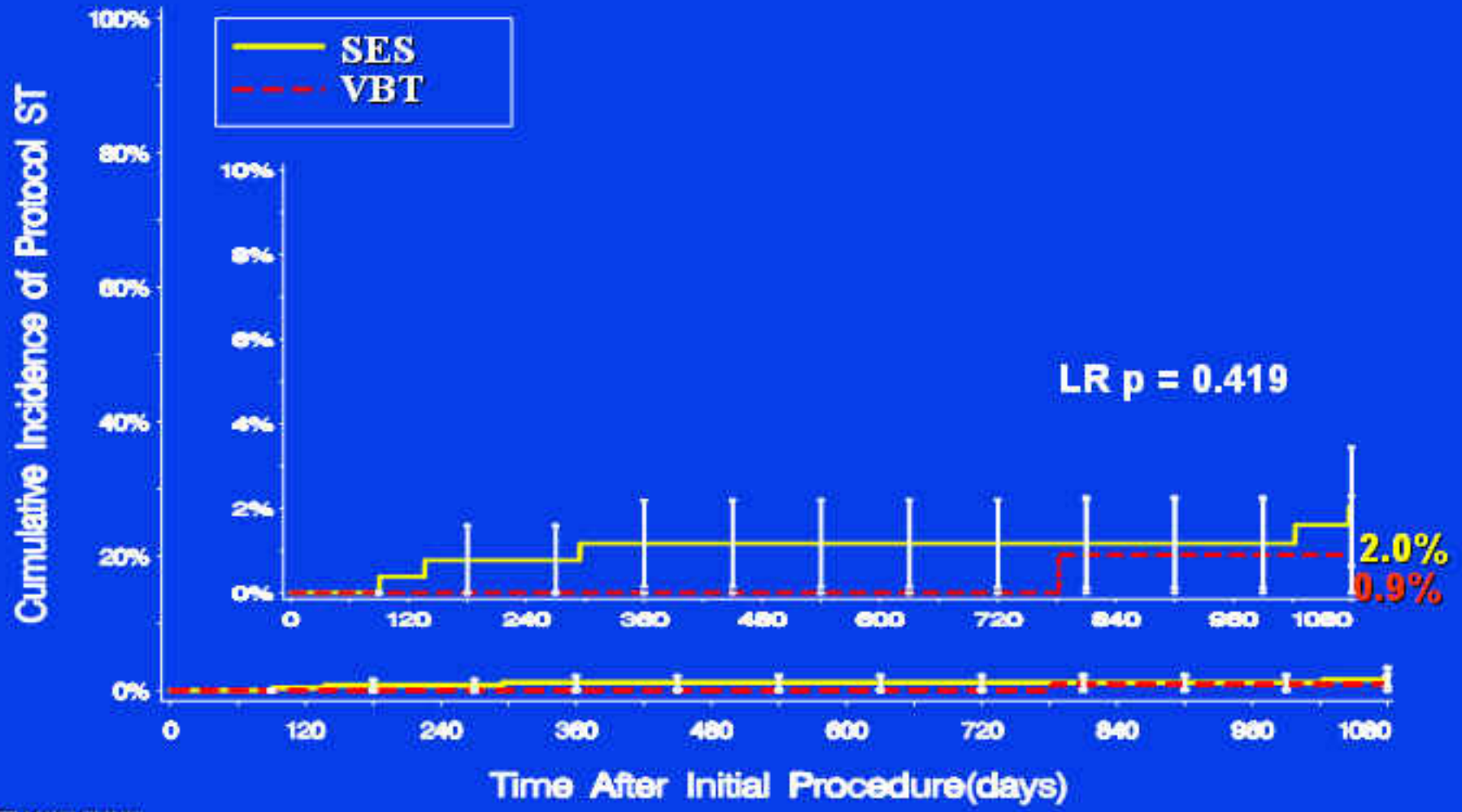
ASA + Clopidogrel or Ticlopidine	VBT 125 Patients	SES 259 Patients	p-value
Pre-procedure	84.8% (106/125)	79.4% (204/257)	0.213
Post-procedure	41.6% (52/125)	47.9% (123/257)	0.274
Discharge	87.2% (109/125)	87.9% (226/257)	0.869
30-days	86.3% (107/124)	83.3% (210/252)	0.547
6-months	75.0% (87/116)	70.1% (176/251)	0.384
9-months	62.8% (71/113)	61.0% (150/246)	0.815
1-year	55.7% (64/115)	52.0% (127/244)	0.571
2-year	41.2% (47/114)	42.4% (100/236)	0.908
3-year	57.8% (63.109)	56.1% (128/228)	0.815

VBT patients were required to take ASA indefinitely and Clopidogrel or Ticlopidine for 12 months if they received a stent, or for 6 months if they did not receive a stent.
SES patients were required to take ASA indefinitely and Clopidogrel or Ticlopidine for ≥ 12 weeks.

Cumulative Incidence of Protocol Stent Thrombosis to 1080 Days

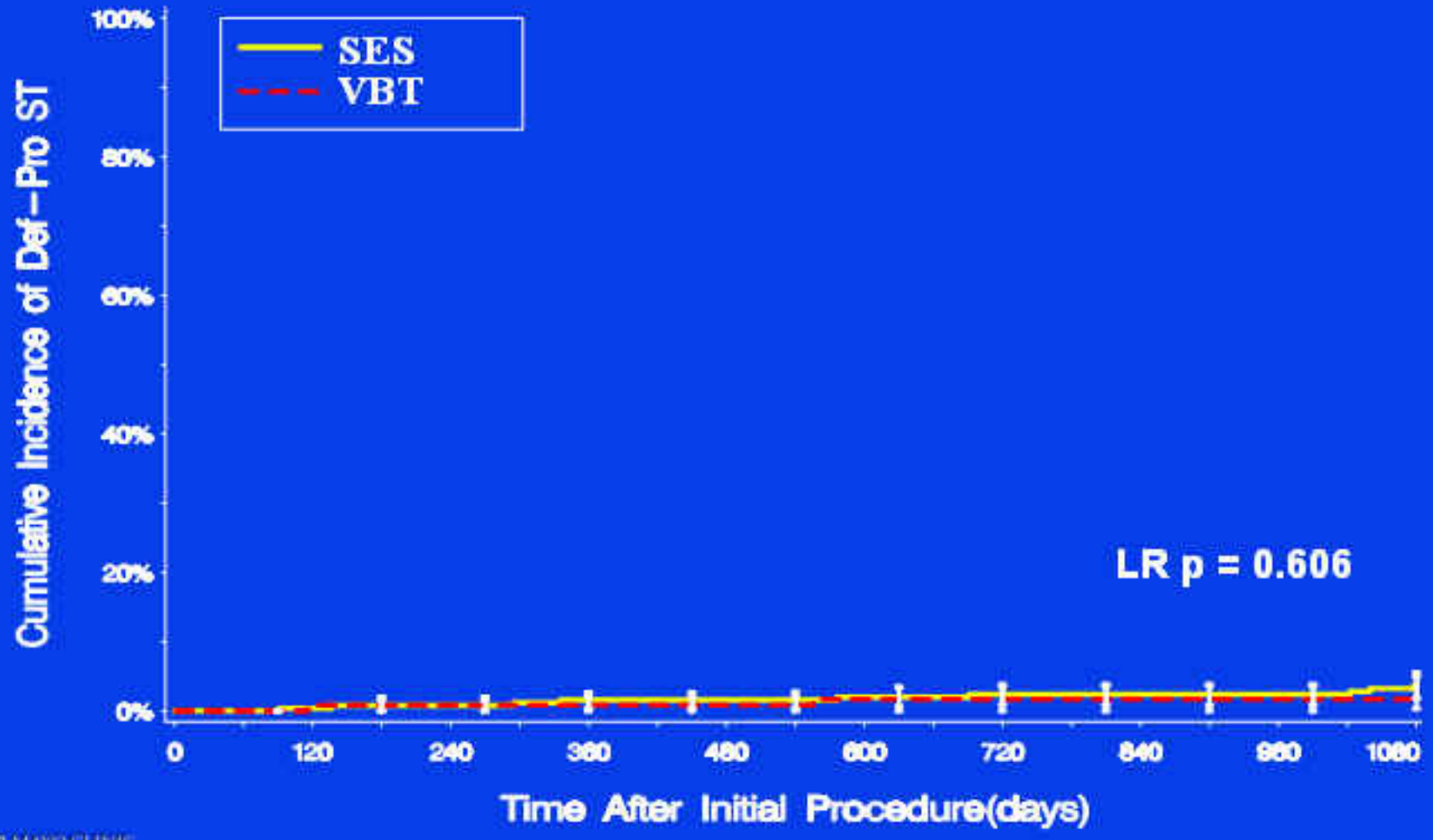


Cumulative Incidence of Protocol Stent Thrombosis to 1080 Days



MAYO CLINIC

Cumulative Incidence of Definite/Probable ARC Thrombosis to 1080 Days



APT Use in Patients with Stent Thrombosis

- At the time of stent thrombosis using the protocol definition:
  - 1 VBT patient was taking clopidogrel but stopped ASA
  - 4 of 5 SES patients were taking ASA but stopped clopidogrel
- At the time of ARC defined "definite" stent thrombosis:
  - 4 of 9 patients were taking both ASA and clopidogrel
  - 5 of 9 were taking neither drug
- Of the 3 patients with "probable" ARC defined thrombosis:
  - 1 patient was taking dual antiplatelet therapy
  - 1 patient was taking ASA but not clopidogrel
  - 1 patient was taking neither drug
- Thus, for patients with protocol defined stent thrombosis, almost all patients were not taking either ASA or clopidogrel. For patients with ARC defined thrombosis, approximately half were on dual APT and half were not taking either drug

SISR
3-Year Follow-Up
Limitations

- Primary endpoint was target vessel failure at 9 months. Yearly follow-up afterwards
- Trial not powered for long-term follow-up
- Antiplatelet regimens after 9 months were not mandated and varied according to clinical practice

SISR Trial: Study Administration

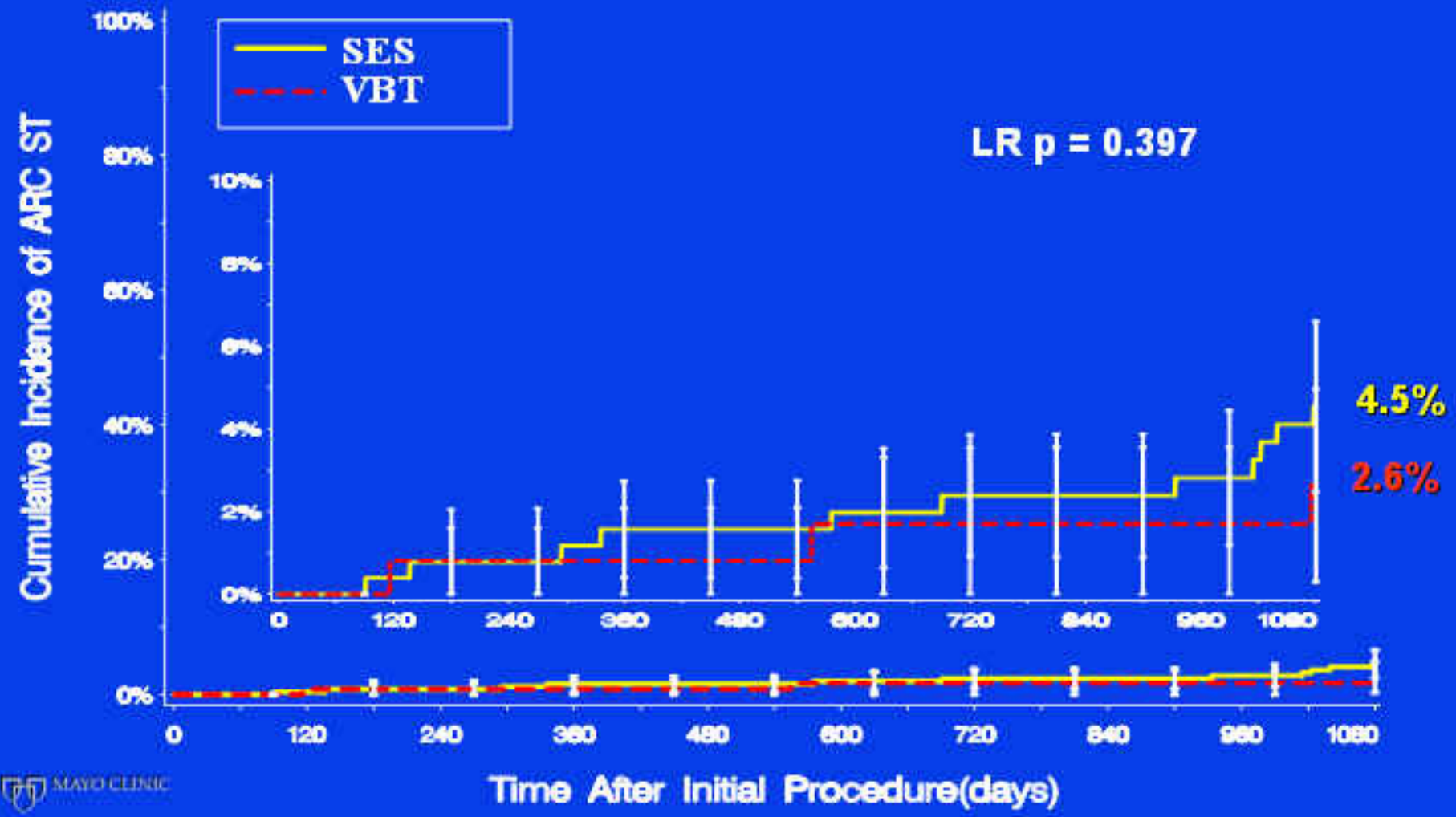
- **Principal Investigator:**
  - David R. Holmes
    Mayo Clinic, Rochester, MN
- **Data Coordinating Center:**
  - Harvard Clinical Research Institute (HCRI)
    Boston, MA
- **QCA Core Laboratory:**
  - Brigham and Women's Hospital
    Angiographic Core Lab
    Boston, MA
- **ECG Core Laboratory:**
  - Harvard clinical Research Institute (HCRI)
    Boston, MA
- **IVUS Core Lab:**
  - Cardiovascular Core Analysis Laboratory
    Stanford, CA
- **Sponsor:**
  - Cordis Corporation,
    a *Johnson & Johnson* Co.
    Warren, NJ

QCA Baseline and 6-Month Follow-up

	VBT 125 lesions	SES 259 lesions	p-value
Pre-procedure DS (%)	67.5 ± 11.8	70.4 ± 12.9	0.04
Lesion length (mm)	16.8 ± 8.56	17.2 ± 8.0	0.61
Radiation length (mm)	39.7 ± 11.0		
Final stent length (mm)	16.8 ± 7.6	32.5 ± 12.3	N/A
6-Month Follow-up			
Diameter stenosis (%)*	41.0 ± 21.1	32.4 ± 20.6	<0.001
Acute gain (mm)*	1.02 ± 0.40	1.27 ± 0.48	<0.001
Net gain (mm)*	0.68 ± 0.60	1.00 ± 0.61	<0.001
Late loss (mm)*	0.33 ± 0.54	0.27 ± 0.55	0.33
Binary Restenosis (%)*	29.5	19.8	0.07

* Includes analysis segment defined as within the radiation or stent zones including the proximal and distal 5mm margins

Cumulative Incidence of Any ARC Stent Thrombosis to 1080 Days



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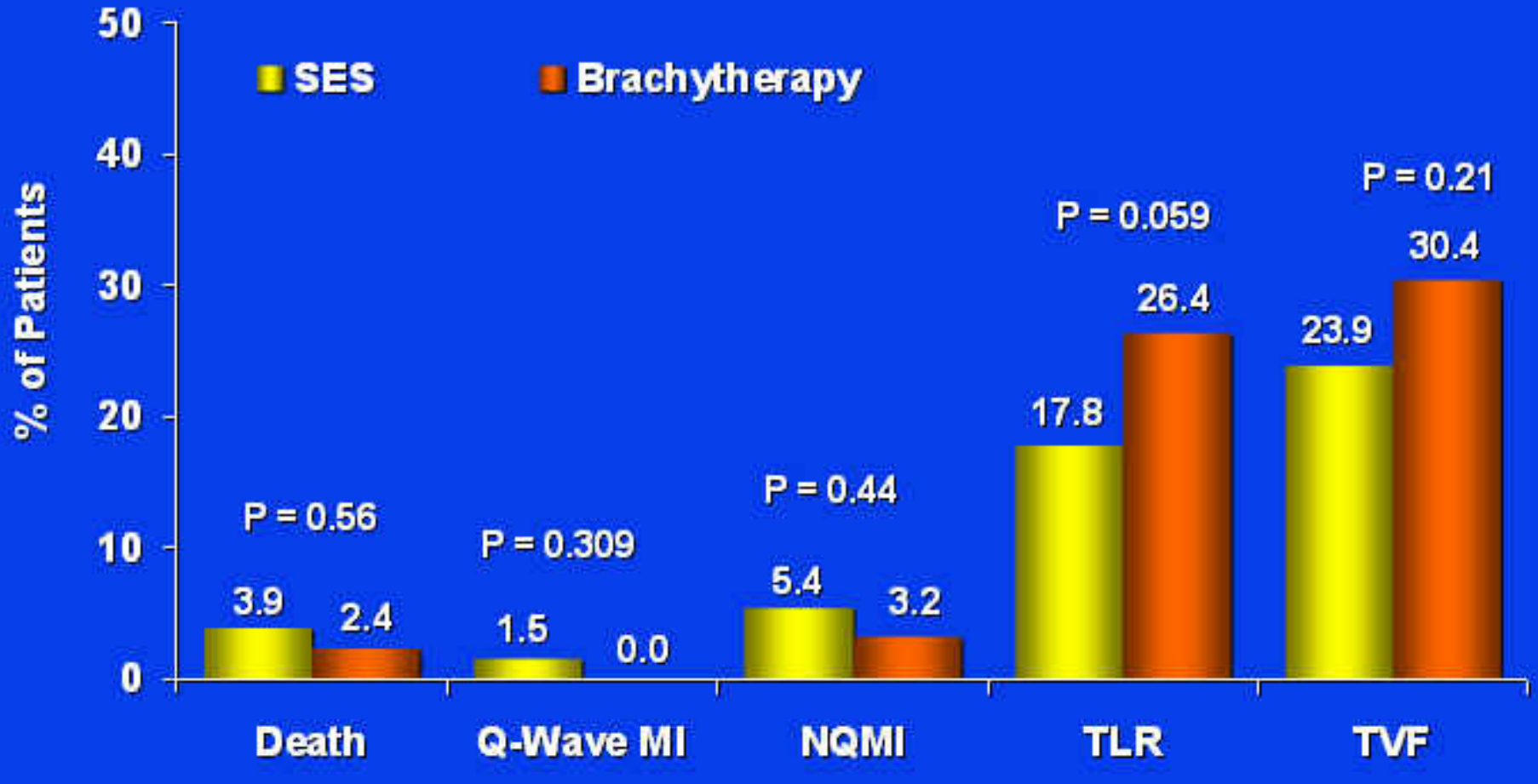
SISR
3-Year Follow-Up
Background

- Although vascular brachytherapy was approved for treatment of in-stent restenosis, system delivery issues, potential for late thrombosis and documentation of late catch-up with loss of initial gain led to use of drug-eluting stents

SISR
3-Year Follow-Up
Background

- Two large trials randomized patients with in-stent restenosis of bare metal stents to either VBT or DES
- SISR Trial

Clinical Outcomes Through 3 Years



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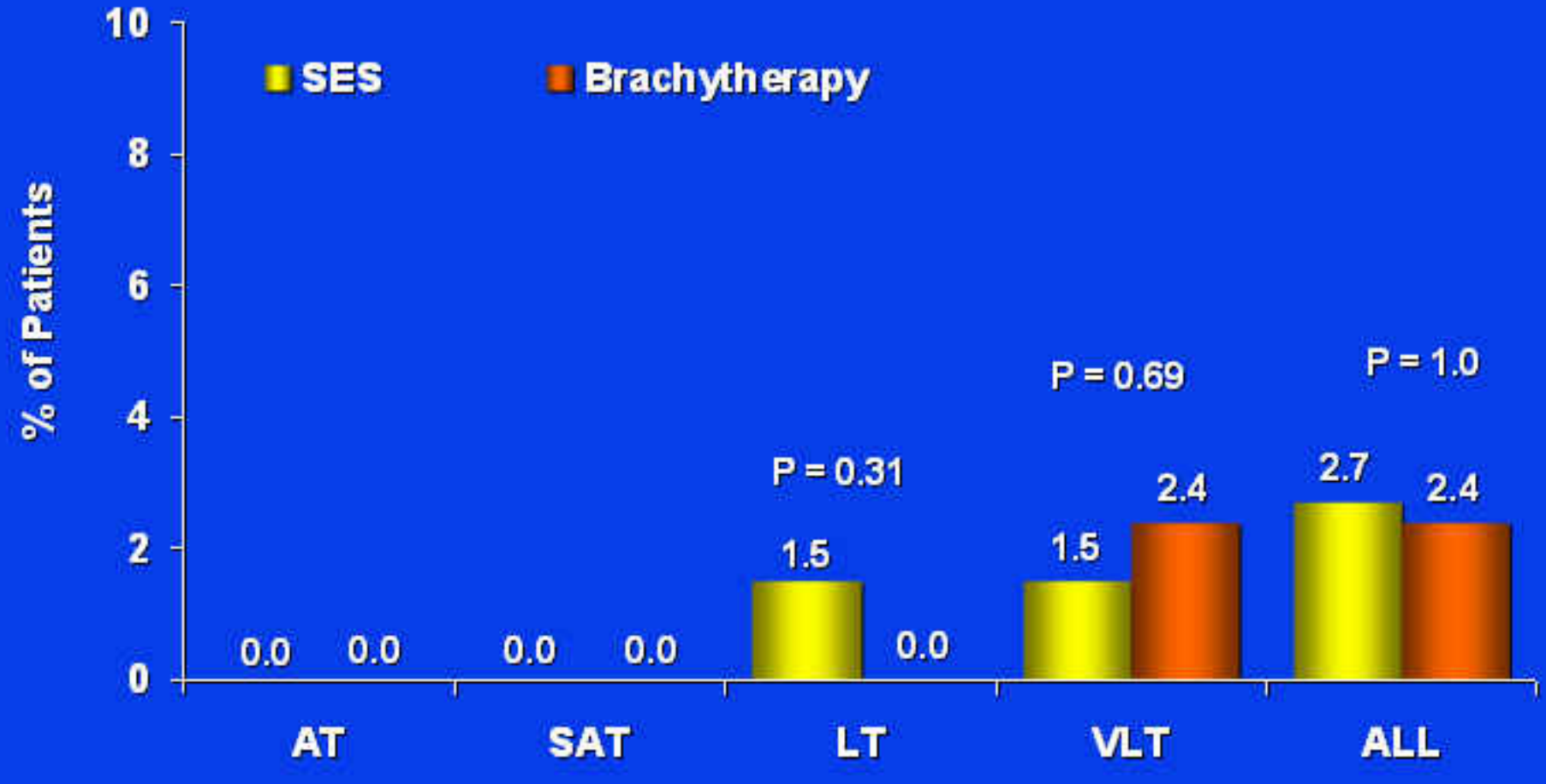
Stent Thrombosis Through 3 Years
ARC Definite



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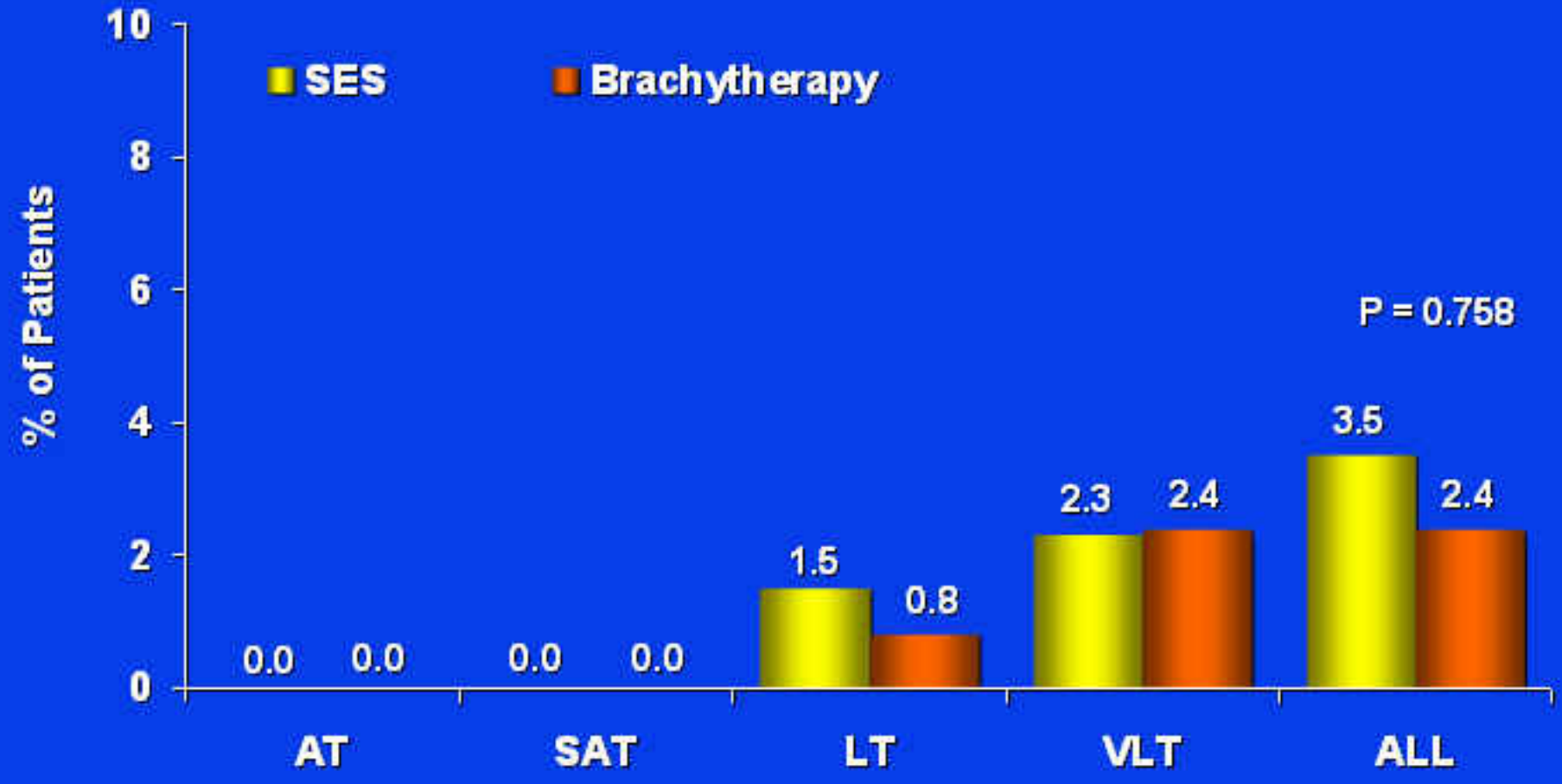
Stent Thrombosis Through 3 Years
ARC Definite or Probable



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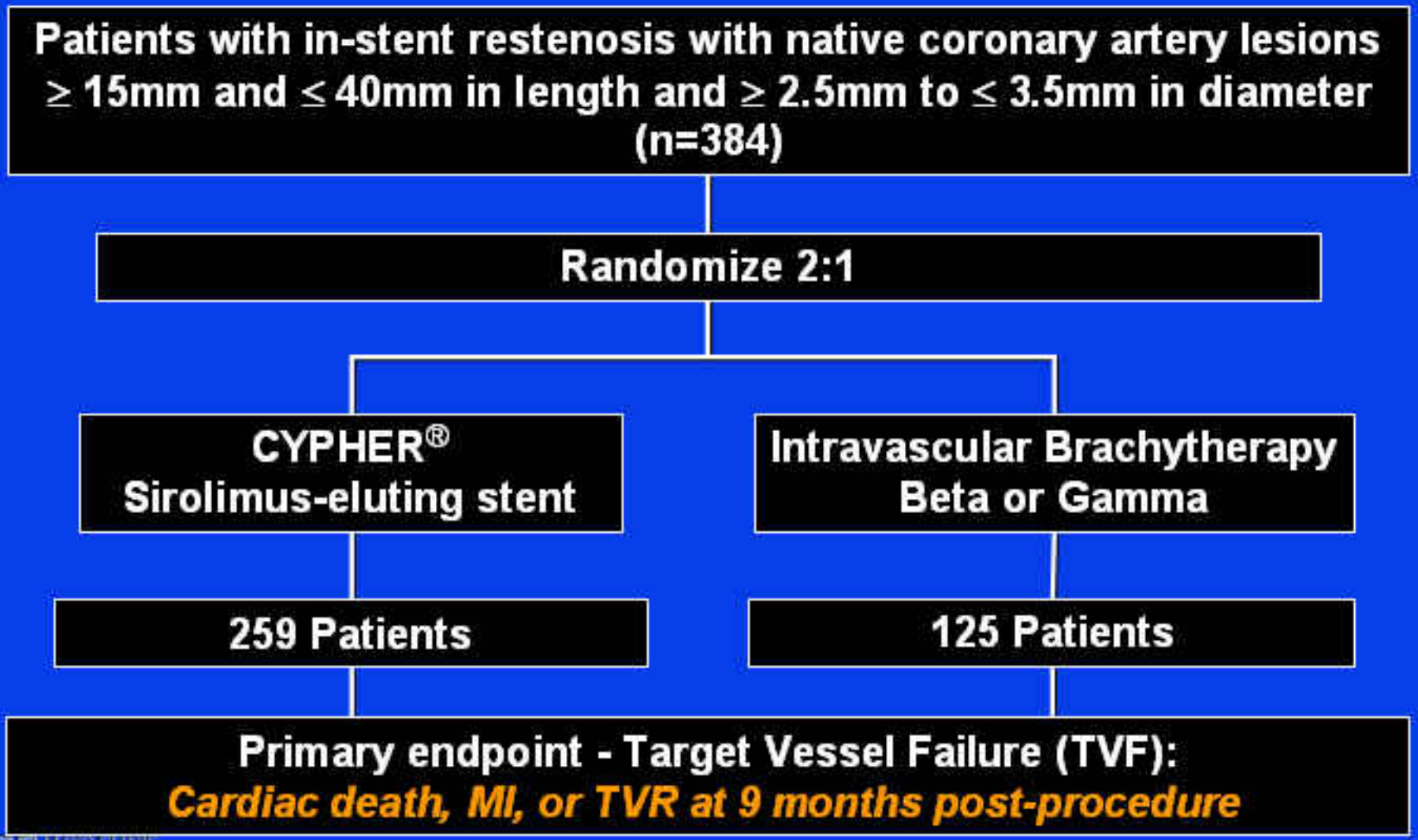
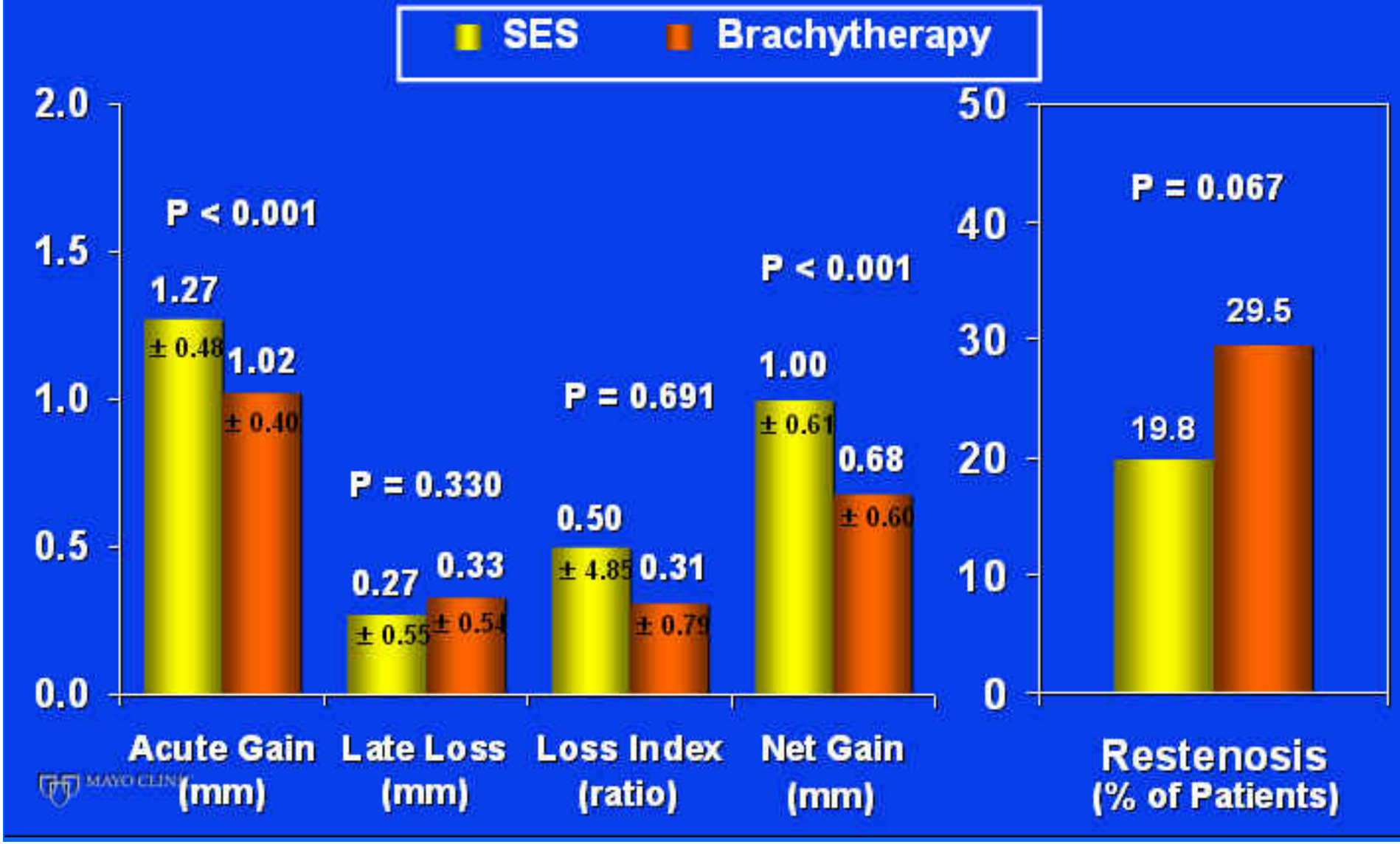
Study Design



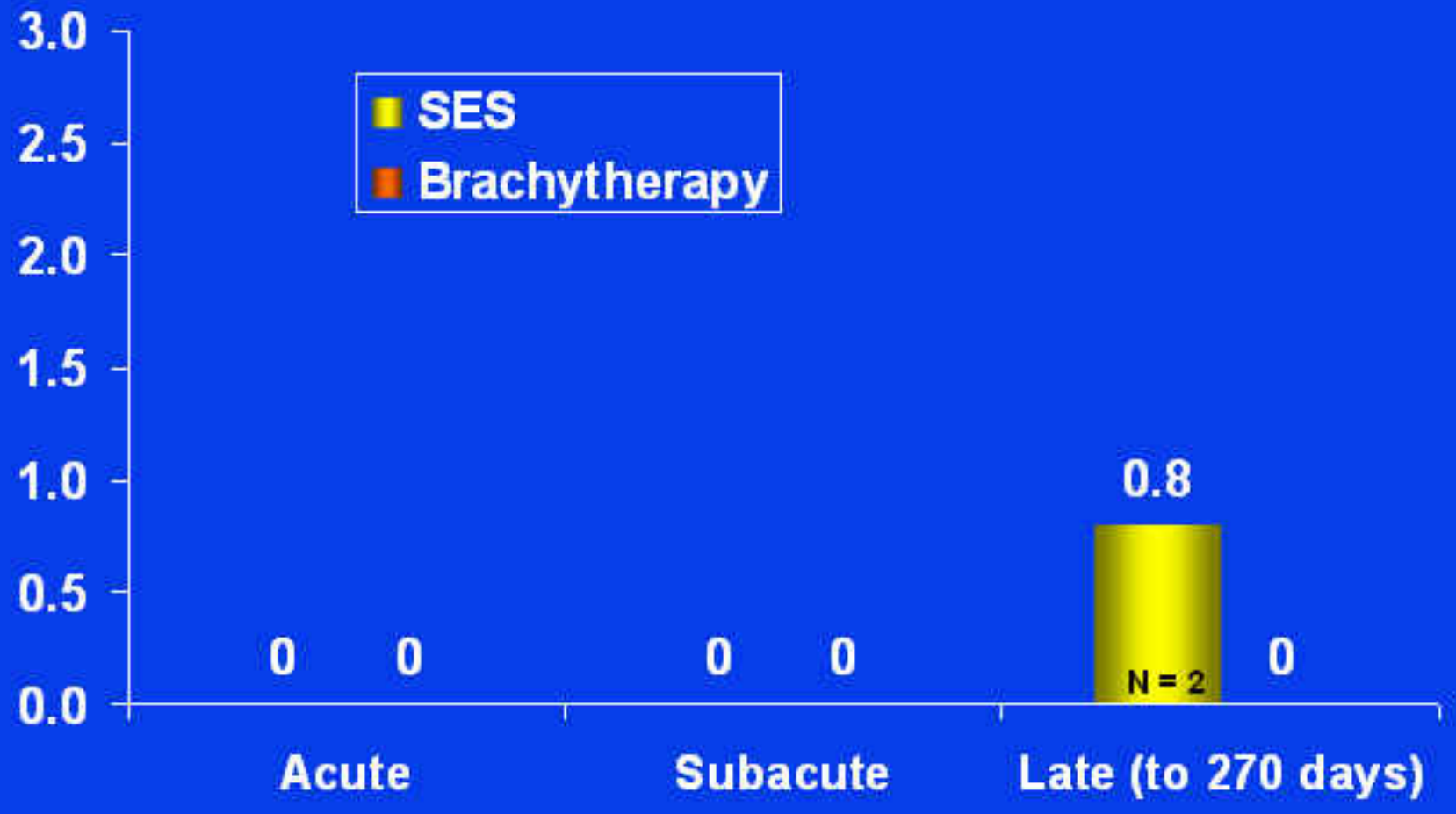
Major Inclusion Criteria

- ISR in a native coronary artery which has previously undergone stent placement (≥ 4 weeks)
- RVD ≥ 2.5mm and ≤ 3.5mm in diameter
- Lesion ≥ 15mm and ≤ 40mm in length which allows treatment with ≤ 3 18mm stents
- ≥ 1 prior PCI at the target lesion are acceptable candidates
- The vessel 1 cm distal to the target lesion is ≥ 2.5mm in diameter
- Lesion cannot be located in a vessel containing a 2nd lesion requiring treatment at time of index procedure
- Stable angina, or silent ischemia

Angiographic Outcomes Through 6-Months (Analysis Segment)



Stent Thrombosis at 9-Month Follow-Up



SISR
3-Year Follow-Up
Statistical Analysis

- Trial designed and powered for 9-month primary endpoint of target vessel failure
  - Cardiac death
  - Myocardial infarction or
  - Target vessel revascularization
- Longer-term follow-up: safety endpoints –
  - Death
  - MI
  - Stent thrombosis
  - Efficacy endpoint – target lesion revascularization
- Kaplan-Meier analysis

Background

- Drug-eluting stents became widely applied for the treatment of in-stent restenosis of bare metal stents even though there was limited data on safety and efficacy in this setting
- The randomized multicenter SISR trial documented that sirolimus-eluting stents were superior to vascular brachytherapy in improving target vessel failure at 9 months

Background

- Vascular brachytherapy was developed, tested and subsequently approved for treatment of in-stent restenosis
- System delivery issues, late thrombosis and late diminution of sustained efficacy (catch-up) limited application of vascular brachytherapy

3-Year Outcome

	VBT n=125		SES n=259		All Pts 384 Pts 384 Lesions		
	%	#	%	#	%	#	P
Emergent CABG	0.0	0/125	0.0	0/259	0.0	0/384	--
TLR	26.4	33/125	17.8	46/259	20.6	79/384	0.059
TL-CABG	6.4	8/125	3.1	8/259	4.2	16/384	0.171
TL-PTCA	23.2	29/125	15.8	41/259	18.2	70/384	0.091
TVR not target lesion	8.8	11/125	6.9	18/259	7.6	29/384	0.540
TV/non-TL-CABG	2.4	3/125	0.4	1/259	1.0	4/384	0.103
TV/non-TL-PTCA	7.2	9/125	6.6	17/259	6.8	26/384	0.830
TVF to 270 days	21.6	27/125	12.4	32/259	15.4	59/384	0.023
TVF to 1080 days	30.4	38/125	23.9	62/259	26.0	100/384	0.214
TVR (all)	29.6	37/125	20.8	54/259	23.7	91/384	0.073

Definite or Probable ARC Thrombosis
Out to 3 Years Outcome

	VBT n=125		SES n=259		All Pts 384 Pts 384 Lesions		
	%	#	%	#	%	#	P
Acute thrombosis (0-1)	0.0	0/125	0.0	0/259	0.0	0/384	--
Subacute thrombosis (2-30)	0.0	0/125	0.0	0/259	0.0	0/384	--
Late thrombosis (31-360)	0.8	1/125	1.5	4/259	1.3	5/384	1.000
Very late thrombosis (361-1080)	2.4	3/125	2.3	6/259	2.3	9/384	1.000
All Thrombosis (0-1080)	2.4	3/125	3.5	9/259	3.1	12/384	0.758

Definite ARC Thrombosis
Out to 3 Years Outcome

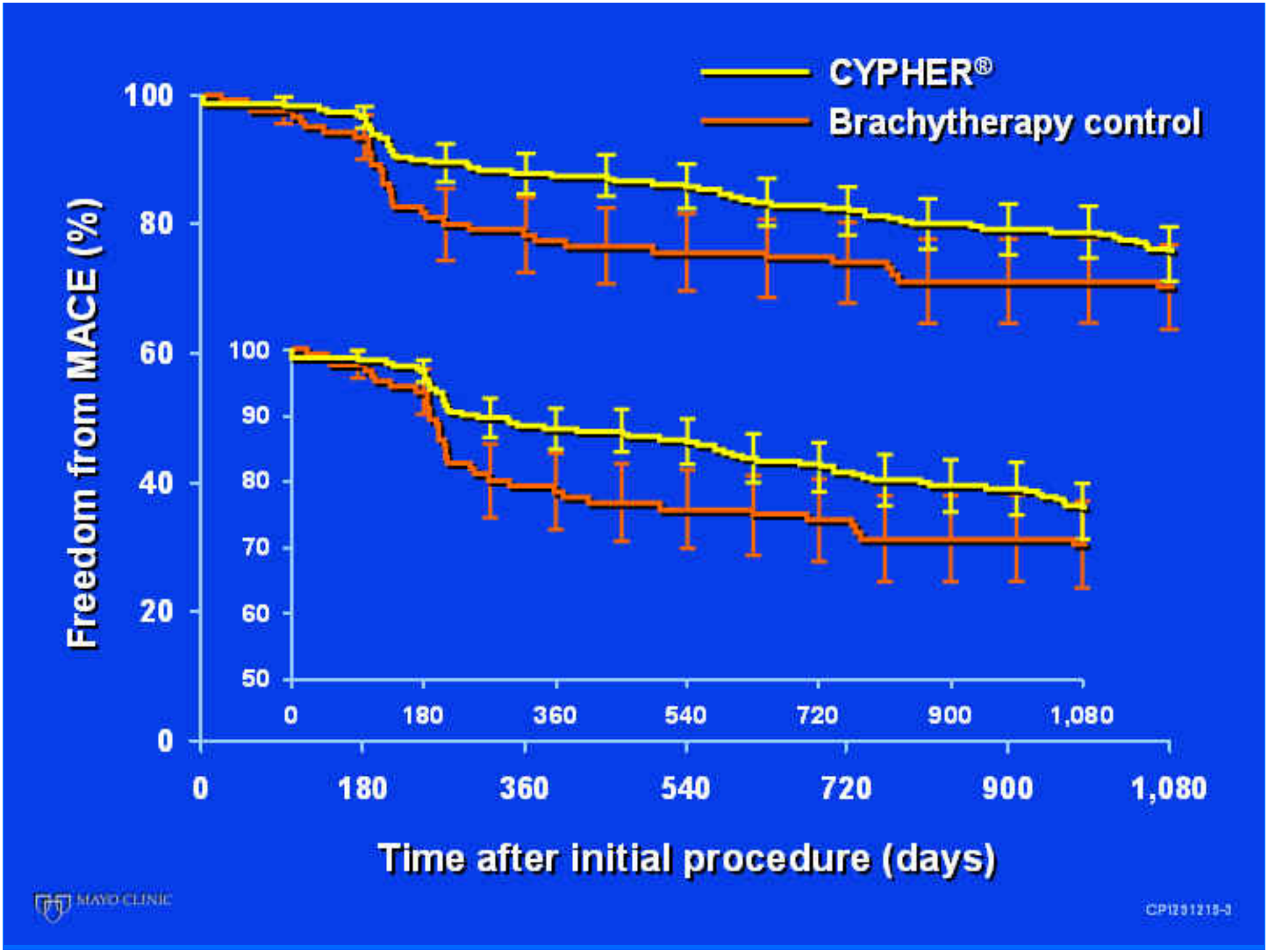
	VBT n=125		SES n=259		All Pts 384 Pts 384 Lesions		
	%	#	%	#	%	#	P
Acute thrombosis (0-1)	0.0	0/125	0.0	0/259	0.0	0/384	--
Subacute thrombosis (2-30)	0.0	0/125	0.0	0/259	0.0	0/384	--
Late thrombosis (31-360)	0.0	0/125	1.5	4/259	1.0	4/384	1.309
Very late thrombosis (361-1080)	2.4	3/125	1.5	4/259	1.8	7/384	0.687
All thrombosis (0-1080)	2.4	3/125	2.7	7/259	2.6	10/384	1.000

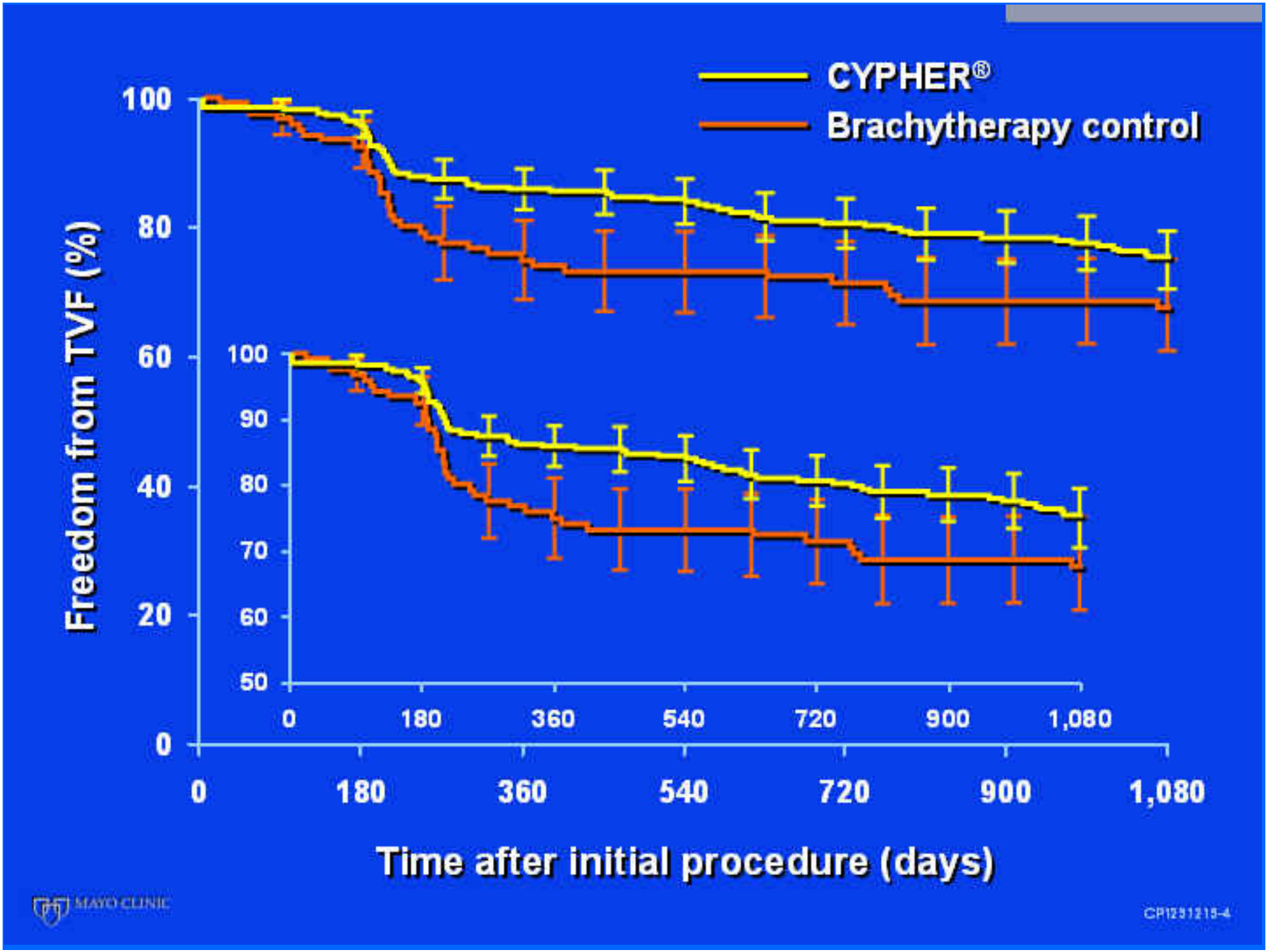
Probable ARC Thrombosis
Out to 3 Years Outcome

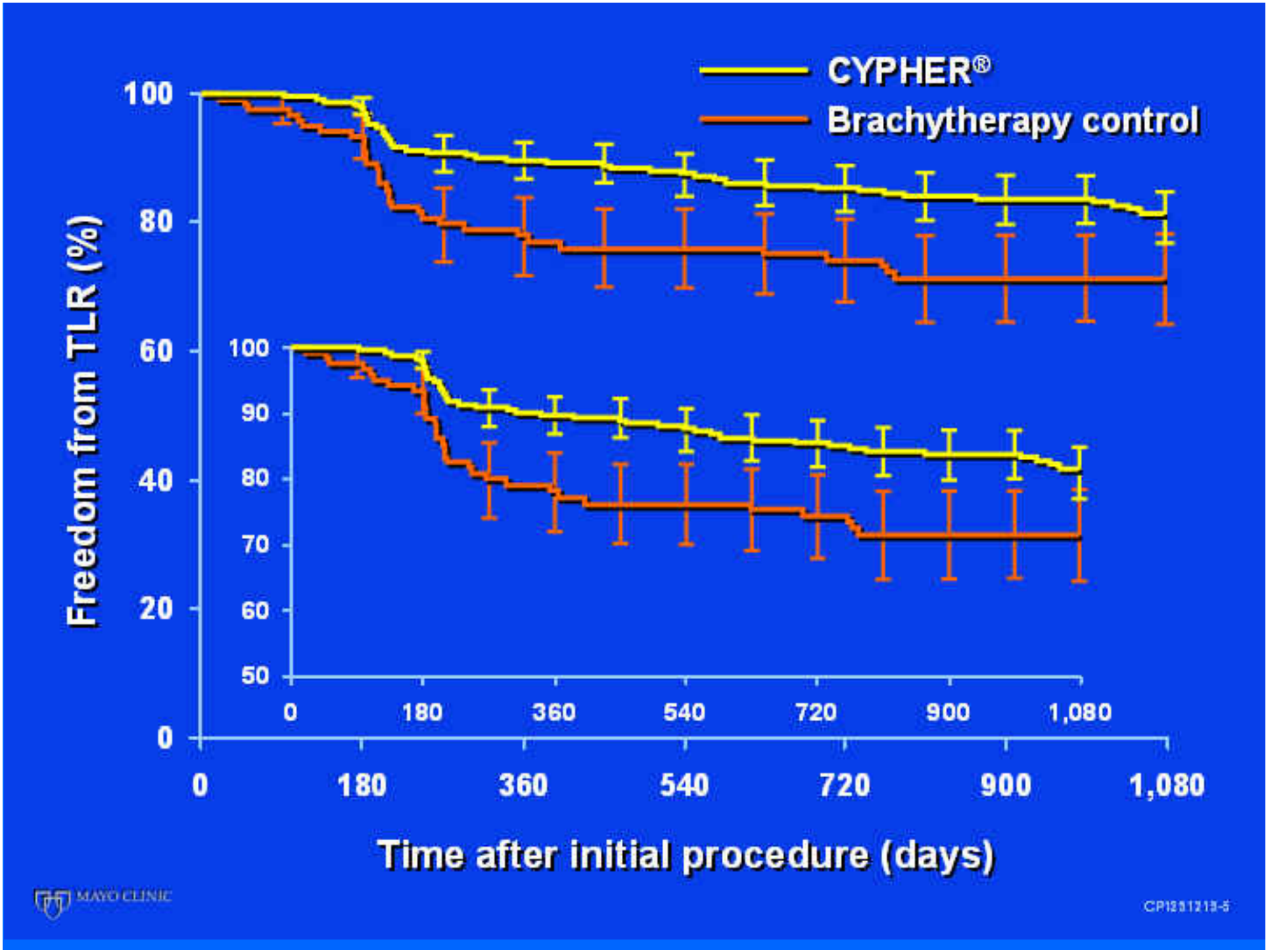
	VBT n=125		SES n=259		All Pts 384 Pts 384 Lesions		
	%	#	%	#	%	#	P
Acute thrombosis (0-1)	0.0	0/125	0.0	0/259	0.0	0/384	--
Subacute thrombosis (2-30)	0.0	0/125	0.0	0/259	0.0	0/384	--
Late thrombosis (31-360)	0.8	1/125	0.0	0/259	0.3	1/384	0.326
Very late thrombosis (361-1080)	0.0	0/125	0.8	2/259	0.5	2/384	1.000
All thrombosis (0-1080)	0.8	1/125	0.8	2/259	0.8	3/384	1.000

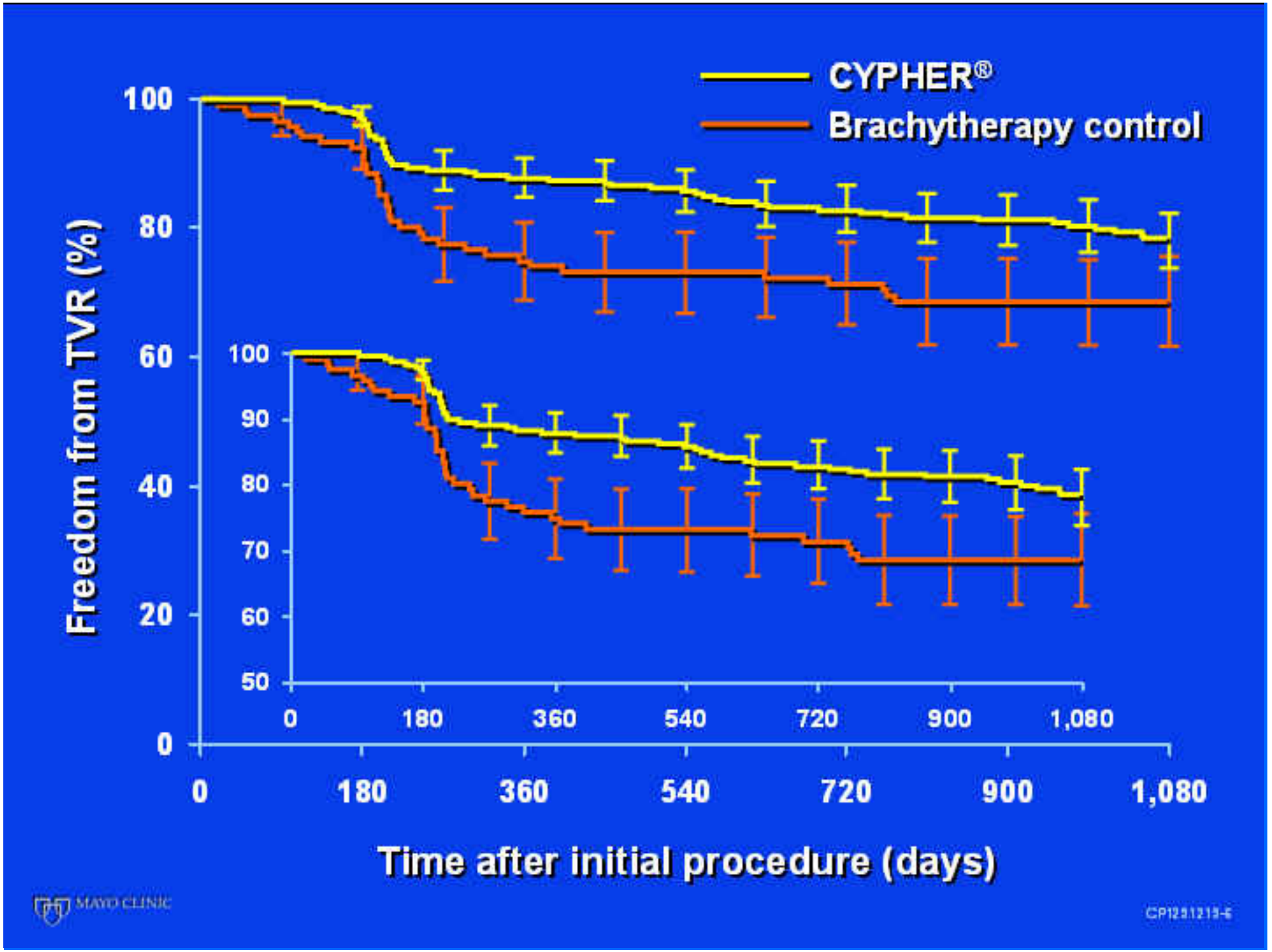
Non-hierarchical complications to 1,080 days	CYPHER® (259 patients, 259 lesions)	Brachytherapy control (125 patients, 125 lesions)	All patients (384 patients, 384 lesions)	Difference [95% CI]	P
MACE (death, Q wave or non-Q wave MI, Em CABG, TLR)	23.6% (61/259)	28.0% (35/125)	25.0% (96/384)	-4.4% [-14.1%, 4.6%]	0.379
Death	3.9% (10/259)	2.4% (3/125)	3.4% (13/384)	1.5% [-3.3%, 4.9%]	0.560
Cardiac	1.5% (4/259)	0.8% (1/125)	1.3% (5/384)	0.7% [-3.0%, 3.2%]	1.000
Non-cardiac	2.3% (6/259)	1.6% (2/125)	2.1% (8/384)	0.7% [-3.5%, 3.6%]	1.000
Myocardial infarction (Q wave or WHO non-Q wave)	6.2% (16/259)	3.2% (4/125)	5.2% (20/384)	3.0% [-2.3%, 7.1%]	0.327
All Q wave MI	1.5% (4/259)	0.0% (0/125)	1.0% (4/384)	1.5% [-1.6%, 3.9%]	0.309
Target vessel Q wave MI	1.5% (4/259)	0.0% (0/125)	1.0% (4/384)	1.5% [-1.6%, 3.9%]	0.309
Non-target vessel Q wave MI	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
All WHO non-q wave MI	5.4% (14/259)	3.2% (4/125)	4.7% (18/384)	2.2% [-3.0%, 6.2%]	0.444
Target vessel WHO non-Q wave MI	5.0% (13/259)	3.2% (4/125)	4.4% (17/384)	1.8% [-3.3%, 5.7%]	0.598
Non-target vessel WHO non-Q wave MI	0.4% (1/259)	0.0% (0/125)	0.3% (1/384)	0.4% [-2.6%, 2.2%]	1.000
All target vessel MI (Q wave or WHO non-Q wave MI)	5.8% (15/259)	3.2% (4/125)	4.9% (19/384)	2.6% [-2.7%, 6.6%]	0.325
All non-target vessel MI (Q wave or WHO non-Q wave MI)	0.4% (1/259)	0.0% (0/125)	0.3% (1/384)	0.4% [-2.6%, 2.2%]	1.000
Emergent CABG	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Target lesion revascularization	17.8% (46/259)	26.4% (33/125)	20.6% (79/384)	-8.6% [-18.0%, -0.0%]	0.059
TL-CABG	3.1% (8/259)	6.4% (8/125)	4.2% (16/384)	-3.3% [-9.2%, 0.9%]	0.171
TL-PTCA	15.8% (41/259)	23.2% (29/125)	18.2% (70/384)	-7.4% [-16.4%, 0.8%]	0.091
Target vessel revascularization not involving target lesion	6.9% (18/259)	8.8% (11/125)	7.6% (29/384)	-1.9% [-8.6%, 3.5%]	0.540
TV/non-TL-CABG	0.4% (1/259)	2.4% (3/125)	1.0% (4/384)	-2.0% [-6.4%, 0.4%]	0.103
TV/non-TL-PTCA	6.6% (17/259)	7.2% (9/125)	6.8% (26/384)	-0.6% [-7.0%, 4.4%]	0.830
Target vessel failure to 270 days (primary endpoint)	12.4% (32/259)	21.6% (27/125)	15.4% (59/384)	-9.2% [-18.0%, -1.6%]	0.023
Target vessel failure to 1,080 days	23.9% (62/259)	30.4% (38/125)	26.0% (100/384)	-6.5% [-16.3%, 2.8%]	0.214
Target vessel revascularization (all)	20.8% (54/259)	29.6% (37/125)	23.7% (91/384)	-8.8% [-18.4%, 0.3%]	0.073

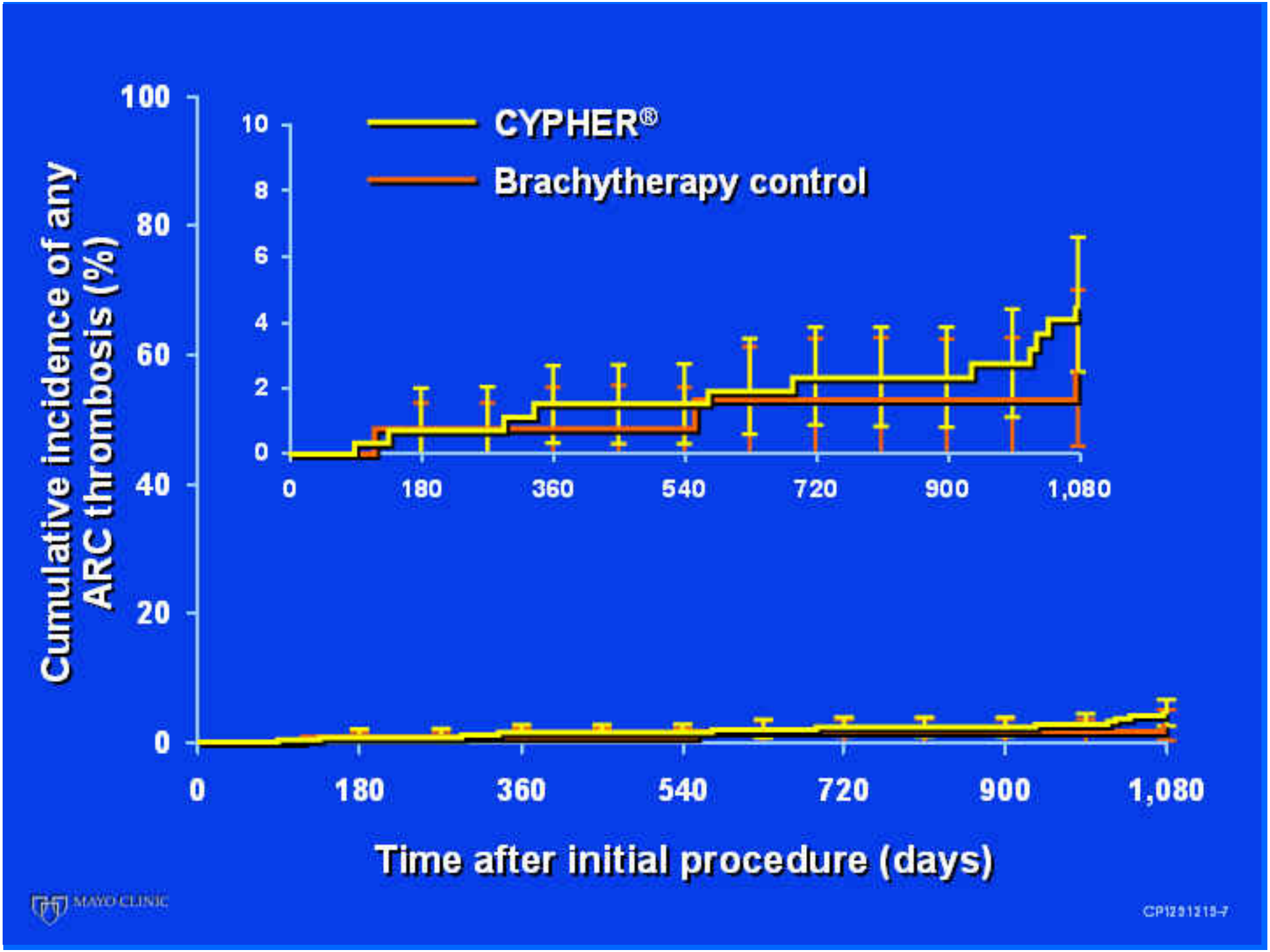
Events to 1,080 days	CYPHER® (259 patients, 259 lesions)	Brachytherapy control (125 patients, 125 lesions)	All patients (384 patients, 384 lesions)	Difference [95% CI]	P
Protocol thrombosis					
Acute thrombosis (0-1)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Subacute thrombosis (2-30)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Late thrombosis (31-360)	1.2% (3/259)	0.0% (0/125)	0.8% (3/384)	1.2% [-1.9%, 3.3%]	0.554
Very late thrombosis (361-1080)	0.8% (2/259)	0.8% (1/125)	0.8% (3/384)	-0.0% [-3.7%, 2.1%]	1.000
All thrombosis (0-1080)	1.9% (5/259)	0.8% (1/125)	1.6% (6/384)	1.1% [-2.6%, 3.7%]	0.668
Any ARC thrombosis					
Acute thrombosis (0-1)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Subacute thrombosis (2-30)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Late thrombosis (31-360)	1.5% (4/259)	0.8% (1/125)	1.3% (5/384)	0.7% [-3.0%, 3.2%]	1.000
Very late thrombosis (361-1080)	3.1% (8/259)	2.4% (3/125)	2.9% (11/384)	0.7% [-4.0%, 4.0%]	1.000
All thrombosis (0-1080)	4.2% (11/259)	2.4% (3/125)	3.6% (14/384)	1.8% [-2.9%, 5.4%]	0.562
Definite or probable ARC thrombosis					
Acute thrombosis (0-1)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Subacute thrombosis (2-30)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Late thrombosis (31-360)	1.5% (4/259)	0.8% (1/125)	1.3% (5/384)	0.7% [-3.0%, 3.2%]	1.000
Very late thrombosis (361-1080)	2.3% (6/259)	2.4% (3/125)	2.3% (9/384)	-0.1% [-4.7%, 3.0%]	1.000
All thrombosis (0-1080)	3.5% (9/259)	2.4% (3/125)	3.1% (12/384)	1.1% [-3.6%, 4.5%]	0.758
Definite ARC thrombosis					
Acute thrombosis (0-1)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Subacute thrombosis (2-30)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Late thrombosis (31-360)	1.5% (4/259)	0.0% (0/125)	1.0% (4/384)	1.5% [-1.6%, 3.9%]	0.309
Very late thrombosis (361-1080)	1.5% (4/259)	2.4% (3/125)	1.8% (7/384)	-0.9% [-5.4%, 2.0%]	0.687
All thrombosis (0-1080)	2.7% (7/259)	2.4% (3/125)	2.6% (10/384)	0.3% [-4.3%, 3.5%]	1.000
Probable ARC thrombosis					
Acute thrombosis (0-1)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Subacute thrombosis (2-30)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Late thrombosis (31-360)	0.0% (0/259)	0.8% (1/125)	0.3% (1/384)	-0.8% [-4.4%, 0.8%]	0.326
Very late thrombosis (361-1080)	0.8% (2/259)	0.0% (0/125)	0.5% (2/384)	0.8% [-2.3%, 2.8%]	1.000
All thrombosis (0-720)	0.8% (2/259)	0.8% (1/125)	0.8% (3/384)	-0.0% [-3.7%, 2.1%]	1.000
Possible ARC thrombosis					
Acute thrombosis (0-1)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Subacute thrombosis (2-30)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Late thrombosis (31-360)	0.0% (0/259)	0.0% (0/125)	0.0% (0/384)	0.0% [-3.0%, 1.5%]	—
Very late thrombosis (361-1080)	0.8% (2/259)	0.0% (0/125)	0.5% (2/384)	0.8% [-2.3%, 2.8%]	1.000
All thrombosis (0-1080)	0.8% (2/259)	0.0% (0/125)	0.5% (2/384)	0.8% [-2.3%, 2.8%]	1.000

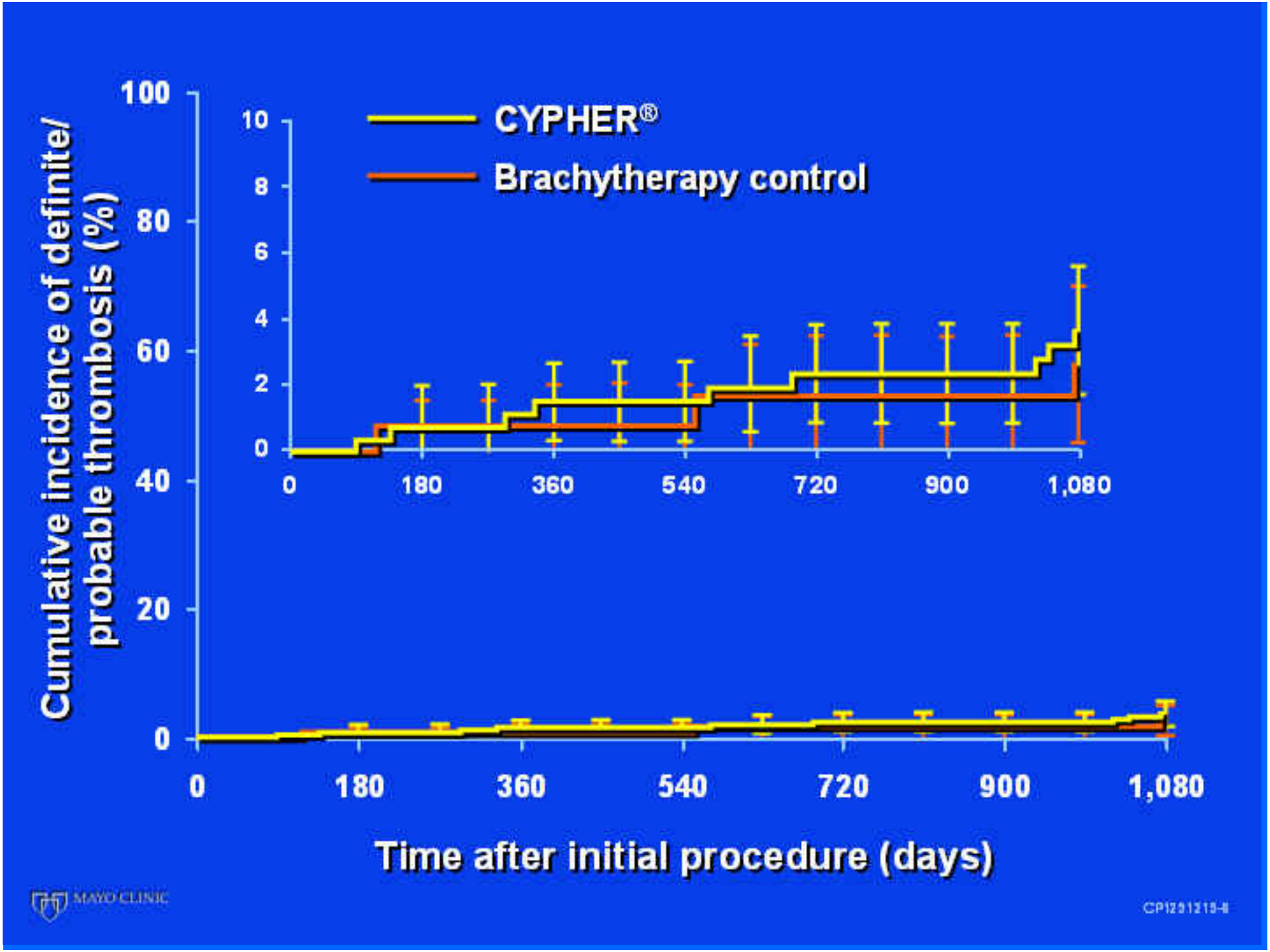

CYPHER®
Brachytherapy control
Freedom from MACE (%)
100
80
60
40
20
0
0
180
360
540
720
900
1,080
Time after initial procedure (days)
100
90
80
70
60
50
0
180
360
540
720
900
1,080
MAYO CLINIC
CP1231218-3

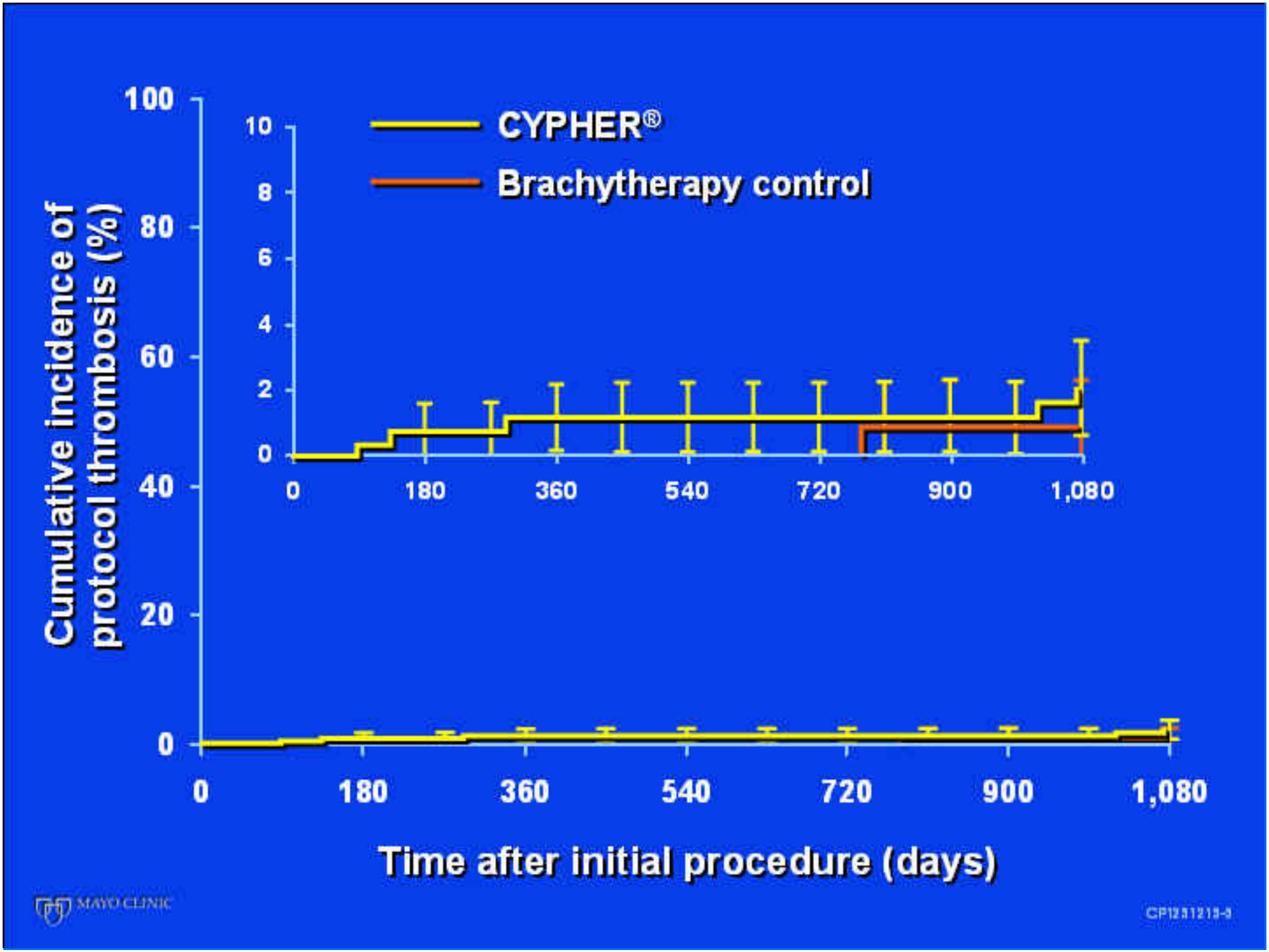

CYPHER®
Brachytherapy control
Freedom from TVF (%)
100
80
60
40
20
0
0
180
360
540
720
900
1,080
Time after initial procedure (days)
100
90
80
70
60
50
0
180
360
540
720
900
1,080
MAYO CLINIC


CYPHER®
Brachytherapy control
Freedom from TLR (%)
100
80
60
40
20
0
0
180
360
540
720
900
1,080
Time after initial procedure (days)
100
90
80
70
60
50
0
180
360
540
720
900
1,080
MAYO CLINIC


CYPHER®
Brachytherapy control
Freedom from TVR (%)
100
80
60
40
20
0
0
180
360
540
720
900
1,080
Time after initial procedure (days)
100
90
80
70
60
50
0
180
360
540
720
900
1,080
MAYO CLINIC


CYPHER®
Brachytherapy control
Cumulative incidence of any ARC thrombosis (%)
100
80
60
40
20
0
0
180
360
540
720
900
1,080
Time after initial procedure (days)
10
8
6
4
2
0
0
180
360
540
720
900
1,080
MAYO CLINIC
CP1231215-7


Cumulative incidence of definite/ probable thrombosis (%)
100
80
60
40
20
0
CYPHER®
Brachytherapy control
10
8
6
4
2
0
0
180
360
540
720
900
1,080
0
180
360
540
720
900
1,080
Time after initial procedure (days)
MAYO CLINIC
CP1231215-6


CYPHER®
Brachytherapy control
Cumulative incidence of protocol thrombosis (%)
100
80
60
40
20
0
0
180
360
540
720
900
1,080
10
8
6
4
2
0
0
180
360
540
720
900
1,080
Time after initial procedure (days)
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Background

- Treatment of restenosis in a bare-metal stent (BMS) has been problematic and characterized by high recurrence rates
- Vascular brachytherapy (VBT) was found to improve early outcomes although late catch-up events were observed
- In the SISR trial, the sirolimus-eluting stent was found to be both non-inferior and superior to VBT at 9 months for the primary endpoint of TVF predominantly due to a reduction in TVR
- This presentation documents safety and efficacy outcomes to 3 years

Study Objective

- To demonstrate the non-inferiority or superiority of the sirolimus-eluting Bx VELOCITY® stent (SES) compared to intravascular brachytherapy (VBT) in the treatment of patients with in-stent restenotic coronary lesions within a bare-metal stent

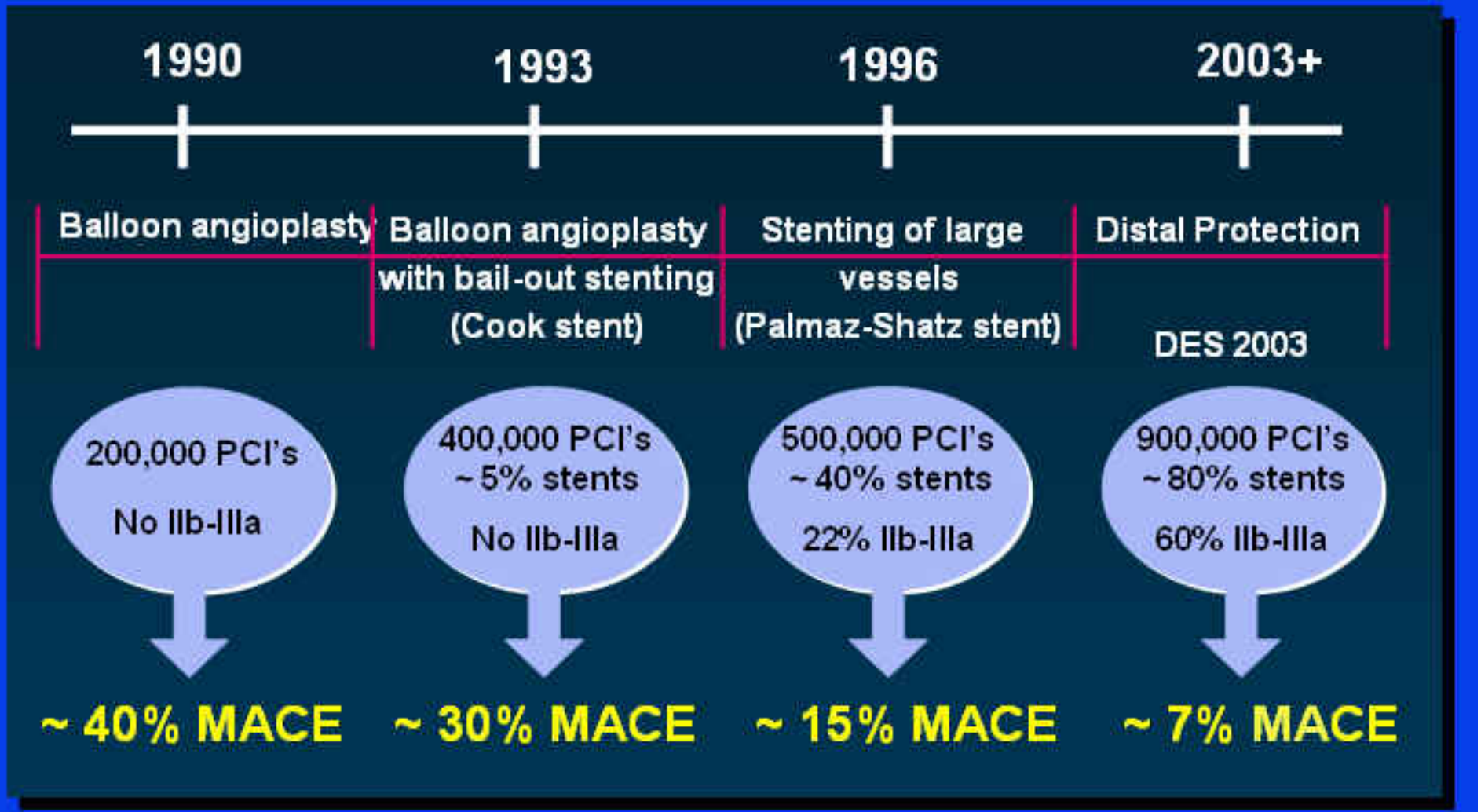
Study Endpoints

- Primary Endpoint:
  - Target vessel failure (TVF) defined as cardiac death, myocardial infarction or target vessel revascularization (TVR) at 9 months
- Secondary Endpoints:
  - Composite of major adverse cardiac events (MACE) defined as death, MI (Q- and non-Q wave), emergent bypass surgery, or repeat target lesion revascularization (TLR)
  - Stent Thrombosis (Protocol and ARC definitions)

Treatment of In-Stent Restenosis
GICS, Korea 2006

David R. Holmes, M.D.
Mayo Clinic
Rochester, MN

Patient Outcomes Have Improved with Advances in Percutaneous Coronary Intervention (PCI)



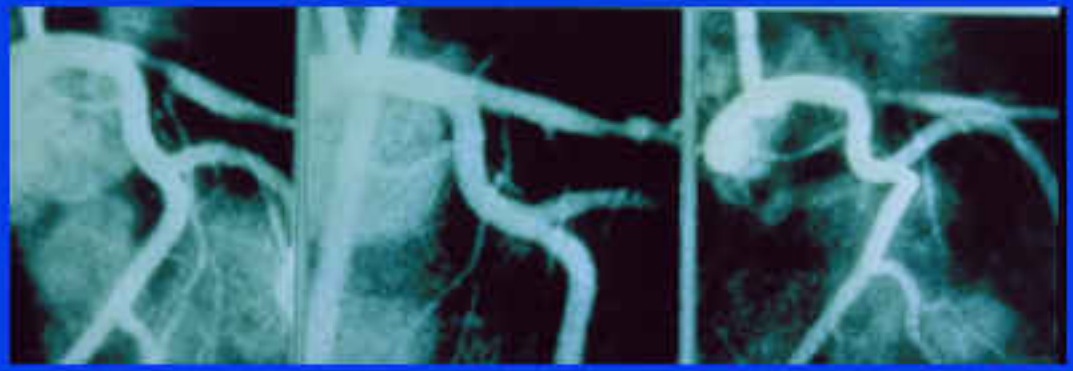
MACE = Death, Myocardial Infarction, Target Vessel Revasc

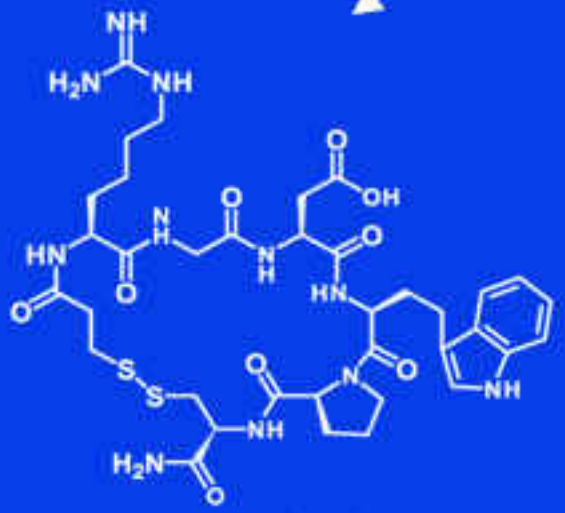
In-Stent Restenosis

	I	II	III	IV
				
	%			
Death	2.5	2.6	3.3	0.0
MI	1.2	2.6	0.0	0.0
TLR	19.1	34.5	50.0	80.4
PTCA	14.8	26.3	36.3	66.7
CABG	4.3	8.2	13.7	16.7

Mehran: Circ 100:1072-8, 1999

P <0.001 by ANOVA





Systemic Local

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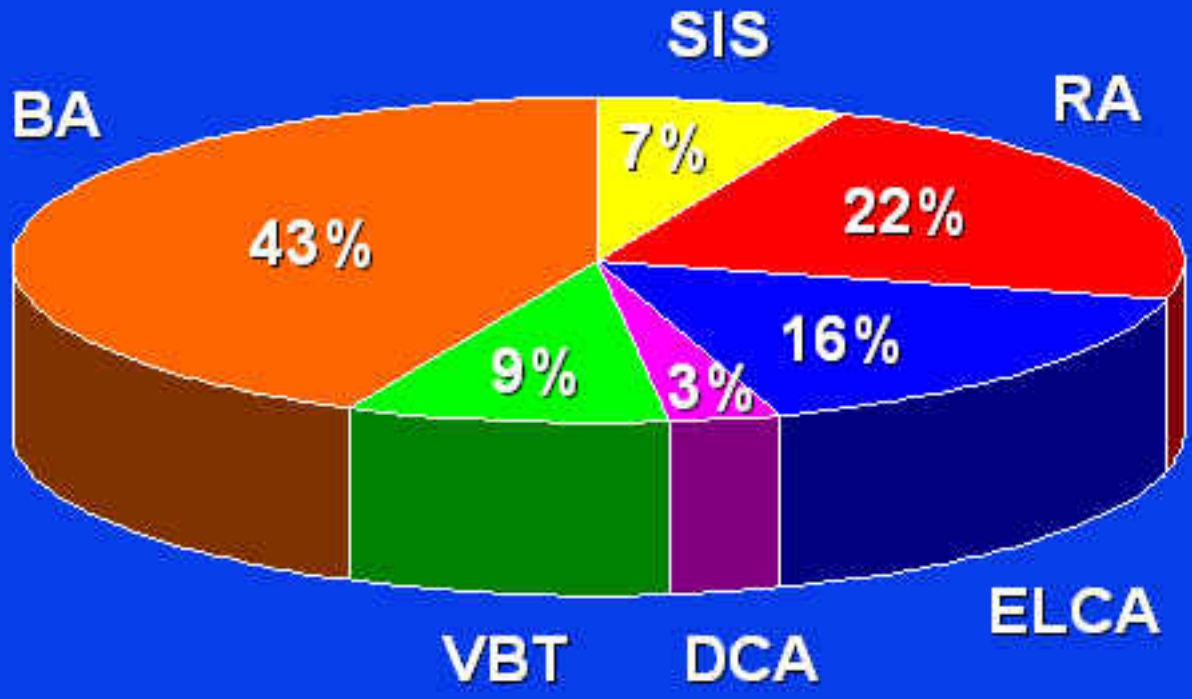
Evidence Based Medicine

Perpetuating other people's mistakes instead of your own

In-Stent Coronary Restenosis
A Meta Analysis

- 28 papers
- 3012 patients



Radke Eur Ht J 24:266-73, 2003

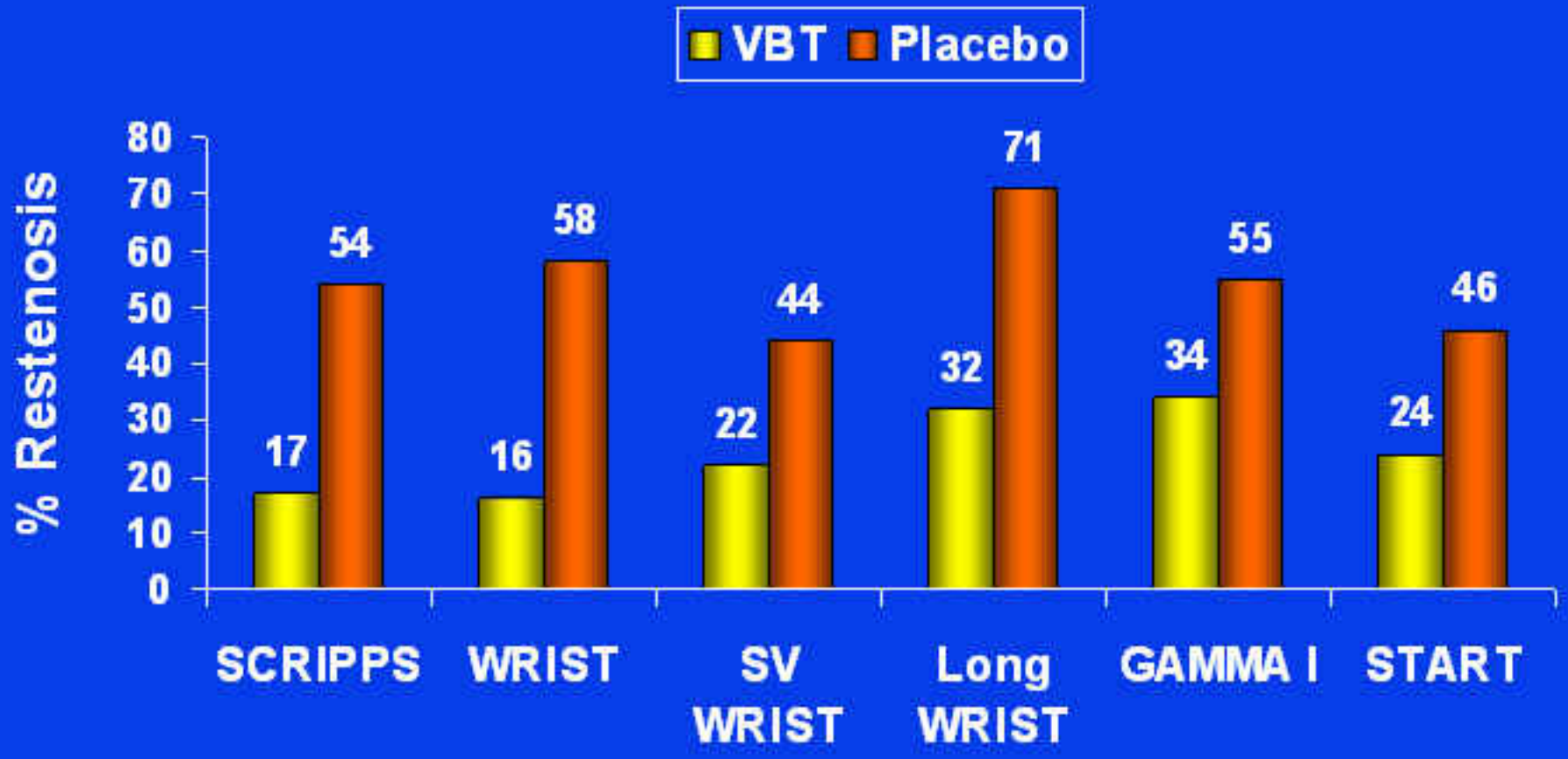
In-Stent Coronary Restenosis

Treatment Modality	Probability of MACE (in %) (95% CI)
BA	28.9 (20.1-35.1)
SIS	31.4 (20.5-42.3)
HSRA	29.7 (15.8-43.7)
ELCA	34.8 (25.1-44.5)
DCA	30.6 (20.2-41.0)
ICR	28.9 (23.6-34.2)

Radke Eur Ht J 24:266-73, 2003

Vascular Brachytherapy

Angiographic Restenosis



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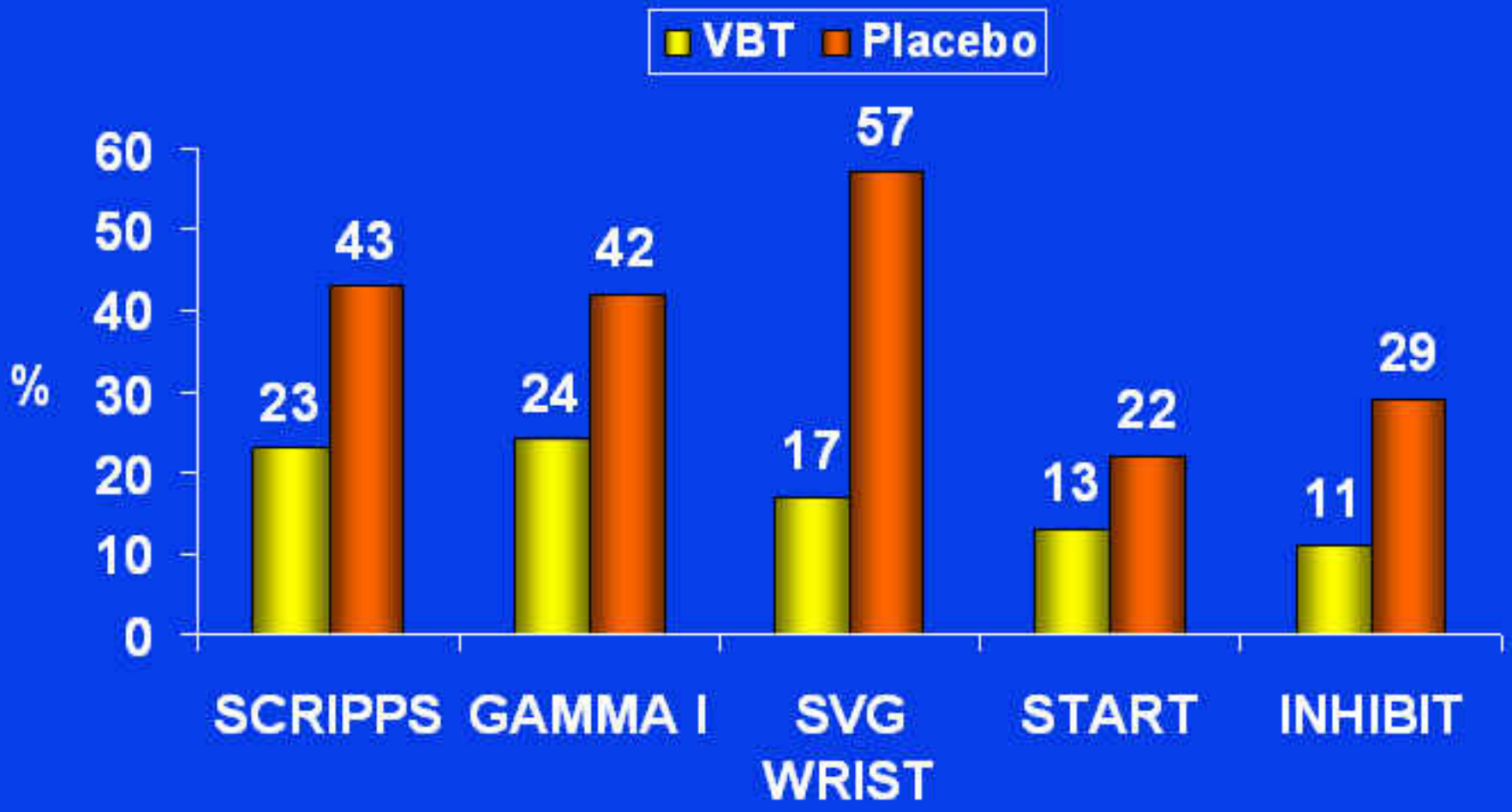
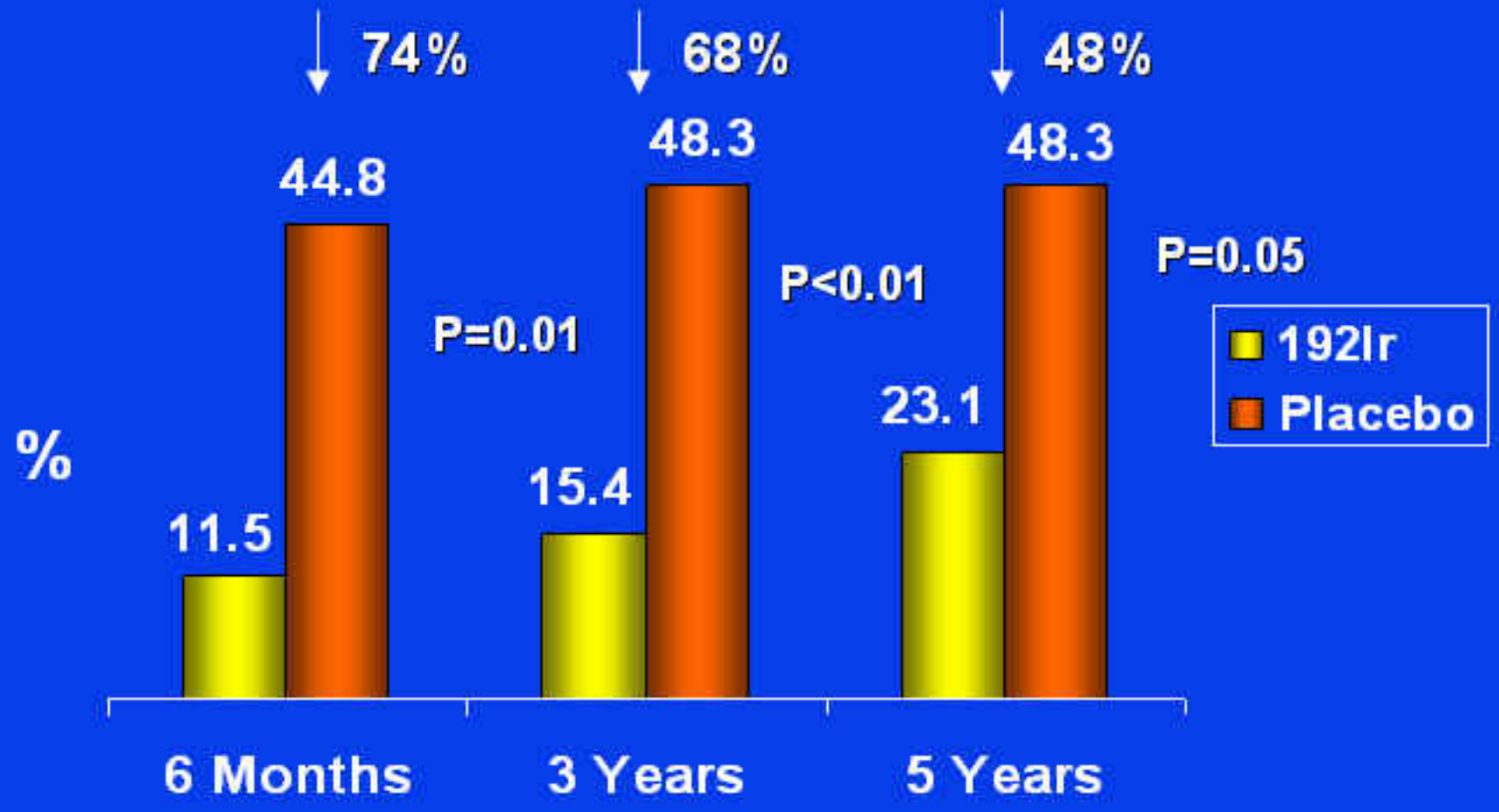
TLR



Vascular Brachytherapy
Is It Lasting?



Grise, Circ 105:2737-2740, 2002

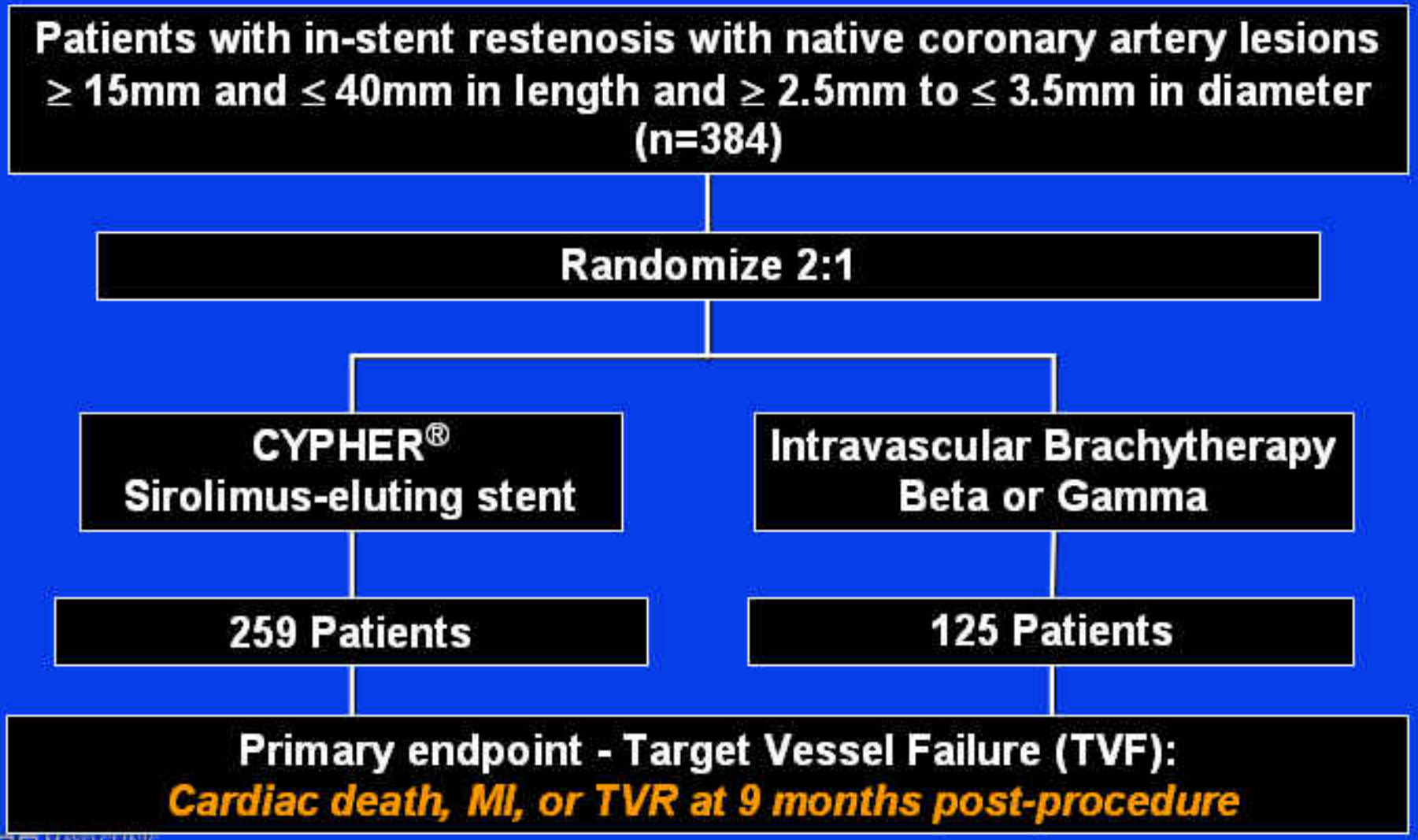
Background

- Stents revolutionized interventional cardiology by greatly improving both initial success and long-term outcomes
- Clinical and angiographic restenosis rates were improved with BMS compared with conventional PTCA, although restenosis rates remained relatively high
- Vascular brachytherapy (VBT) is currently the only approved treatment for in-stent restenosis
- Drug-eluting stents (DES) have shown promise for the treatment of in-stent restenosis in small registry experiences
- No large-scale randomized study has compared outcomes for VBT vs. DES

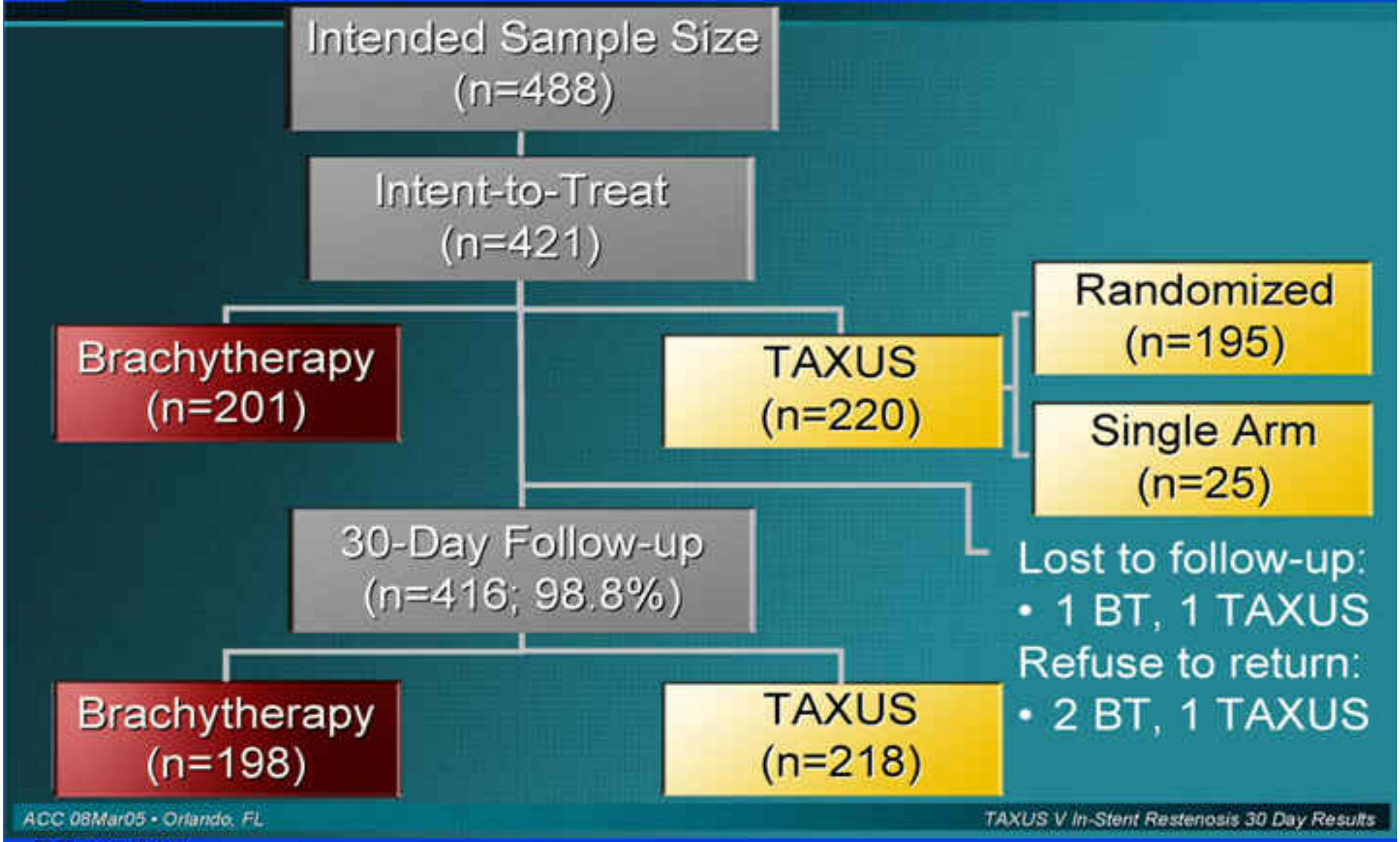
In-stent Restenosis Issues

- Dependable, efficient initial treatment
- Prevention of recurrent restenosis
- Avoidance of late SAT
- Avoidance of late catch-up

Study Design



TAXUS V – ISR
Patient Flow



Baseline Demographics

	CYPHER	VBT	P-value
# of Patients # of Lesions	259 patients 259 lesions	125 patients 125 lesions	
Mean ± SD Age (years)	62.7 ± 10.7	63.5 ± 11.7	0.486
Men (%)	68.2	65.6	0.643
Prior MI (%)	44.4	53.0	0.145
Prior CABG (%)	15.1	12.8	0.642
History of Stroke/TIA (%)	7.5	5.7	0.666
Diabetes Mellitus (%)	33.3	29.6	0.486
- Insulin Dependent (%)	9.3	8.8	1.000
Congestive Heart Failure (%)	8.6	9.7	0.707
Unstable Angina (%)	46.9	50.9	0.552
History of Renal Insufficiency (%)	9.3	3.2	0.036
Mean ± SD Ejection Fraction (%)	56.8 ± 9.0	55.3 ± 8.5	0.132

TAXUS V ISR

Baseline Demographic Characteristics

	Brachy n=201	TAXUS n=220	P value
Age (yrs)	62.7±12.1	62.2±11.0	0.66
Male gender (%)	70.1	61.8	0.08
Diabetes mellitus (%)	30.3	37.3	0.15
Current smoker (%)	14.9	14.5	1.00
RVD (mm)	3.08±0.39	3.07±0.39	0.97
Lesion length (mm)	19.25±9.48	19.08±9.15	0.85
LAD Lesion (%)	33.8	39.1	0.27

Intent-to-Treat Analyses

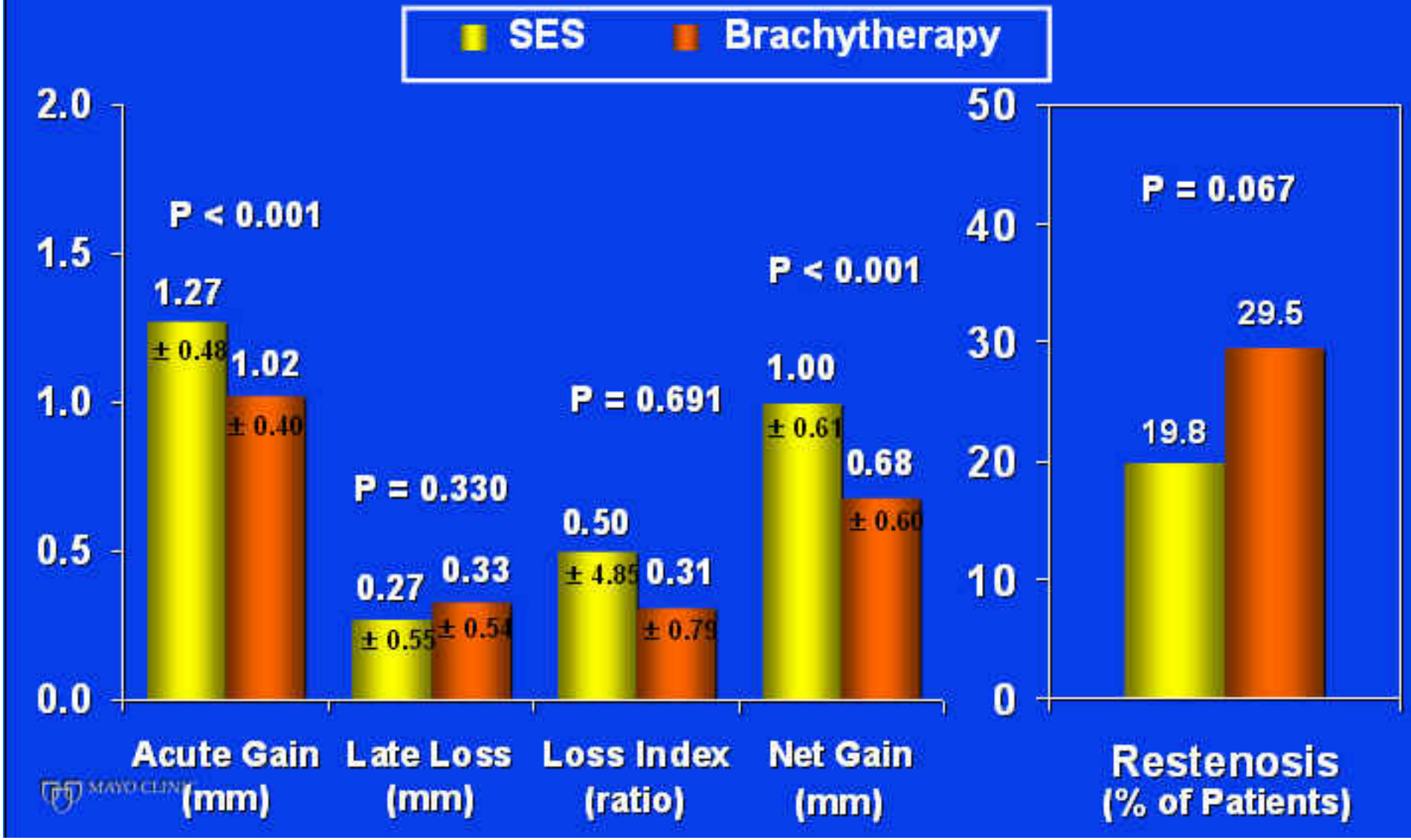
Procedural and Lesion Success

	CYPHER	Brachy-therapy	P-value
Device Success (%) ***<50% residual stenosis (by QCA) using the assigned device only***	96.5	96.8	1.000
Lesion Success (%) ***<50% residual stenosis (by QCA) using any percutaneous method***	98.8	99.2	1.000
Procedural Success (%) ***< 50% residual stenosis (by QCA) without in-hospital MACE***	97.3	99.2	0.282

TAXUS V

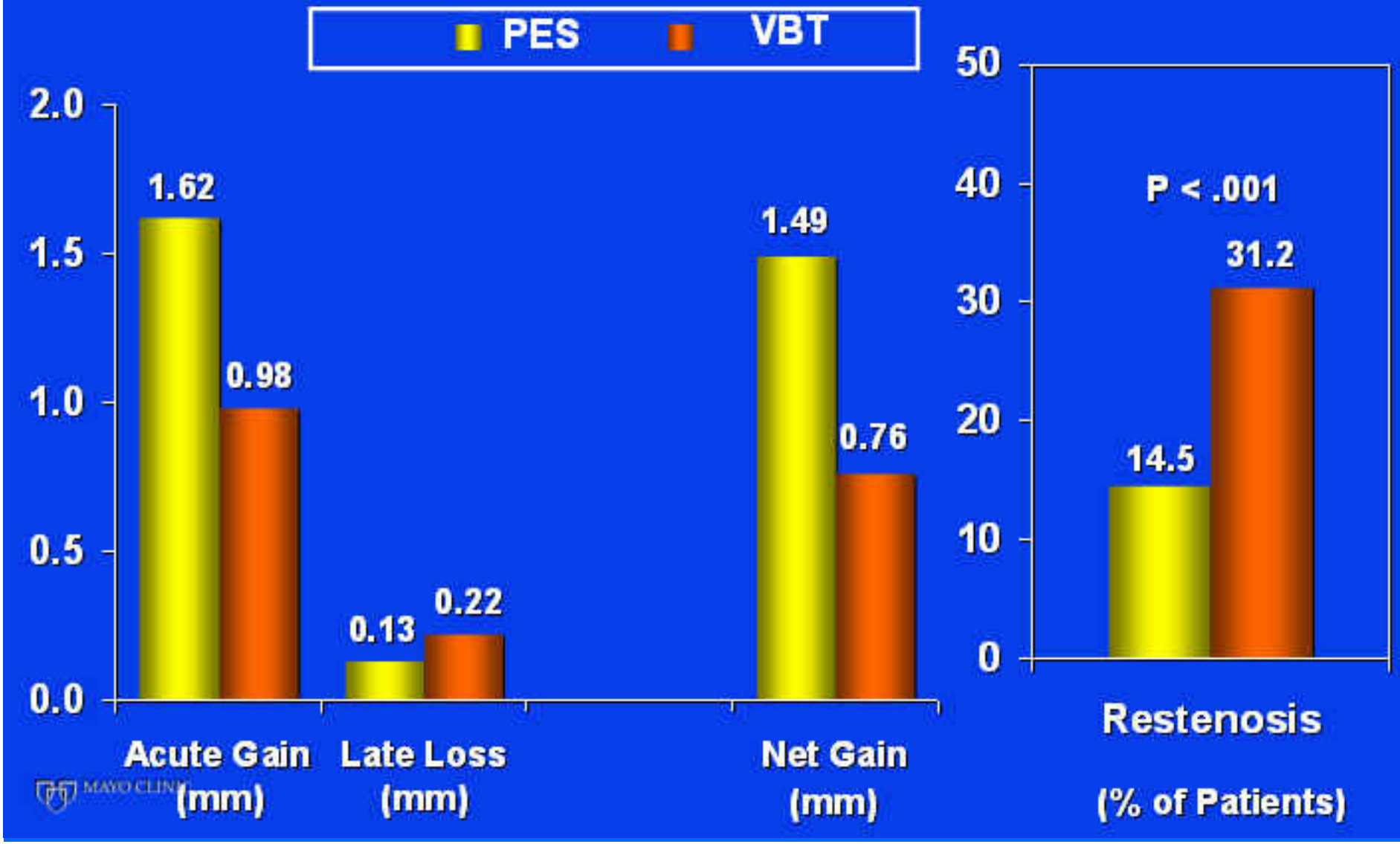
- Vascular brachytherapy delivered in 96%
- 9.8% of VBT patients received a stent for suboptimal result

Angiographic Outcomes Through 6-Months (Analysis Segment)



Intent-to-Treat Analyses

Angiographic Outcomes Through 6-Months (Analysis Segment)



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IVUS Findings at 6-Month Follow-Up

	CYPHER	Brachytherapy	P-value
# of Lesions	63 lesions	23 lesions	
Lumen Volume (mm^3)	190.71 ± 72.46	133.34 ± 71.24	0.006
Plaque Area (mm^2)	7.70 ± 2.64	9.18 ± 1.74	0.041
Plaque Volume (mm^3)	252.08	198.26	0.118
Mean Neointimal Hyperplasia Area (mm^2)	0.50	2.53	<0.001
Neointimal Hyperplasia Volume (mm^3)	11.10 ± 20.38	49.71 ± 48.89	< 0.001

In-Stent Restenosis Patterns

ISR Pattern	CYPHER (n = 45)	Brachytherapy (n = 31)	P-value
Type 1a	0.0	0.0	
Type 1b	15.6	29.0	0.052
Type 1c	46.7	19.4	0.016
Type 1d	8.9	0.0	0.141
Type 2	13.3	25.8	0.230
Type 3	8.9	19.4	0.300
Type 4	6.7	6.5	1.000
ISR Length (mm)	10.73 ± 6.52	12.11 ± 6.29	0.378

Patterns in Yellow:

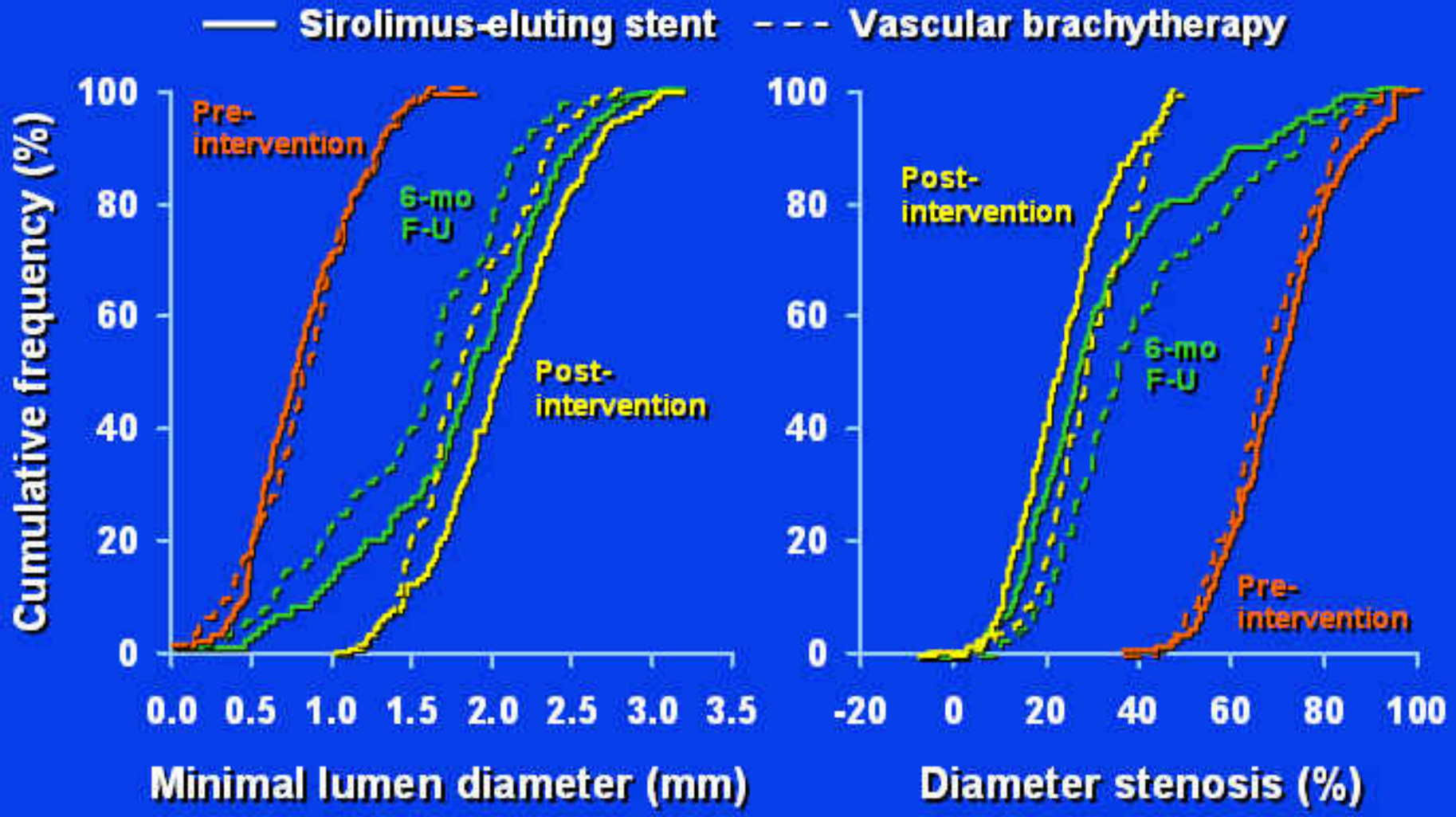
1b: Margin restenosis involving the margin of the stent

1c: Focal body in-stent restenosis

2: Restenosis >10 mm extending to the margins of the stent

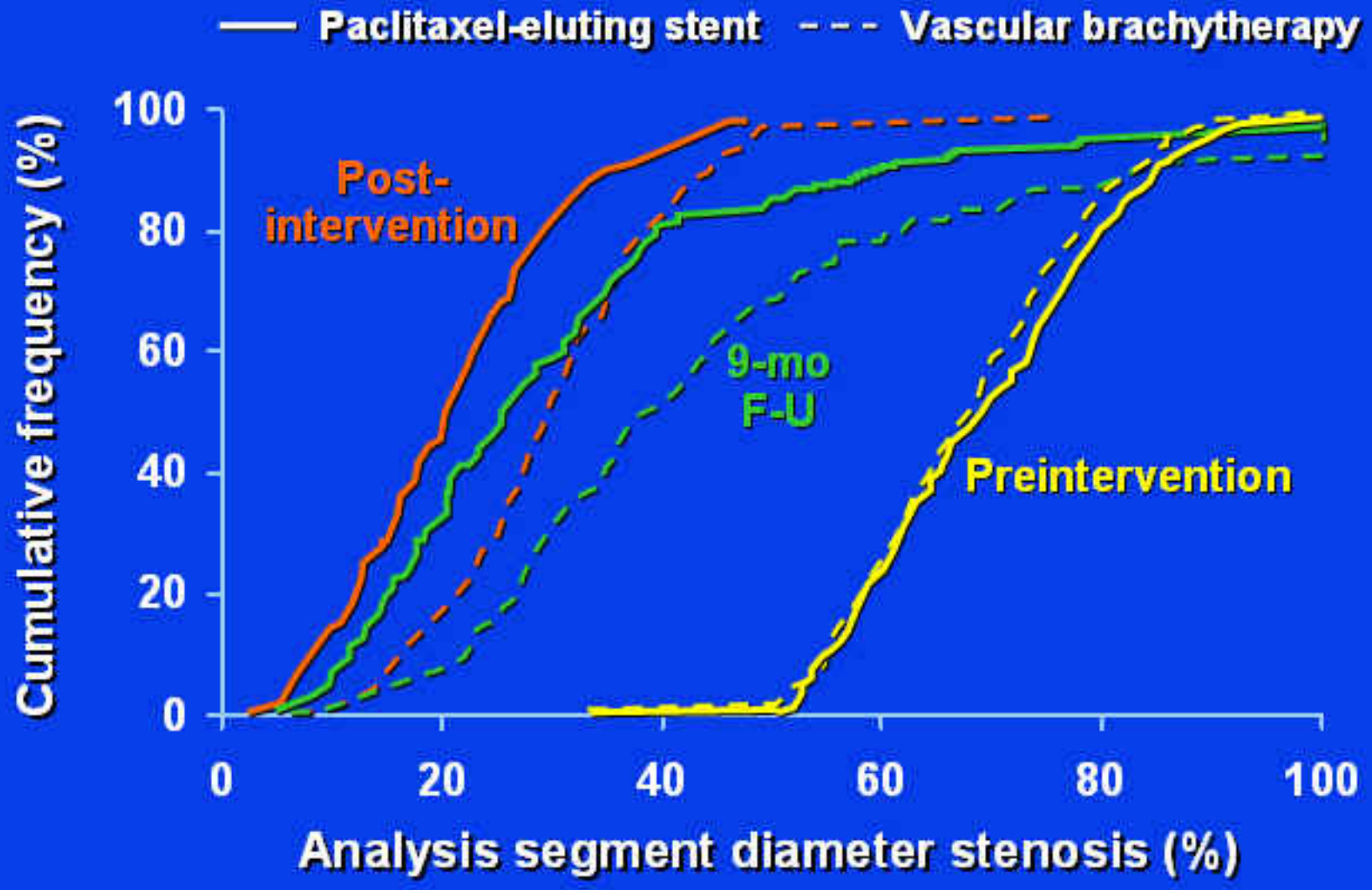
3: Restenosis that is diffuse extending outside of the stent margins

Minimal Lumen Diameter and Diameter Stenosis at Baseline and 6 Months



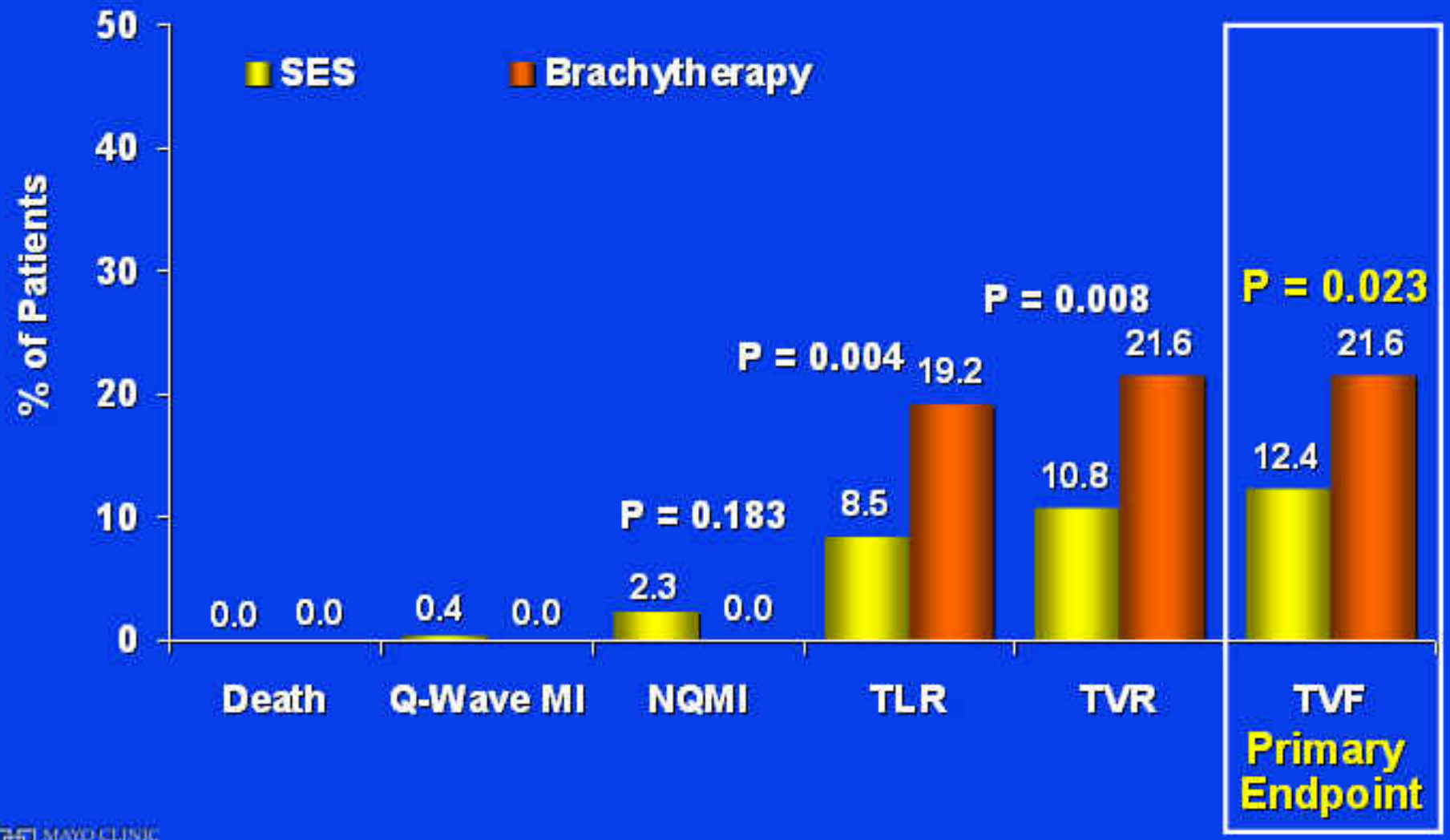
Holmes DR et al: JAMA 295:1264, 2006

Cumulative Frequency Distribution Curves for Analysis Segment Percent Diameter Stenosis

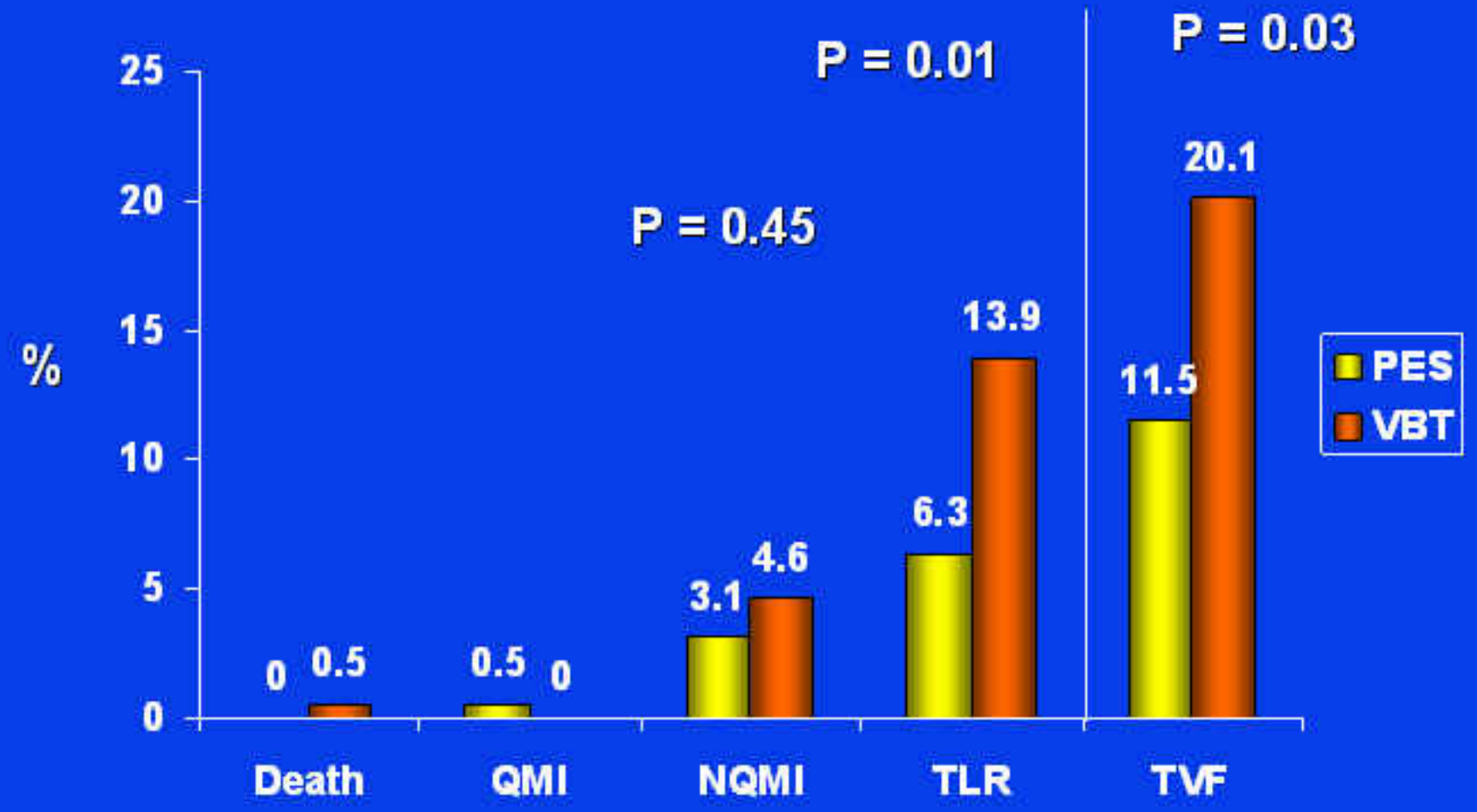


Stone GW et al: JAMA 295:1253, 2006

Clinical Outcomes Through 9-Months



TAXUS V
Clinical Outcomes Through 9 Months



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Stone GW, JAMA 2006; 295:1253-1263

In-Stent Restenosis of BMS

- TAXUS V: 396 patients
  - BAR: 31.2% vs 14.5%
  - TVR: 17.5% vs 10.5%
- SISR: 384 patients
  - BAR: 29.5% vs 19.8%
  - TVR: 21.6% vs 10.8%

In-Stent Restenosis of BMS

- TAXUS V: 396 patients
  - TVF: 19.6% vs 11.5%
  - SAT: 2.6% vs 1.6%
- SISR: 384 patients
  - TVF: 21.6% vs 10.8%
  - SAT: 0% vs .8%

A P-value does not substitute for a brain

Conclusions

Both VBT and SES are effective in reducing neointimal hyperplasia within the treated region

- Vascular brachytherapy demonstrated significant late loss in the 5 mm proximal and distal edges while the Sirolimus-eluting stent did not exhibit this behavior
- These differences contributed to improved lumen dimensions in SES patients measured by both angiography & by IVUS
- SES resulted in significantly less TLR than VBT
- The Sirolimus-eluting stent was superior to vascular brachytherapy in reducing the primary endpoint of Target Vessel Failure

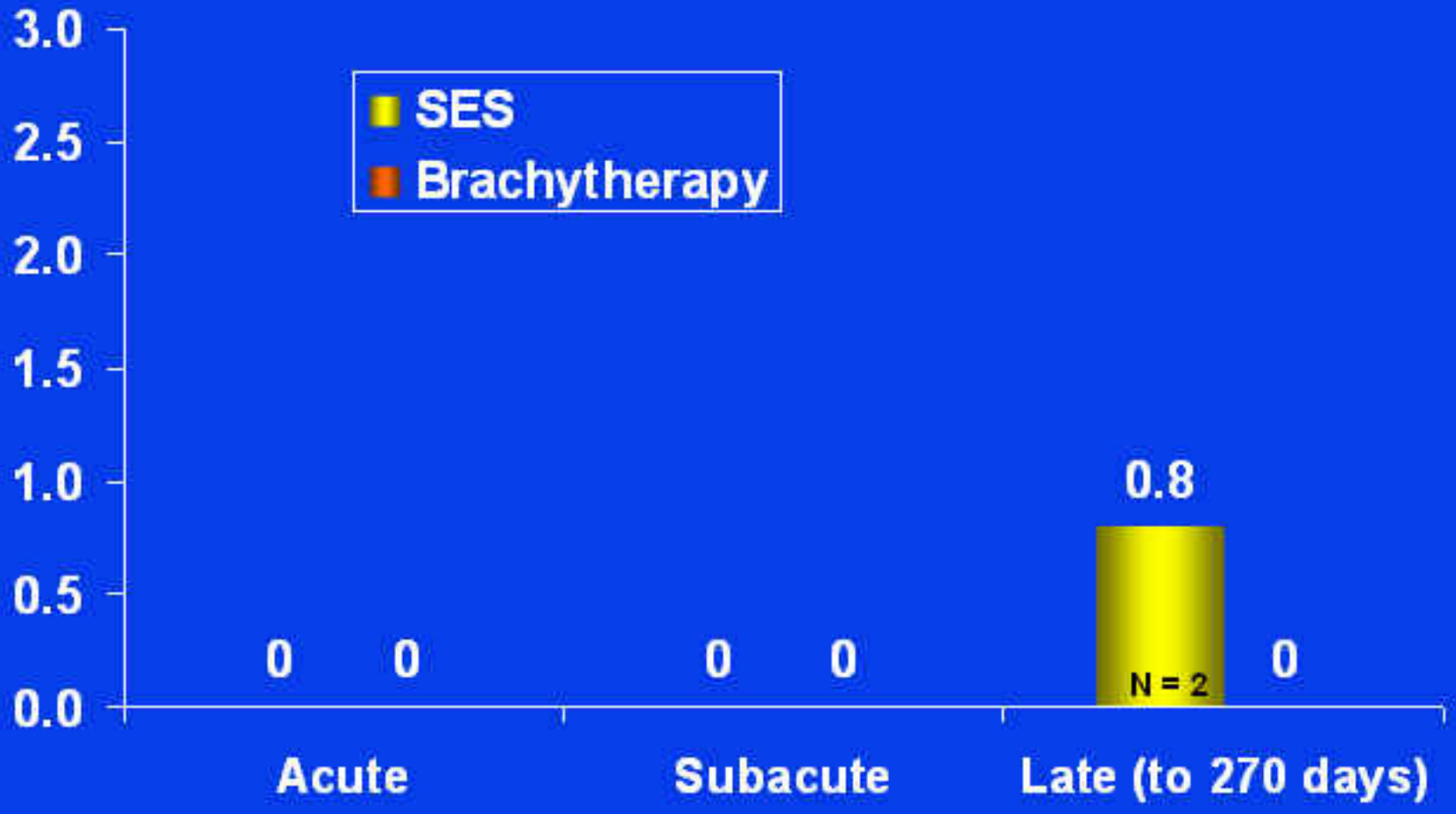
TAXUS V
Conclusions

Treatment of BMS in-stent restenosis with PES rather than VBT reduces clinical and angiographic restenosis at 9 months and improves event-free survival

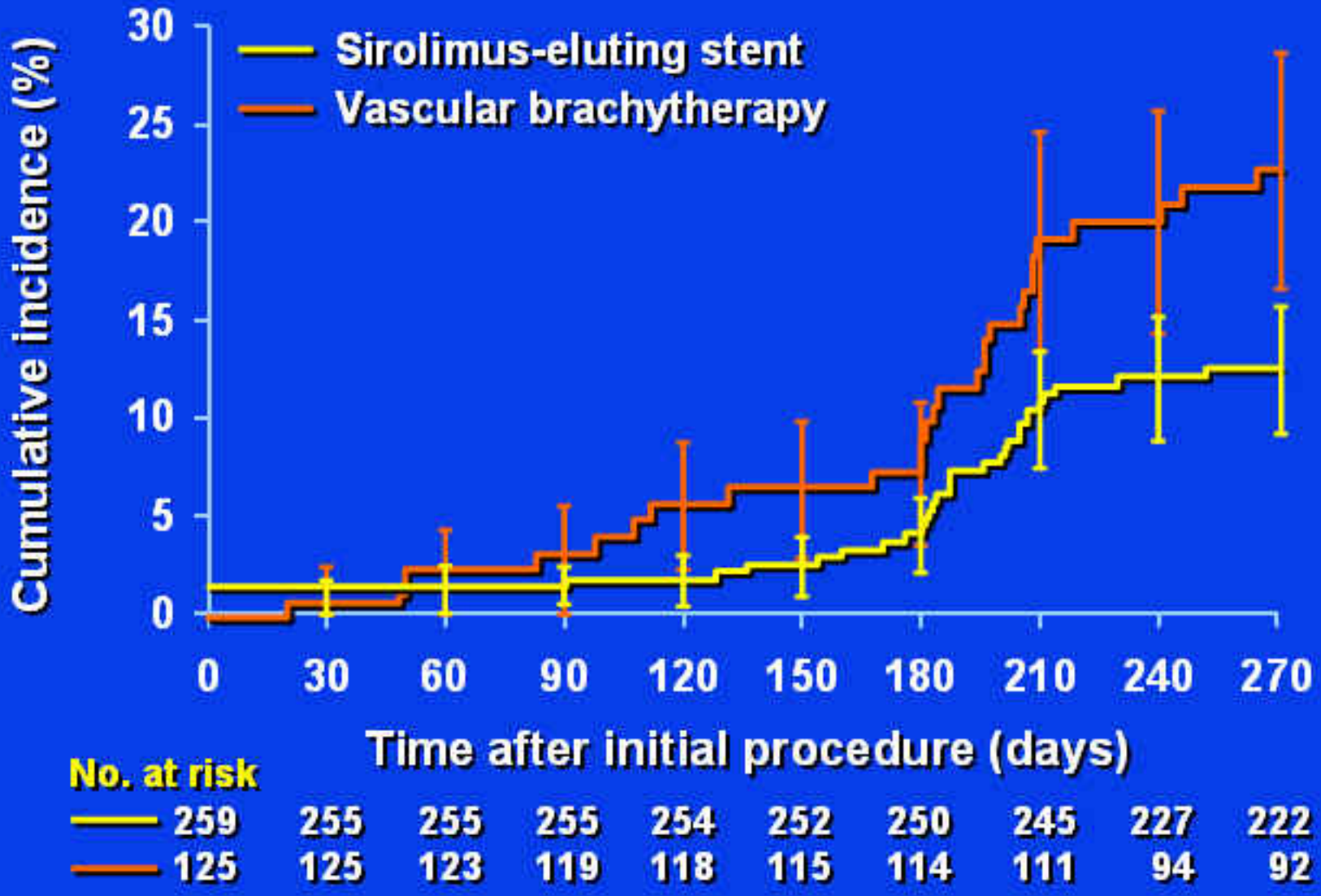
Conclusions

- For treatment of ISR in bare metal stents, both VBT and DES are effective in reducing neointimal hyperplasia
- Acute and net gain with DES is superior to VBT
- Clinical restenosis rates are markedly improved and are superior when DES are placed

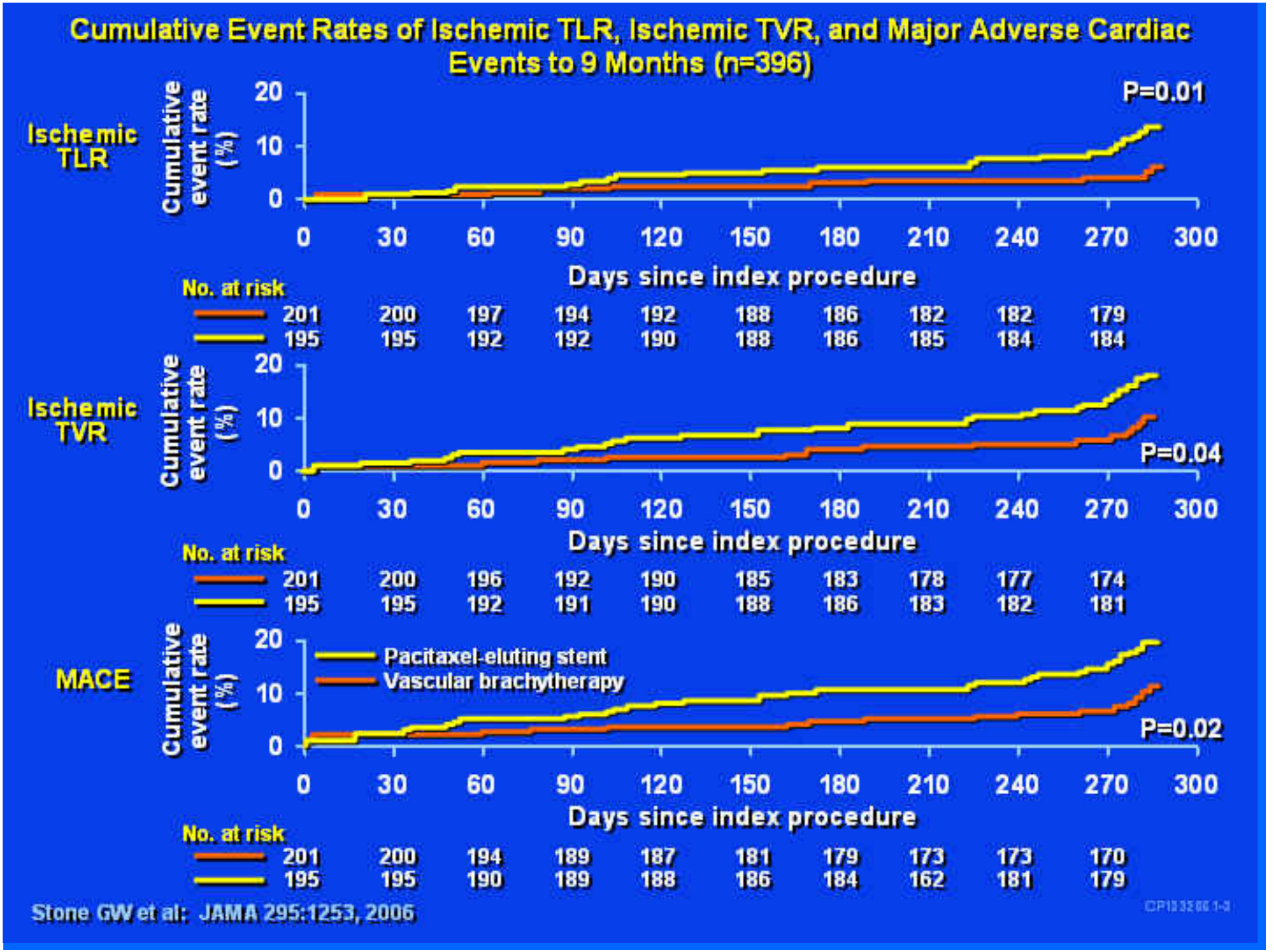
Stent Thrombosis at 9-Month Follow-Up



Target Vessel Failure

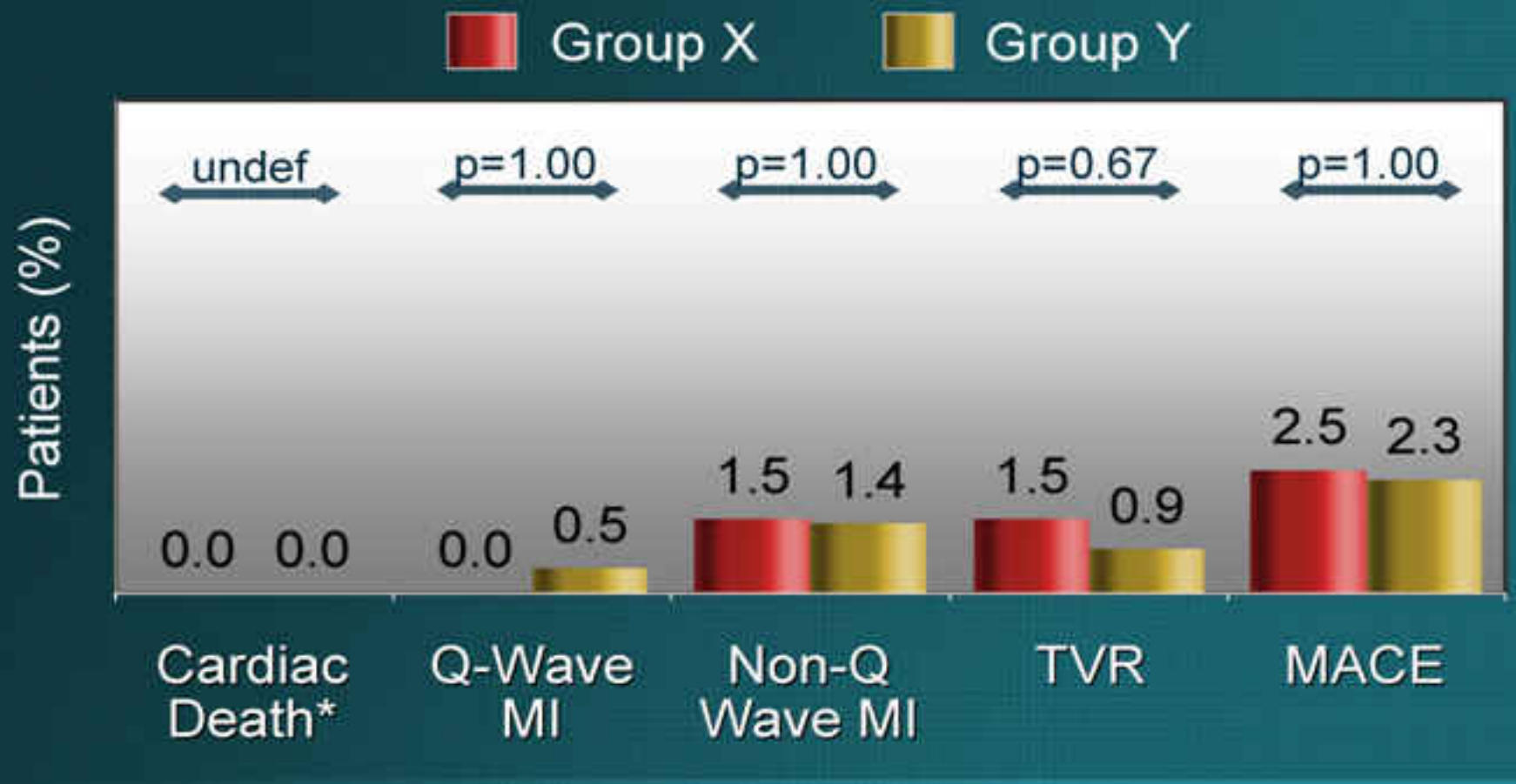


Holmes DR et al: JAMA 295:1264, 2006


Cumulative Event Rates of Ischemic TLR, Ischemic TVR, and Major Adverse Cardiac Events to 9 Months (n=396)
Ischemic TLR
Cumulative event rate (%)
20
10
0
P=0.01
0 30 60 90 120 150 180 210 240 270 300
Days since index procedure
No. at risk
201 200 197 194 192 188 186 182 182 179
195 195 192 192 190 188 186 185 184 184
Ischemic TVR
Cumulative event rate (%)
20
10
0
P=0.04
0 30 60 90 120 150 180 210 240 270 300
Days since index procedure
No. at risk
201 200 196 192 190 185 183 178 177 174
195 195 192 191 190 188 186 183 182 181
MACE
Cumulative event rate (%)
20
10
0
Pacitaxel-eluting stent
Vascular brachytherapy
P=0.02
0 30 60 90 120 150 180 210 240 270 300
Days since index procedure
No. at risk
201 200 194 189 187 181 179 173 173 170
195 195 190 189 188 186 184 162 181 179
Stone GW et al: JAMA 295:1253, 2006

TAXUS V ISR

30-Day MACE Composition



* Non-cardiac death, n=0

DES and AMI - Background

- Primary percutaneous intervention (PCI) is the best therapeutic option for acute myocardial infarction (AMI)
- Bare-metal stents (BMS) implantation in this setting improves procedural success and short-term clinical outcome
- Late clinical outcome is hampered by in-stent restenosis with a high rate of repeat revascularization procedures
- Pivotal randomized trials have proven the effectiveness of sirolimus-eluting stents (SES) to reduce restenosis
- AMI pt were systematically excluded from these studies because of their high-risk profile

Spaulding C et al: ACC, 2006 (oral presentation)

DES and Thrombus

- Paclitaxel uptake evaluated in stented abdominal aortas of adult rats with controlled induced mural thrombus

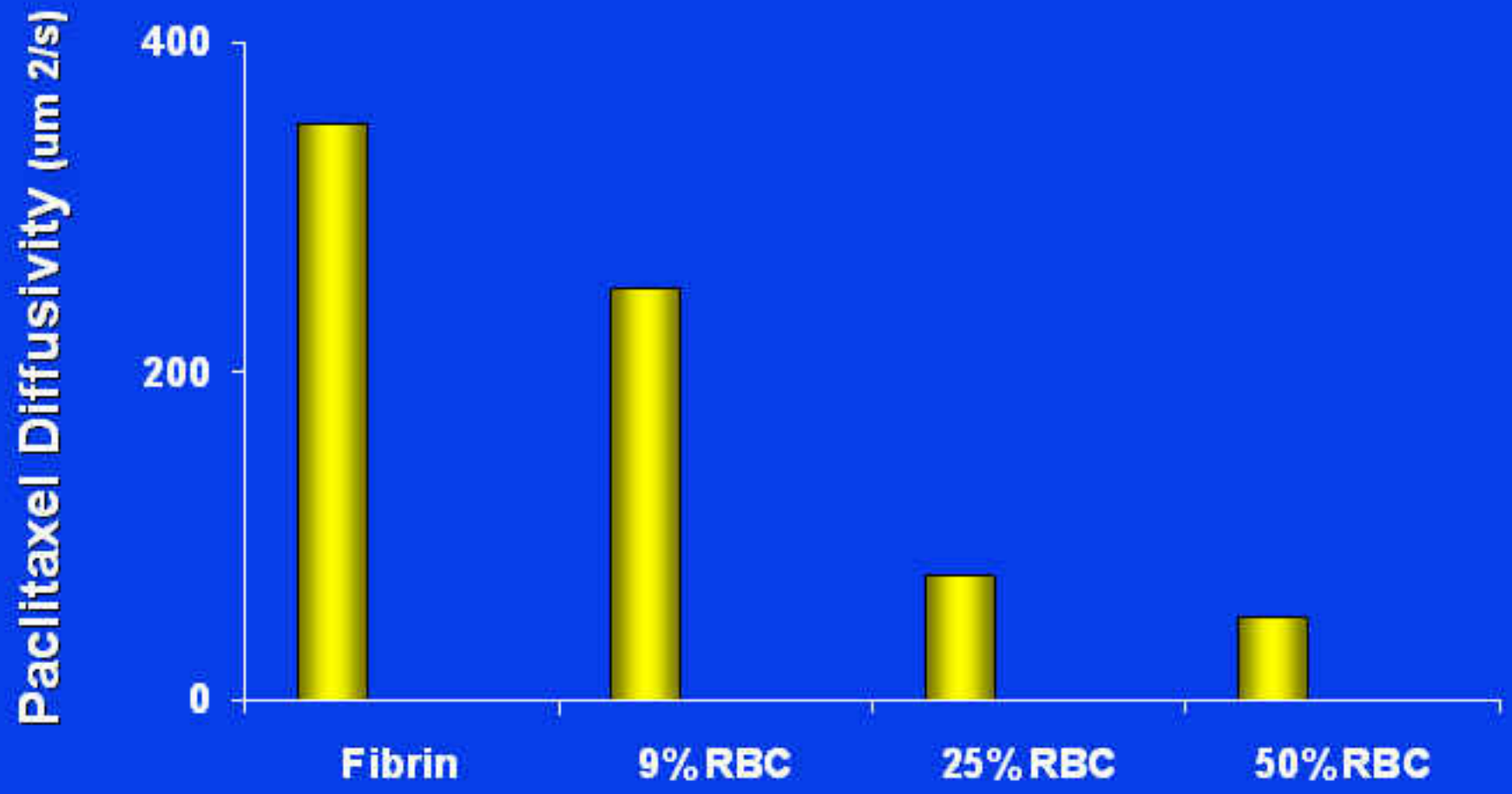
Hwang, Circ 111:1619-1626, 2005

DES and Thrombus

- Diffusivity affected by clot organization
  - Fibrin – 347 um ^{2}/s
  - Fibrin – red cells 34.98 um ^{2}/s
  - Whole blood – 3.55 um ^{2}/s
- Blood cells bind and retain Paclitaxel
  - Clot levels increase linearly with red cell fracture

Hwang, Circ 111:1619-1626, 2005

DES and Thrombus



Hwang, Circ 111:1619-1626, 2005

MAYO CLINIC

DES and Thrombus

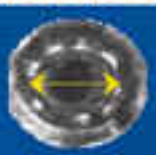
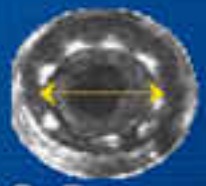
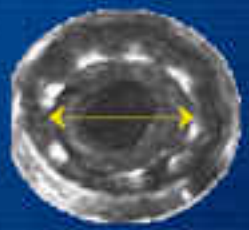
- Clot between artery and stent reduces uptake by 10 fold
- Clot overlying stent shields drug from washout

Hwang, Circ 111:1619-1626, 2005

TAXUS® Stent Dose Increases in Smaller Diameters

TAXUS

Inverse correlation in RVD to surface artery ratio, drug elution, late loss reductions

Stent Diameter	Surface Artery Coverage	Paclitaxel per Circumference (µg/mm)	Late Loss Reduction (mm) TAXUS IV RCT
 2.5 mm	22.4%	0.138 µg/mm²	0.78
 3.0 mm	19.0%	0.117 µg/mm²	0.46
 3.5 mm	16.4%	0.102 µg/mm²	0.48

TAXUS V Small Vessel Data

- TAXUS V Small Vessel Subgroup (N= 203)
  - RVD of 2.09 mm
  - 16.4 mm mean lesion lengths

Multiple Risk Factors within Groups

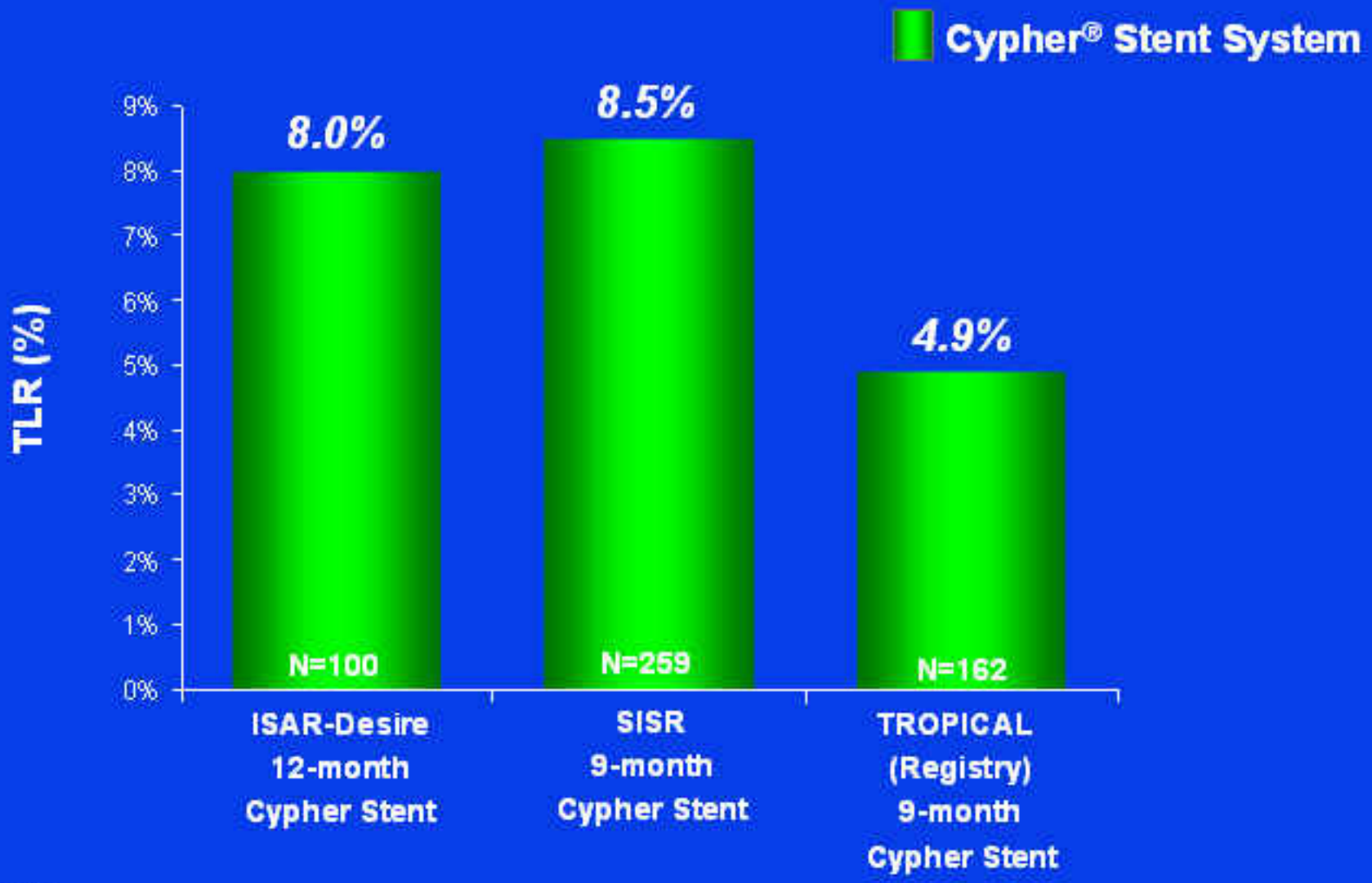
2.25*mm & 2.5mm Stents

- 39.5% multiple stents
- 39.7% lesions >26mm
- 38.3% diabetic
- 36.1 Type C lesions

The safety and efficacy of the TAXUS® Express²™ Stent System have not been established in vessels smaller than 2.5mm, lesions longer than 28mm, or patients with diabetes.
*Caution, investigational use only, unapproved product.

MAYO CLINIC

In-stent Restenosis Data



MAYO CLINIC

The safety and efficacy of the Cypher® Stent System have not been established for the treatment of in-stent restenosis.

In-Stent Restenosis Data

A Prospective, Randomized, Open-Label Trial Evaluating the Slow-Release TAXUS® Express²™ Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis

Late Breaking Trial
At ACC 2006

The safety and efficacy of the TAXUS® Express²™ Stent System have not been established for the treatment of in-stent restenosis.

MAYO CLINIC

Perioperative Events

	Occlusion n=52	Control n=52	P
Cross-clamp time (min)	72±27	75±39	0.63
Furosemide/ 72 hr (mg)	161±134	156±99	0.87
Total chest tube output (mL)	402±230	439±276	0.53
Postoperative AF (%)	23	16	0.56

Healey: AHJ 150:288, 2005

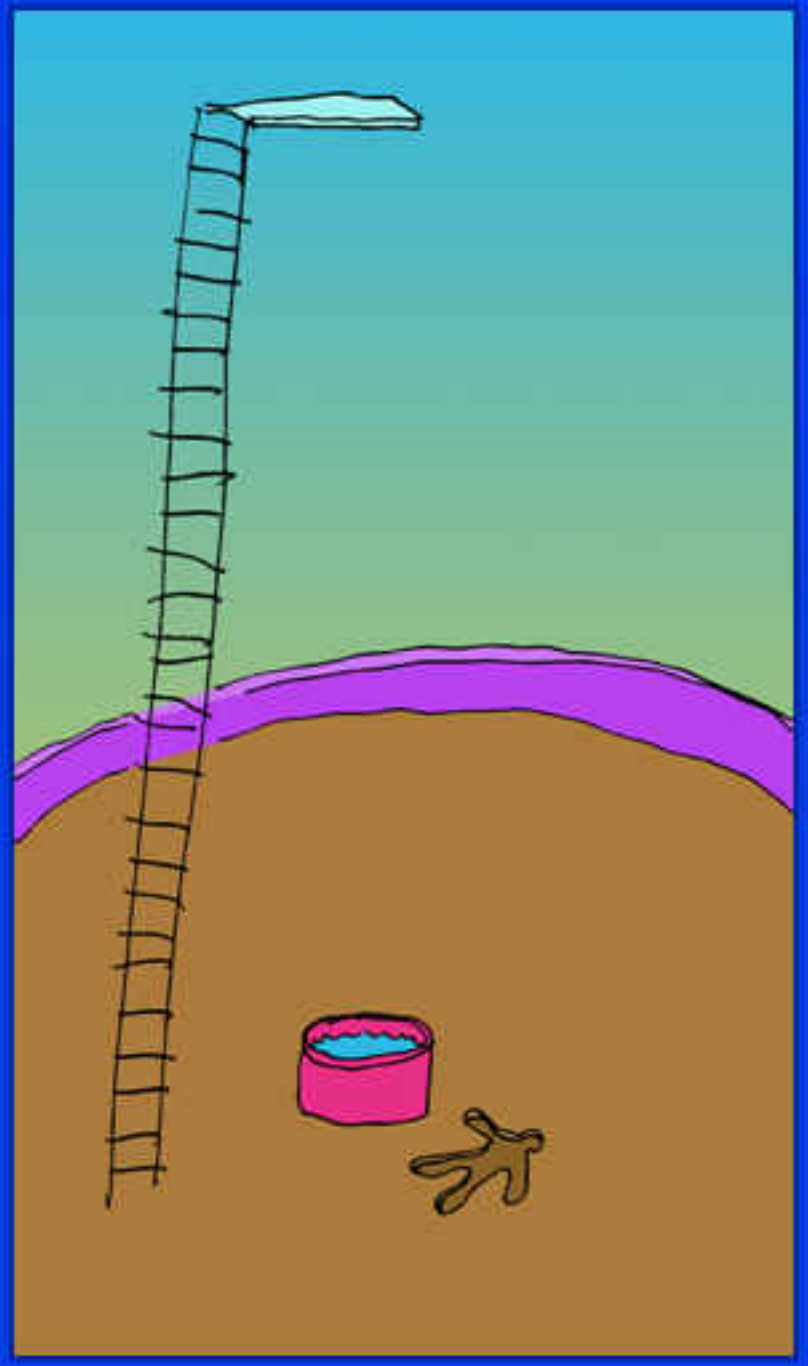
What has been tried?

- Conventional PTCA
- Rotational atherectomy
- Laser
- Cutting balloon
- VBT
- SES
- A thin scar

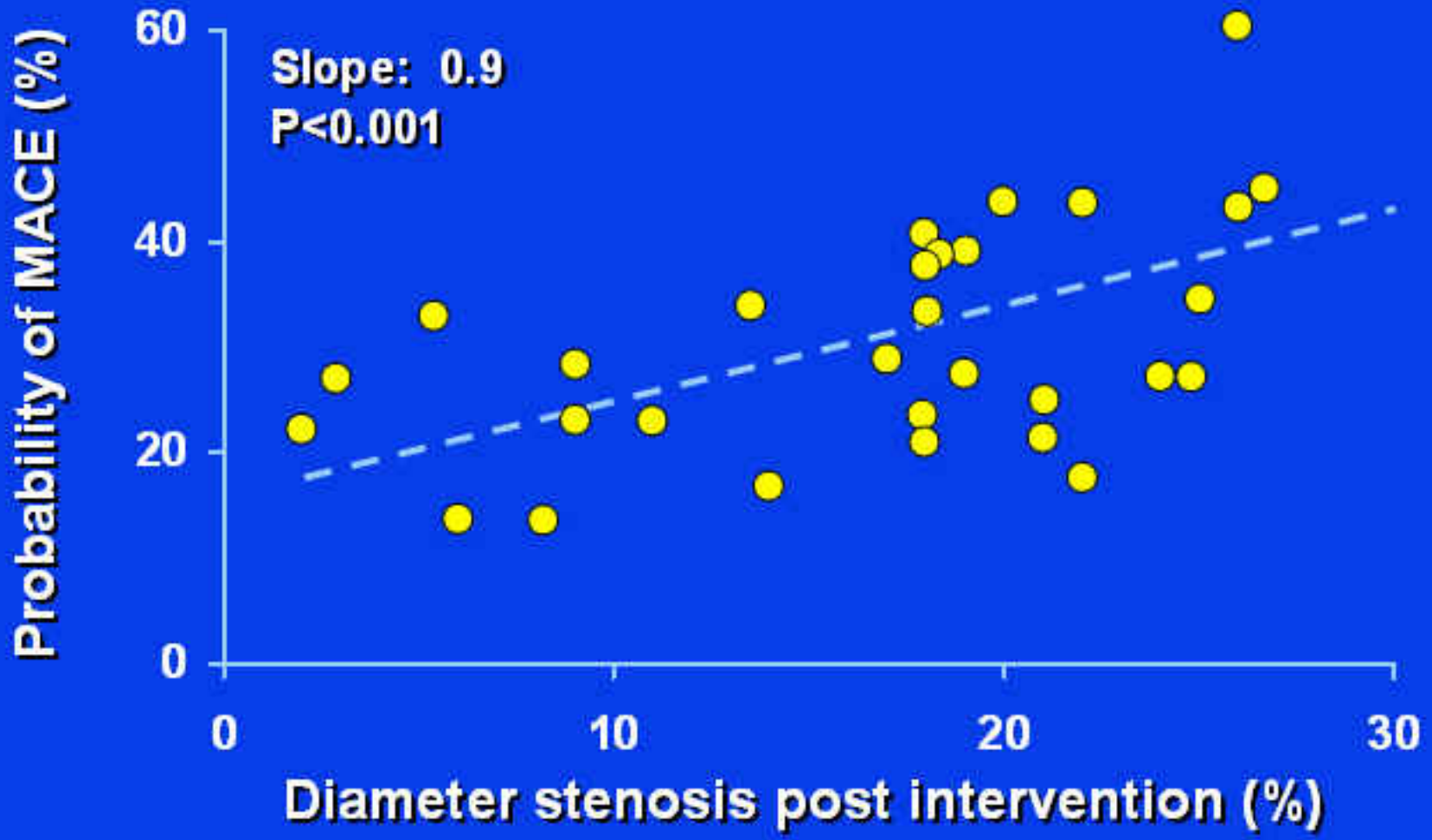
Background

- Stents revolutionized interventional cardiology by greatly improving both initial success and long-term outcomes
- Clinical and angiographic restenosis rates were improved with BMS compared with conventional PTCA, although restenosis rates remained relatively high
- Multiple approaches have been applied and studied
- Vascular brachytherapy (VBT) is currently the only approved treatment for in-stent restenosis
- New approaches continue to be developed and evaluated
- Not all patients world wide receive a DES for every lesion

“Bigger Is Better”



Bigger is Truly Better



Radke: Eur H J 24:271, 2003

In-Stent Coronary Restenosis

- Treatment of ISR associated with 30% MACE
- Repeat PTCA - treatment of choice if acute procedural result is excellent
- VBT should be considered in refractory diffuse ISR

Radke Eur Ht J 24:266-73, 2003

RESCUT Trial

- Randomized multicenter prospective trial
- 428 patients with ISR of bare metal stents
- Randomization to cutting balloon vs conventional PTCA
- Primary endpoint – angiographic restenosis (≥ 50% diameter reduction)
- Secondary endpoints - MACE

Albiero, et al; 43:943-9, 2004

RESCUT Trial

	CBA 214	PTCA 214	P
First ISR	84.6	81.5	.06
Stent length	18.6	18.3	.73
Implant interval	10.1	8.7	.22
Focal ISR	51%	38%	.01
Diffuse/prolif	49%	62%	
Lesion length			
< 20	87%	84%	
> 20	13%	16%	

Albiero, et al; 43:943-9, 2004

RESCUT Trial

	CBA 229	PTCA 237	P
1 Balloon	82.3	75.4	.03
Final balloon length	11.3	18.3	< .01
Watermelon	6.5	25.1	< .01
Additional stent	3.9	8.0	.07
Dissection post	4.8	6.8	.48

Albiero, et al; 43:943-9, 2004

RESCUT Trial
QCA

	CBA	PTCA	P
MLD			
Pre	0.83	0.84	
Post	2.17	2.16	
Late loss	.56	.62	.42
Restenosis	29.8%	31.4%	.82
Focal	23%	21%	.26
Diffuse	77%	79%	.55

Albiero, et al; 43:943-9, 2004

RESCUT Trial
MACE

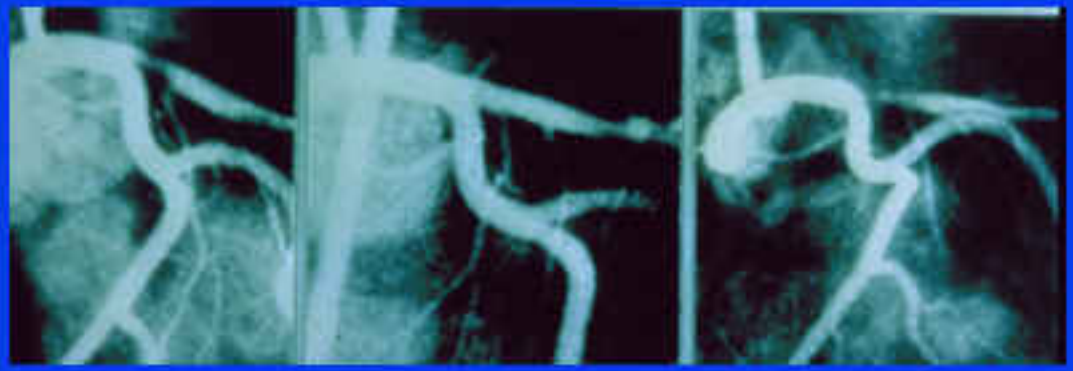
	CBA	PTCA	P
In-hospital			
Death	0	0	
MI	.5	.9	
CABG	0	0	
7-mo cumul			
Death	1.4	.9	.99
MI	1.4	1.4	
TLR	13.5	13.1	.99
MACE	16.4	15.4	.79

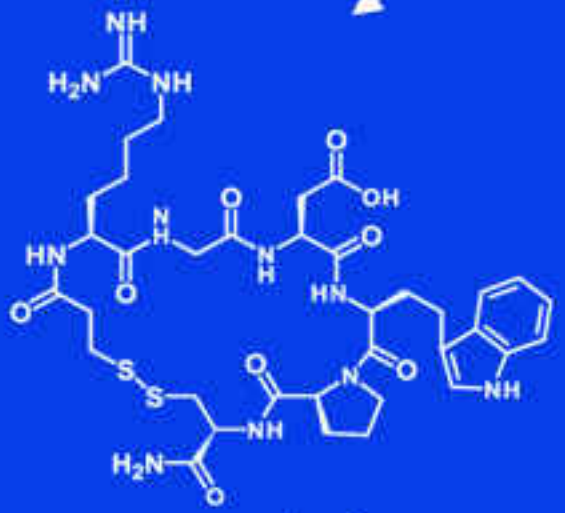
Albiero, et al; 43:943-9, 2004

RESCUT Trial
Binary Restenosis Recurrence
Multivariate Analysis

	OR	P
Previous restenosis	0.35 (0.152-0.805)	.01
Time to last stent	1.03 (0.996-1.070)	.08
Baseline length	.940 (.904-.978)	.002
# balloons used	.417 (.217-.799)	.009

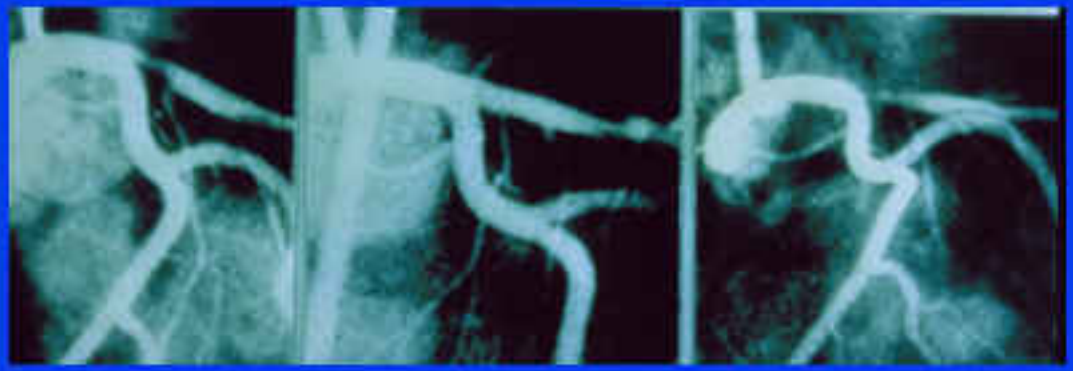
Albiero, et al; 43:943-9, 2004

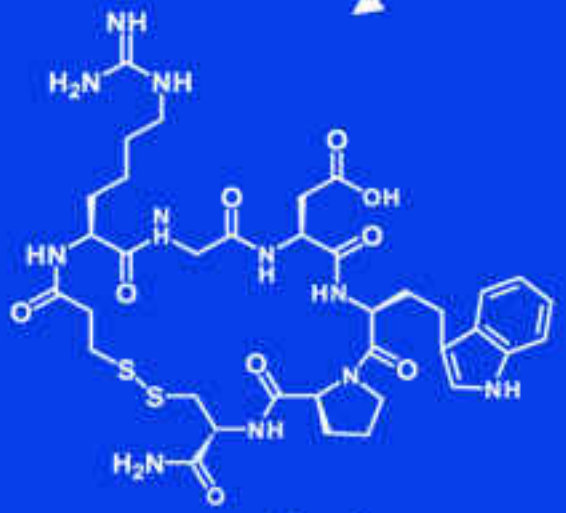




Systemic Local

MAYO CLINIC





Systemic Local

ISAR DESIRE Trial

- Randomized open label active controlled trial
- 300 patients with ISR
- Sirolimus vs paclitaxel vs PTCA
- Primary endpoint: angiographic restenosis $\geq$ 50% DS-in segment

Kastrati, et al; 293:165-171, 2005

Primary Endpoint Analysis

ISAR DESIRE

300 Patients

SES	PES	PTCA
91	92	92

Kastrati, et al; 293:165-171, 2005

ISAR DESIRE

	SES	PES	PTCA	P
Age	63.2	65.4	64.3	.27
DM	31	27	25	.63
Prior MI	45	55	47	.33
LAD	46	42	48	.39
Focal ISR	60	51	58	.85
Length	12.4	11.5	12.3	.87
MLD	0.91	0.97	0.95	.53

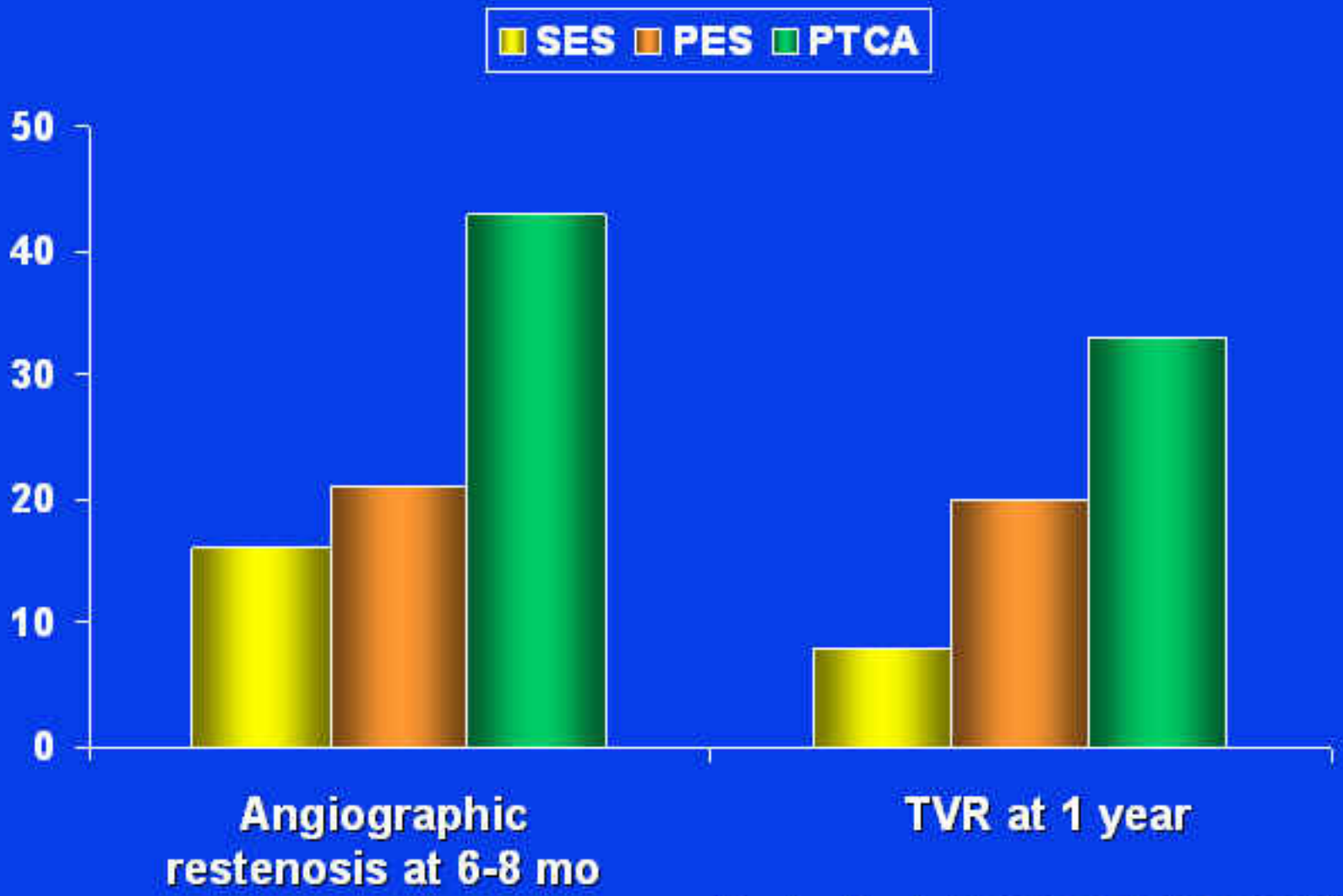
Kastrati, et al; 293:165-171, 2005

Results of QCA Analysis at F/U

Characteristic	SES (n=91)	PES (n=92)	PTCA (n=92)
MLD, mm	2.12 (1.63-2.56)	2.02 (1.62-2.40)	1.40 (0.93-1.80)
DS, %	23.1 (13.2-35.5)	26.6 (19.0-45.7)	45.8 (30.4-61.6)
Net lumen gain	1.12 (0.76-1.54)	1.02 (0.52-1.39)	0.41 (0.03-0.88)
Restenosis, # (%)	13 (14.3)	20 (21.7)	41 (44.6)

Kastrati, et al; 293:165-171, 2005

Angiographic Restenosis & TVR



Kastrati, et al; 293:165-171, 2005

Clinical Outcome at 1 Year

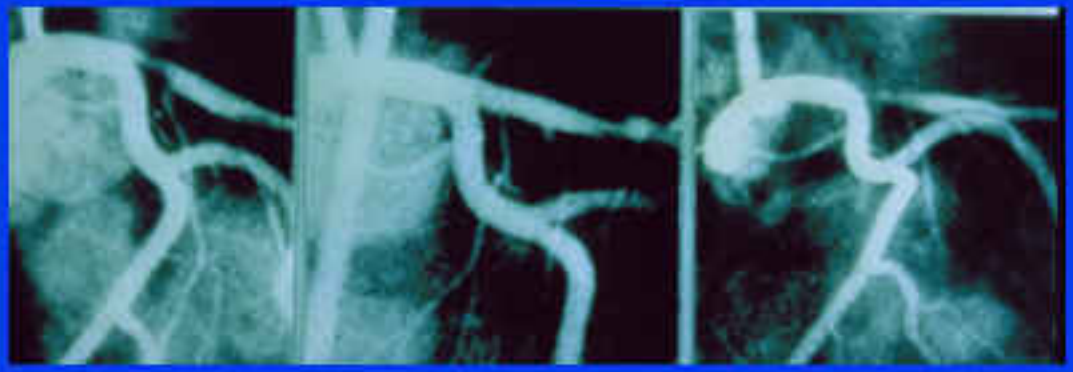
Characteristic	SES (n=100)	PES (n=100)	PTCA (N=100)
Death	2 (2)	1 (1)	3 (3)
MI	1 (1)	2 (2)	0 (0)
TVR	8 (8)	19 (19)	33 (33)

Kastrati, et al; 293:165-171, 2005

Results of QCA Analysis at F/U in DES

Characteristic	SES (n=91)	PES (n=92)	PTCA (n=92)
MLD			
In-stent, mm	2.45 (2.01-2.76)	2.21 (1.80-2.60)	.05
In-seg, mm	2.12 (1.63-2.56)	2.02 (1.62-2.40)	.23
DS			
In-stent, %	12.6 (7.3-22.8)	19.6 (11.3-36.7)	.004
In-seg, %	23.1 (13.2-35.5)	26.6 (19.0-45.7)	.04
Late lumen loss			
In-stent, mm	0.10 (-0.12-0.38)	0.26 (0.01-0.76)	.004
In-seg, mm	0.32 (0.03-0.74)	0.55 (0.23-0.90)	.02
Restenosis			
In-stent	10 (11.0)	17 (18.5)	.15
In-seg	13 (14.3)	20 (21.7)	.19

Kastrati, et al; 293:165-171, 2005



Systemic Local

Study Design

Patients with in-stent restenosis with native coronary artery lesions ≥ 15mm and ≤ 40mm in length and ≥ 2.5mm to ≤ 3.5mm in diameter (n=384)

Randomize 2:1

CYPHER® Sirolimus-eluting stent	Intravascular Brachytherapy Beta or Gamma
259 Patients	125 Patients

Primary endpoint - Target Vessel Failure (TVF):
Cardiac death, MI, or TVR at 9 months post-procedure

Major Inclusion Criteria

- ISR in a native coronary artery which has previously undergone stent placement (≥ 4 weeks)
- RVD ≥ 2.5mm and ≤ 3.5mm in diameter
- Lesion ≥ 15mm and ≤ 40mm in length which allows treatment with ≤ 3 18mm stents
- ≥ 1 prior PCI at the target lesion
- The vessel 1 cm distal to the target lesion is ≥ 2.5mm in diameter
- Stable angina, unstable angina, or silent ischemia

Baseline Demographics

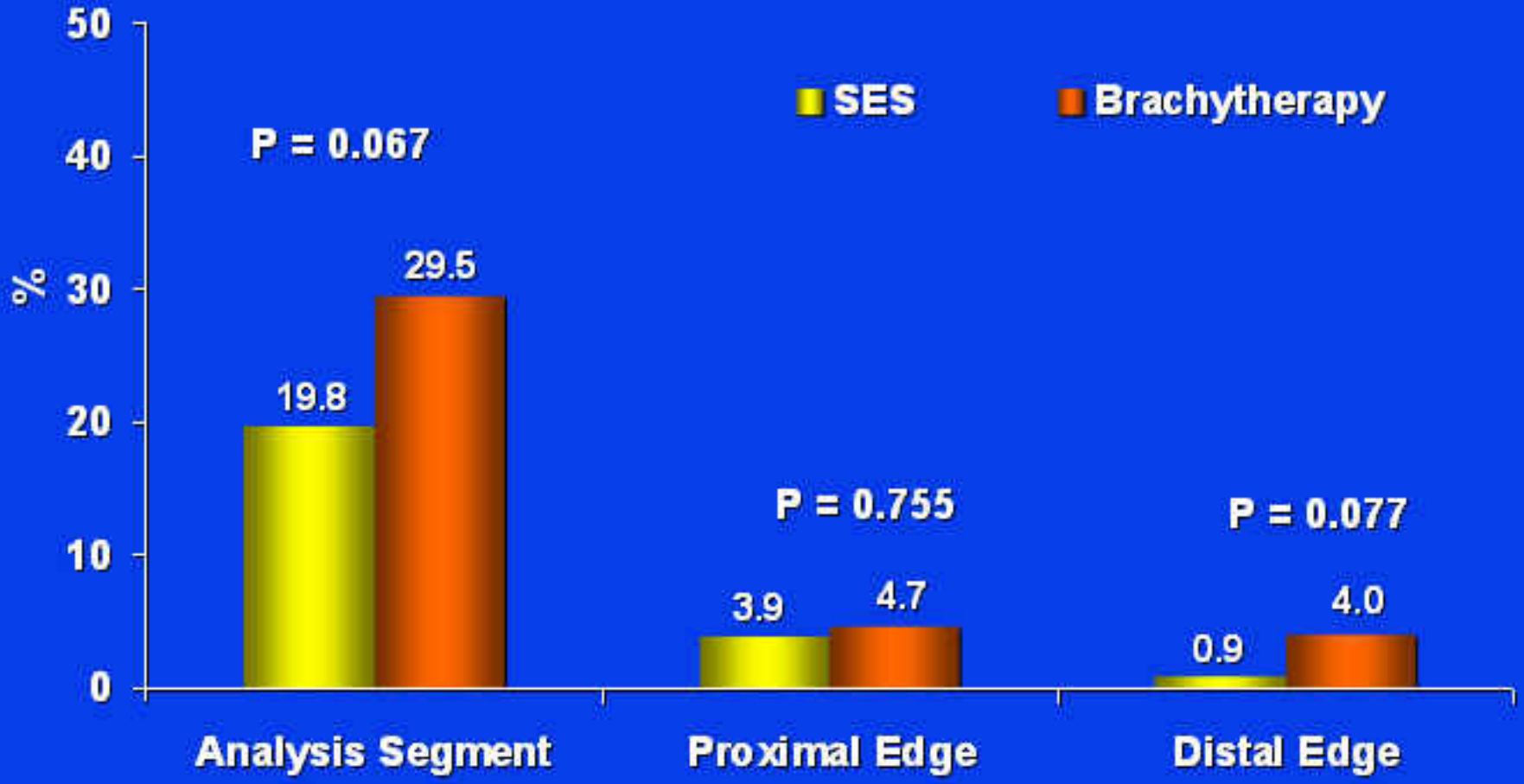
	CYPHER	VBT	P-value
# of Patients # of Lesions	259 patients 259 lesions	125 patients 125 lesions	
Mean ± SD Age (years)	62.7 ± 10.7	63.5 ± 11.7	0.486
Men (%)	68.2	65.6	0.643
Prior MI (%)	44.4	53.0	0.145
Prior CABG (%)	15.1	12.8	0.642
History of Stroke/TIA (%)	7.5	5.7	0.666
Diabetes Mellitus (%)	33.3	29.6	0.486
- Insulin Dependent (%)	9.3	8.8	1.000
Congestive Heart Failure (%)	8.6	9.7	0.707
Unstable Angina (%)	46.9	50.9	0.552
History of Renal Insufficiency (%)	9.3	3.2	0.036
Mean ± SD Ejection Fraction (%)	56.8 ± 9.0	55.3 ± 8.5	0.132

Intent-to-Treat Analyses

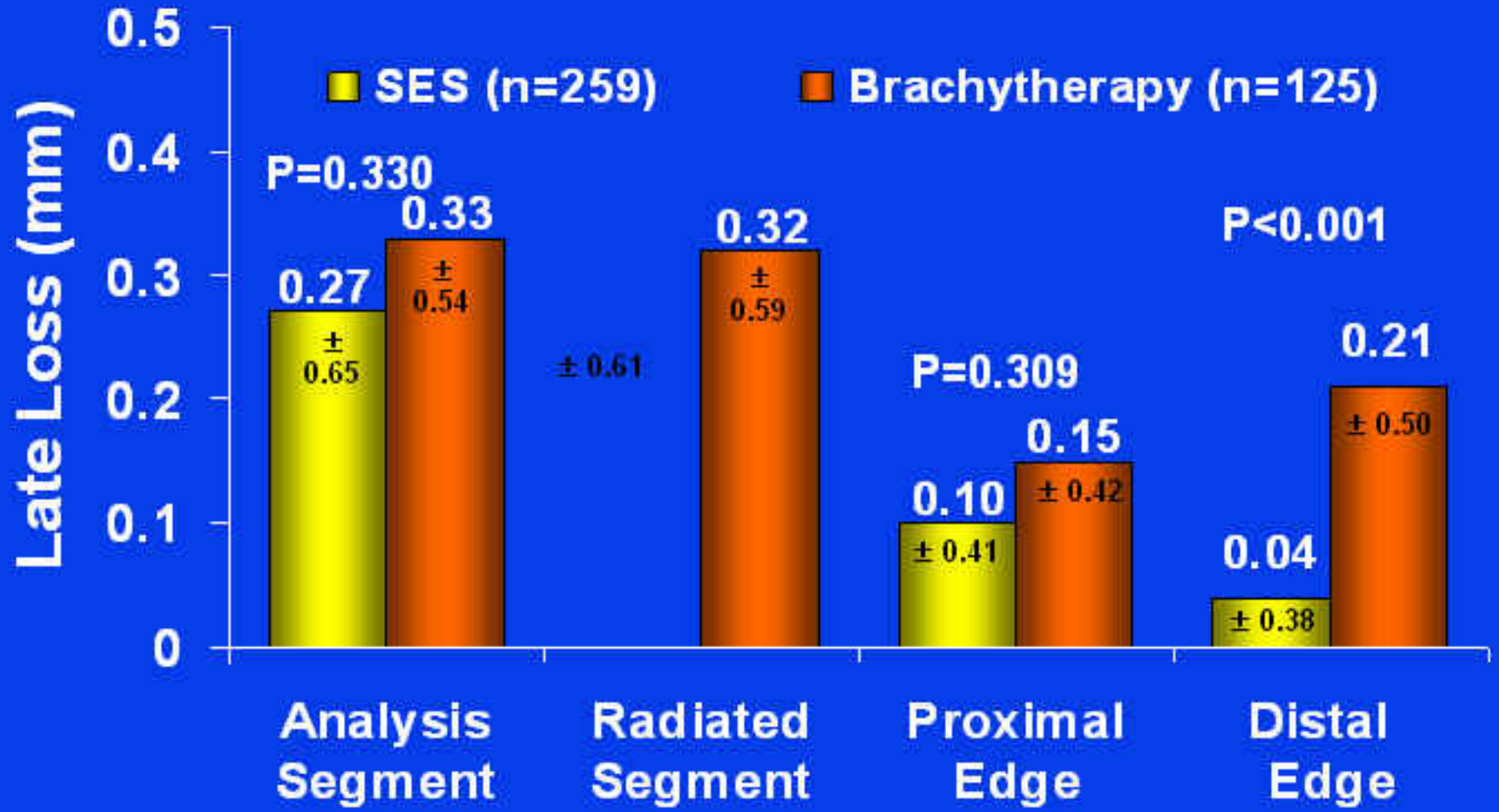
Procedural and Lesion Success

	CYPHER	Brachy-therapy	P-value
Device Success (%) ***<50% residual stenosis (by QCA) using the assigned device only***	96.5	96.8	1.000
Lesion Success (%) ***<50% residual stenosis (by QCA) using any percutaneous method***	98.8	99.2	1.000
Procedural Success (%) ***< 50% residual stenosis (by QCA) without in-hospital MACE***	97.3	99.2	0.282

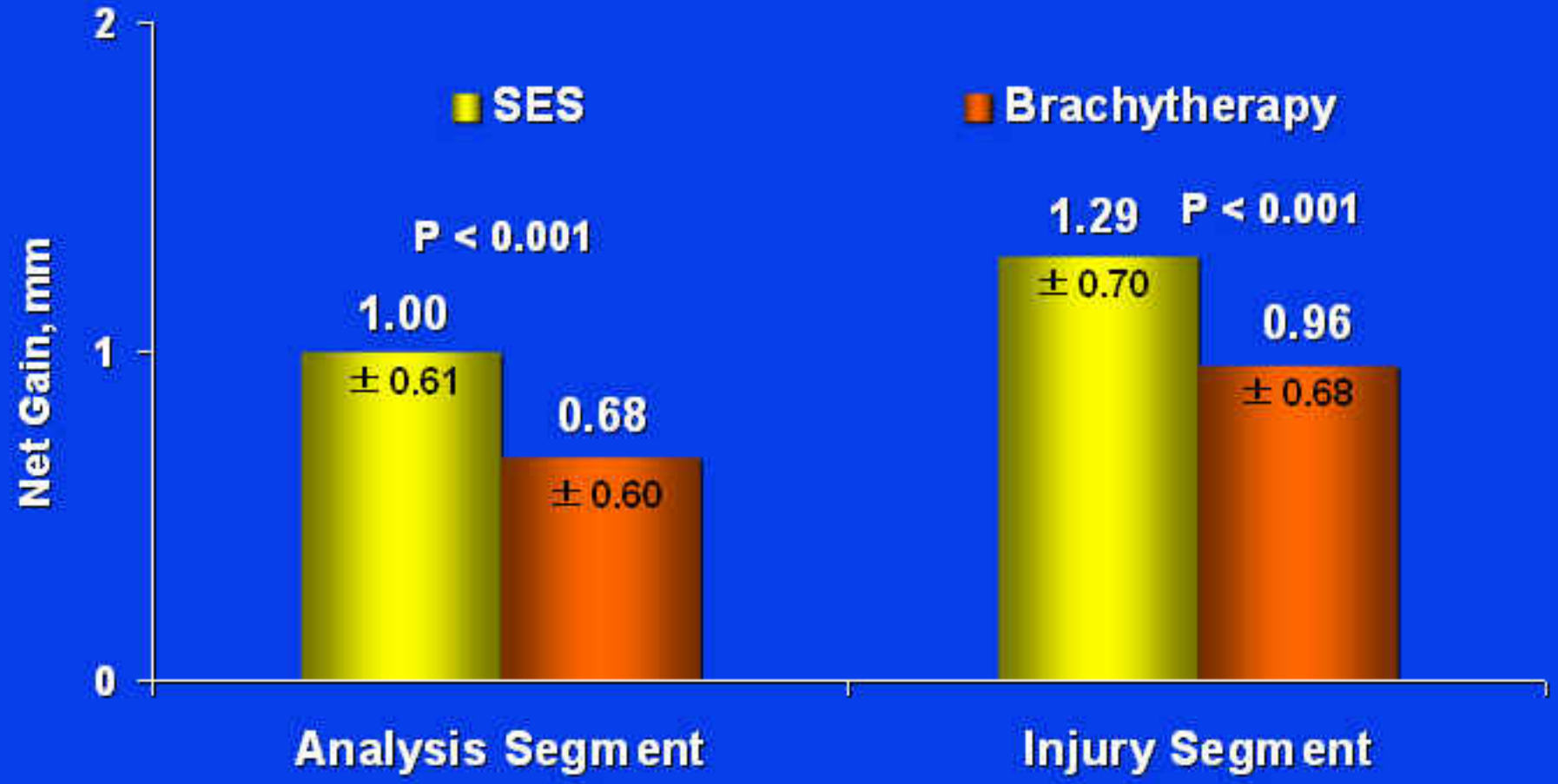
Binary Angiographic Restenosis at 6-Month Follow-Up



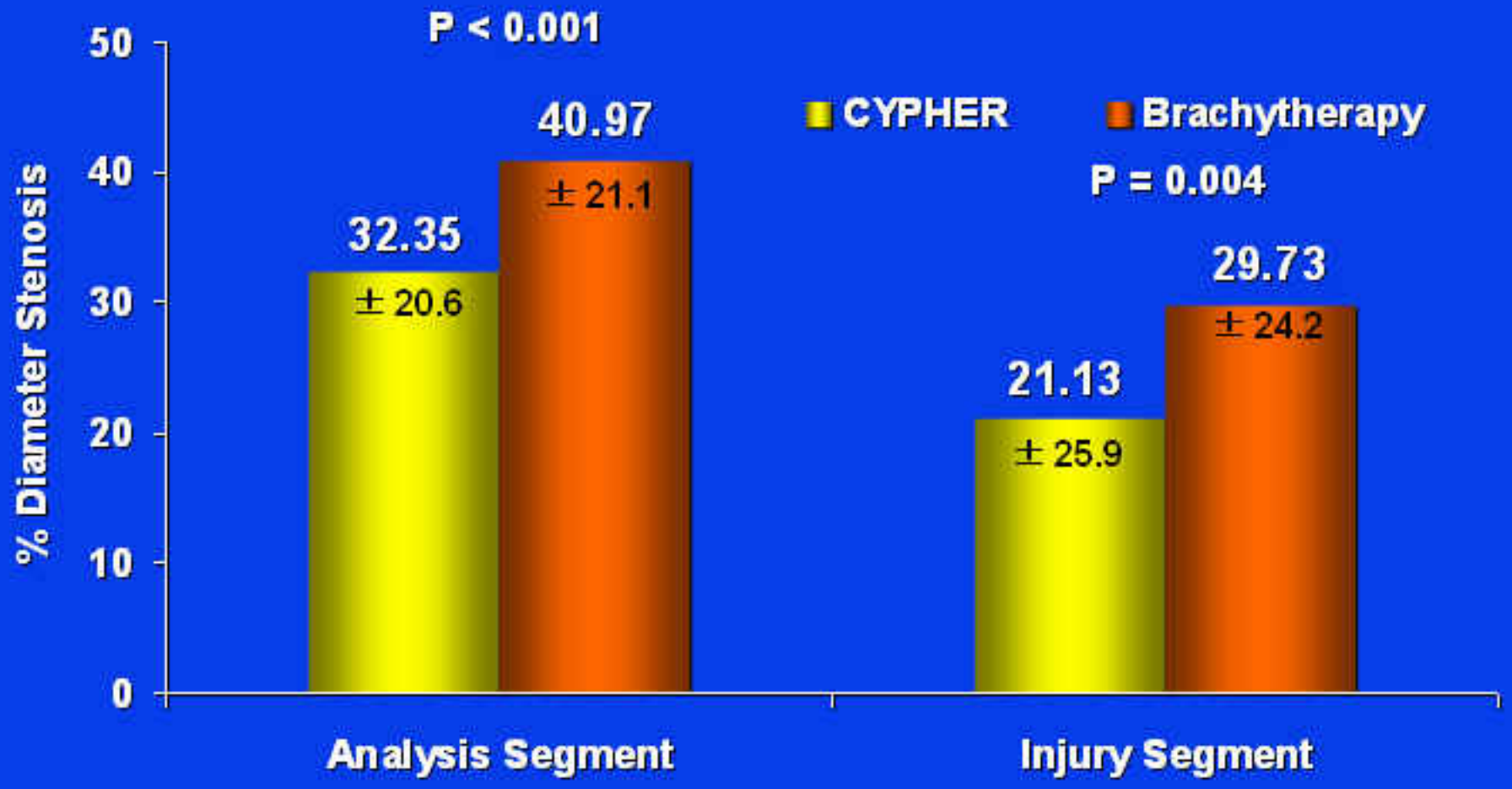
SISR: 6-month Late Loss



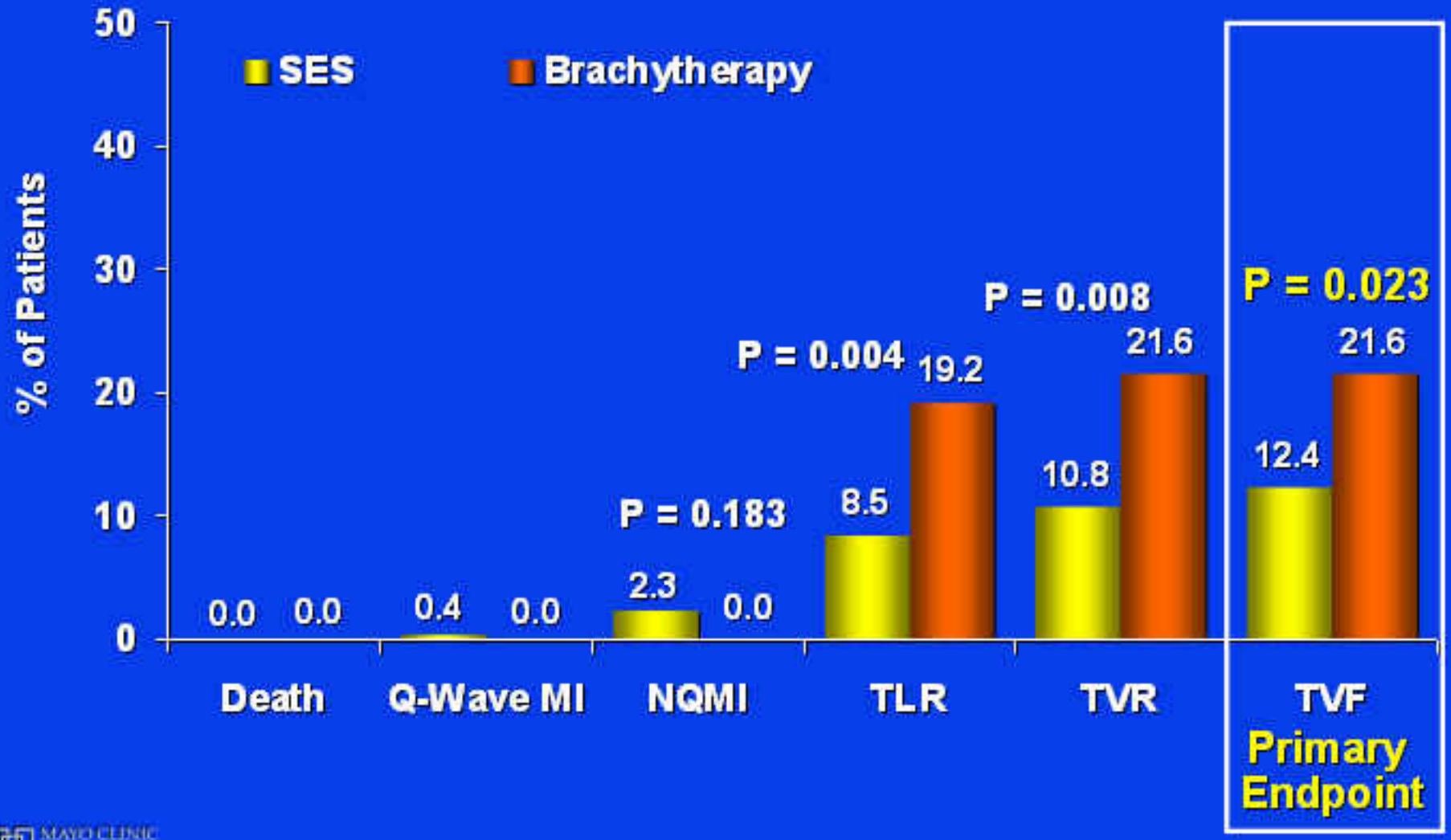
Net Gain at 6-Month Follow-Up



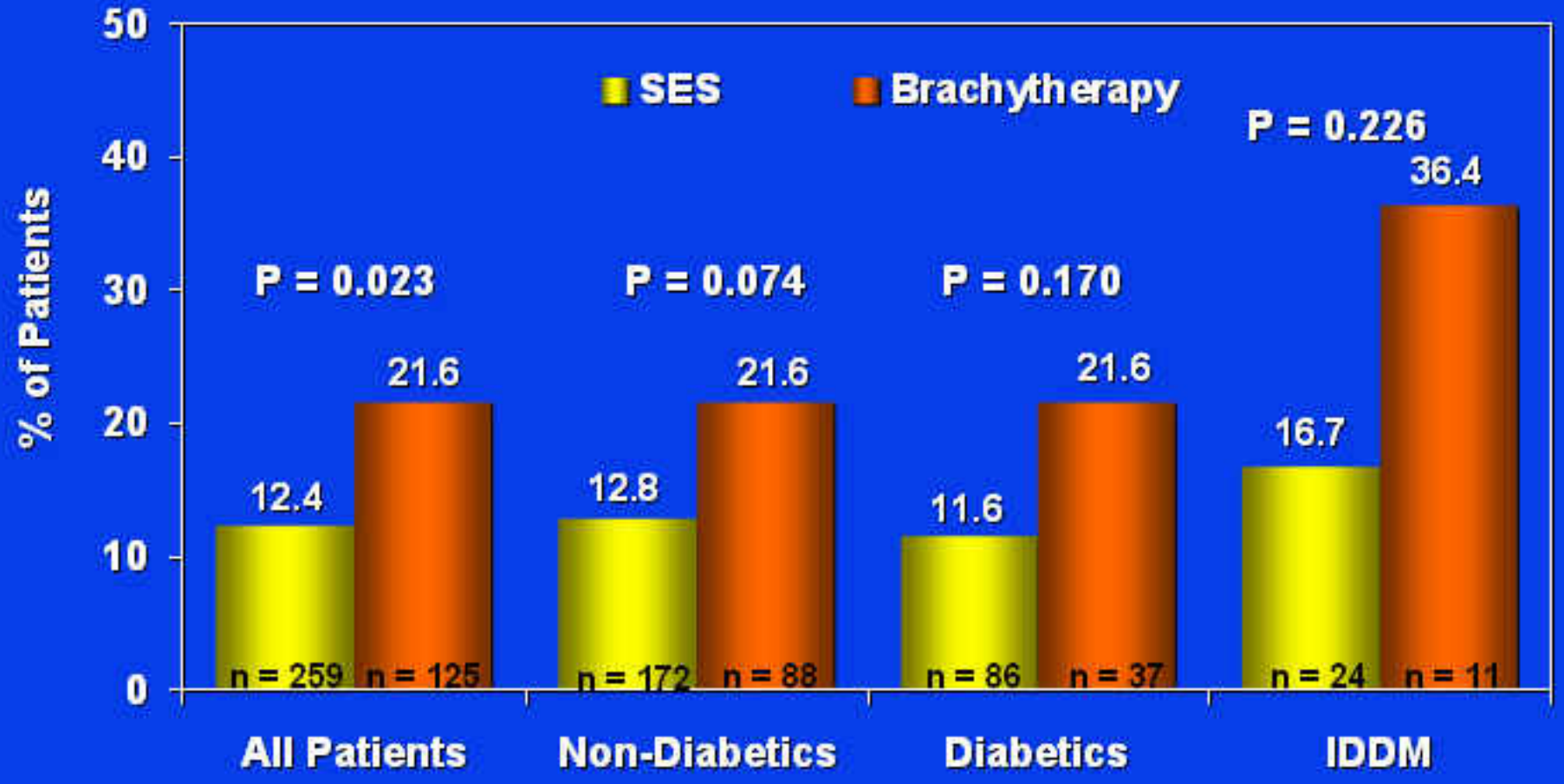
% Diameter Stenosis at 6 Month Follow-Up



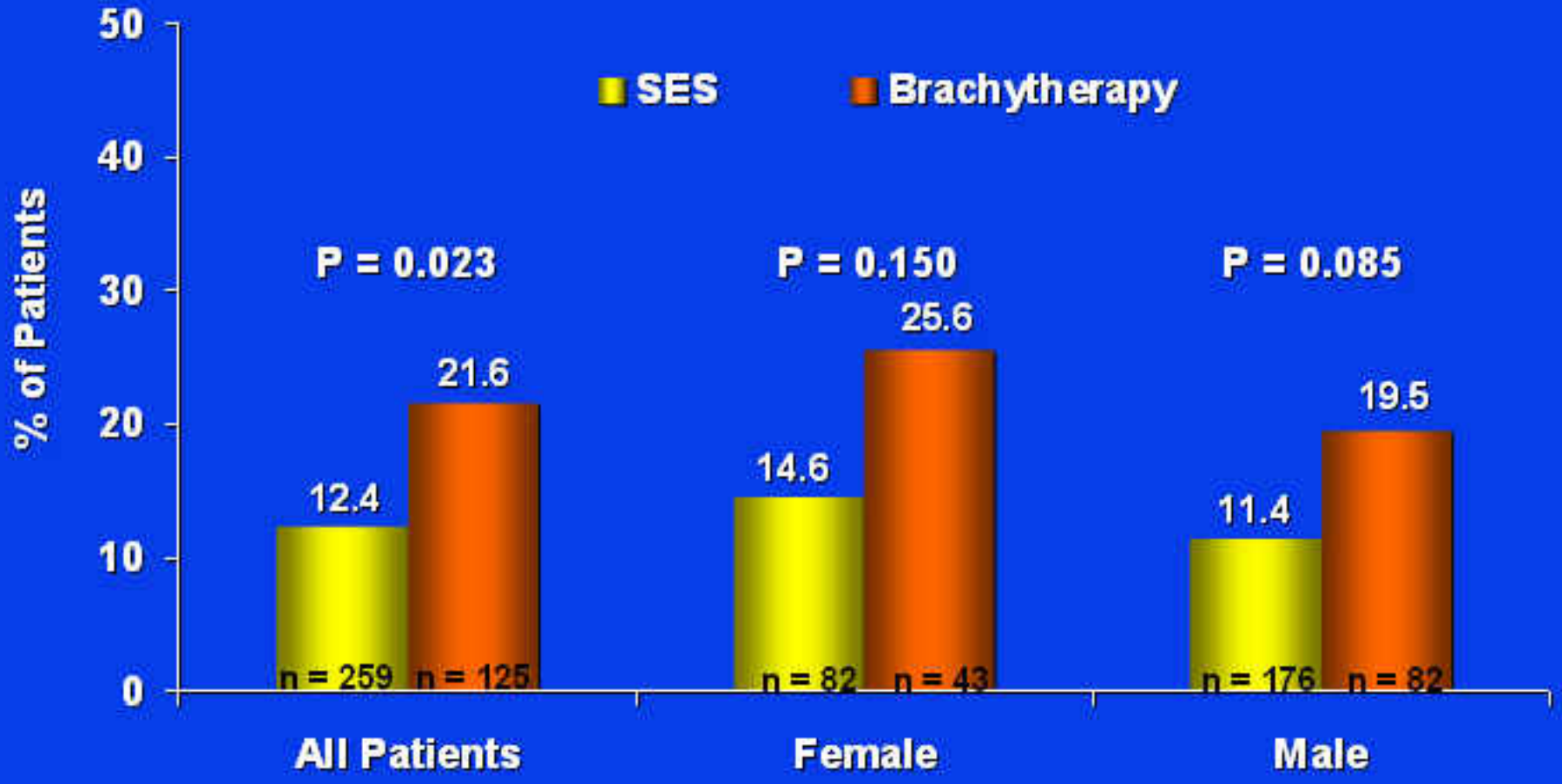
Clinical Outcomes Through 9-Months



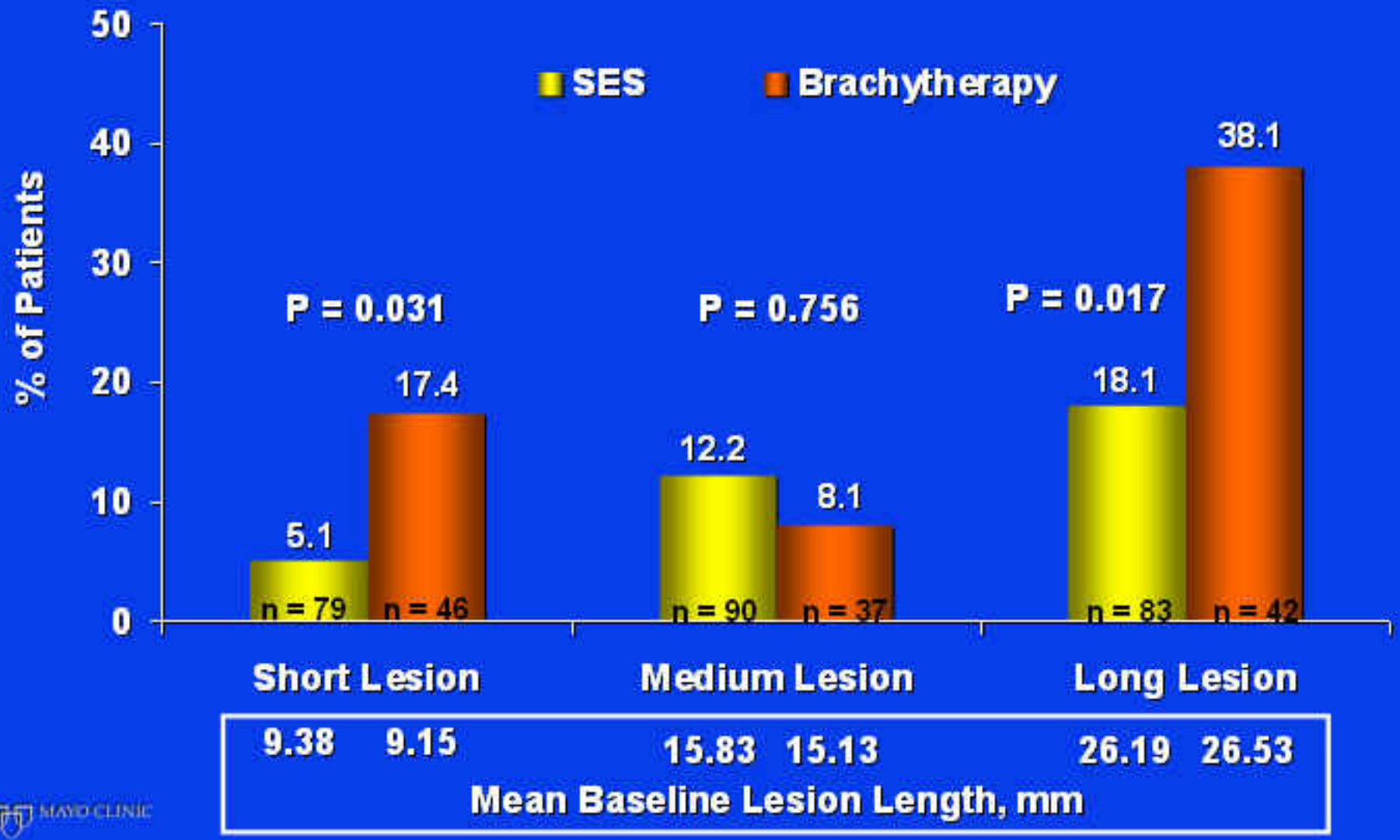
TVF by Diabetic Status



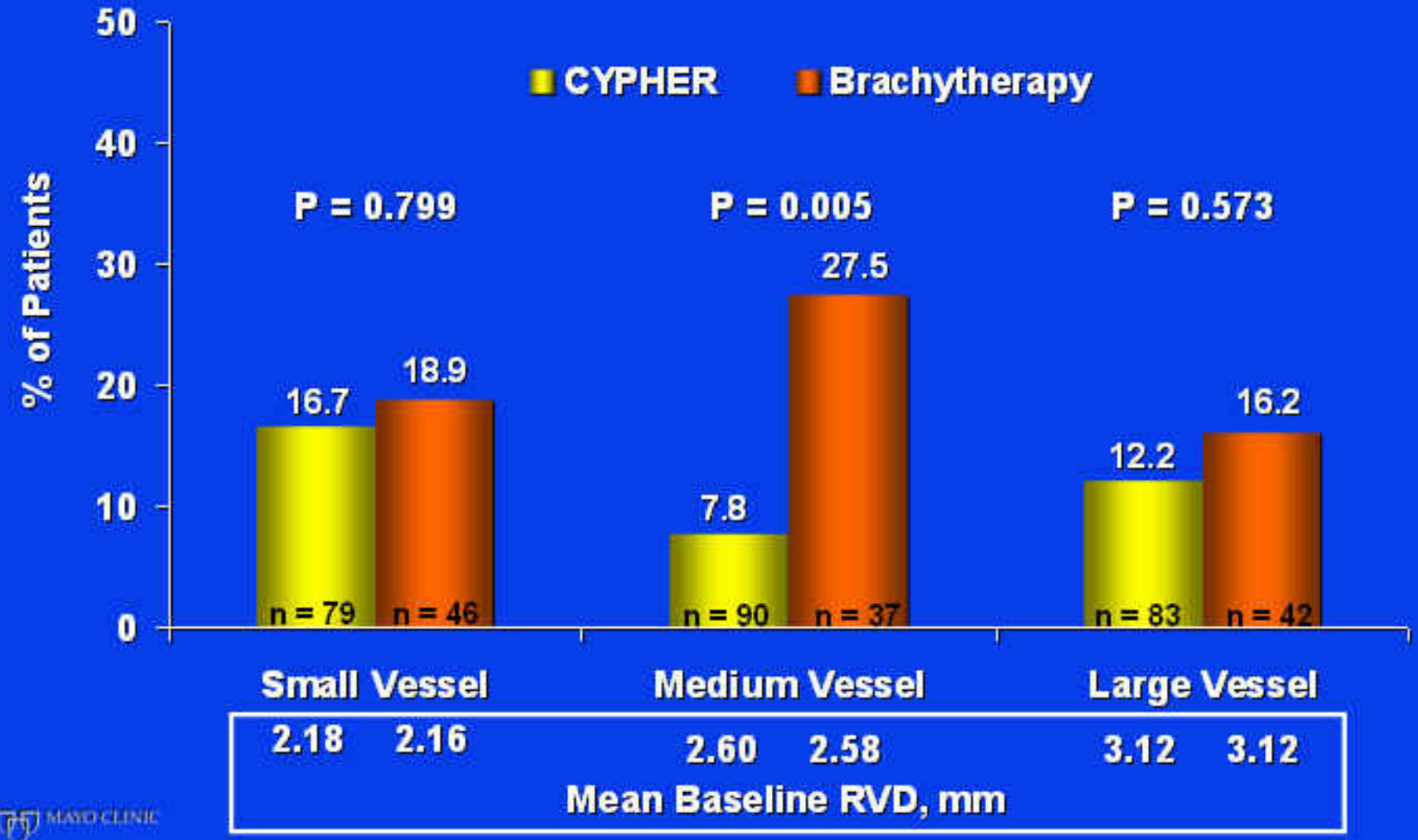
TVF by Gender



TVF by Lesion Length Tercile Analysis



TVF by Baseline Vessel Size Tercile Analysis



Conclusions

Both VBT and SES are effective in reducing neointimal hyperplasia within the treated region

- Vascular brachytherapy demonstrated significant late loss in the 5 mm proximal and distal edges while the Sirolimus-eluting stent did not exhibit this behavior
- These differences contributed to improved lumen dimensions in SES patients measured by both angiography & by IVUS
- SES resulted in significantly less TLR than VBT
- The Sirolimus-eluting stent was superior to vascular brachytherapy in reducing the primary endpoint of Target Vessel Failure

Bare Metal Stents and In-stent Restenosis

- Will remain a significant problem in a smaller and smaller number of patients
- Although VBT is still the only approved treatment and still works, placement of a DES particularly SES will remain the treatment of choice.

Procedural Characteristics

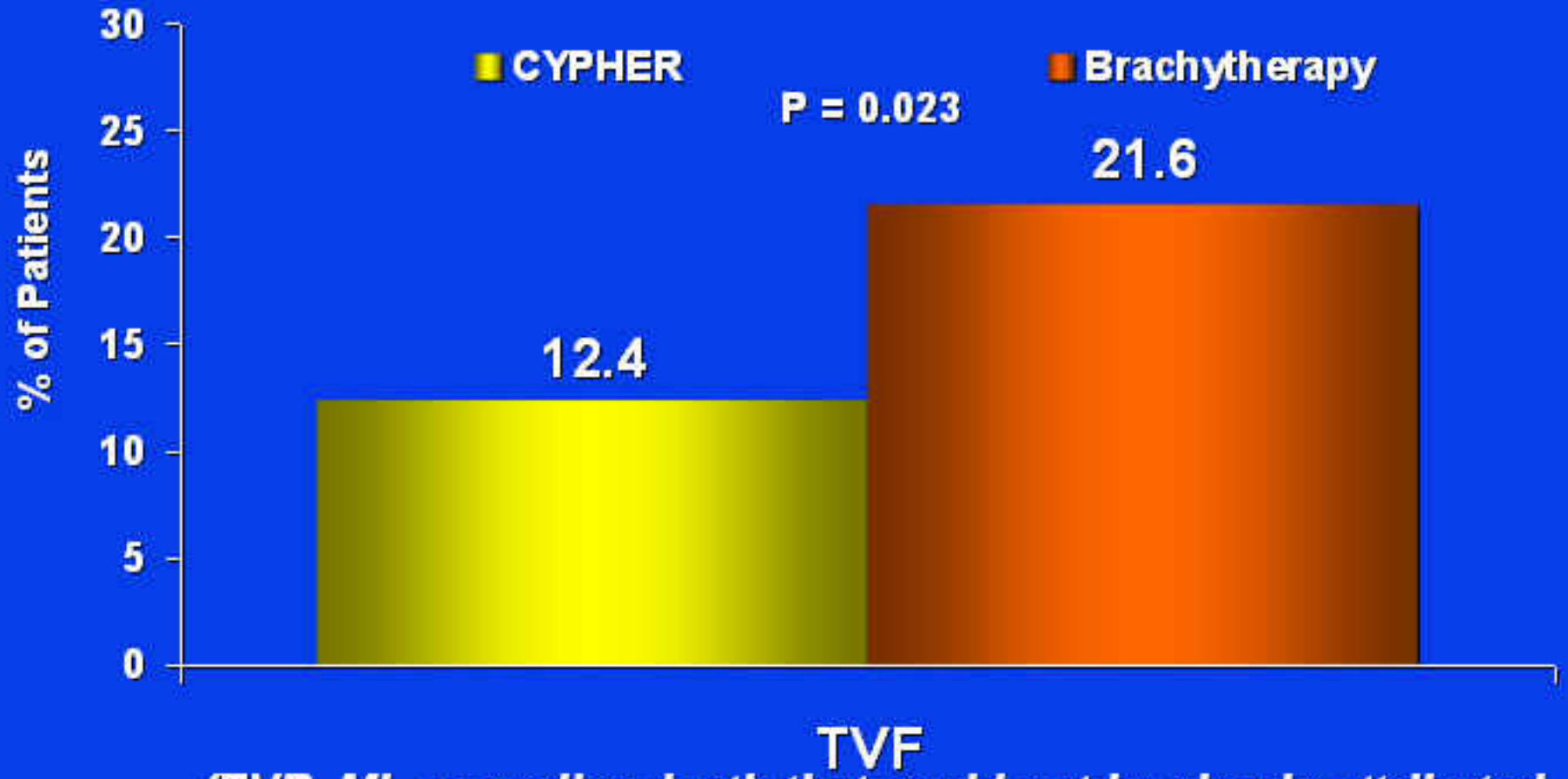
	CYPHER	Brachytherapy	P-value
Post-Procedure Hospital Length of Stay - Mean ± SD	1.1 ± 0.5	1.1 ± 0.4	0.325
IIb/IIIa During Procedure (%)	31.1	36.8	0.297

Statistical Analysis

Primary Endpoint:

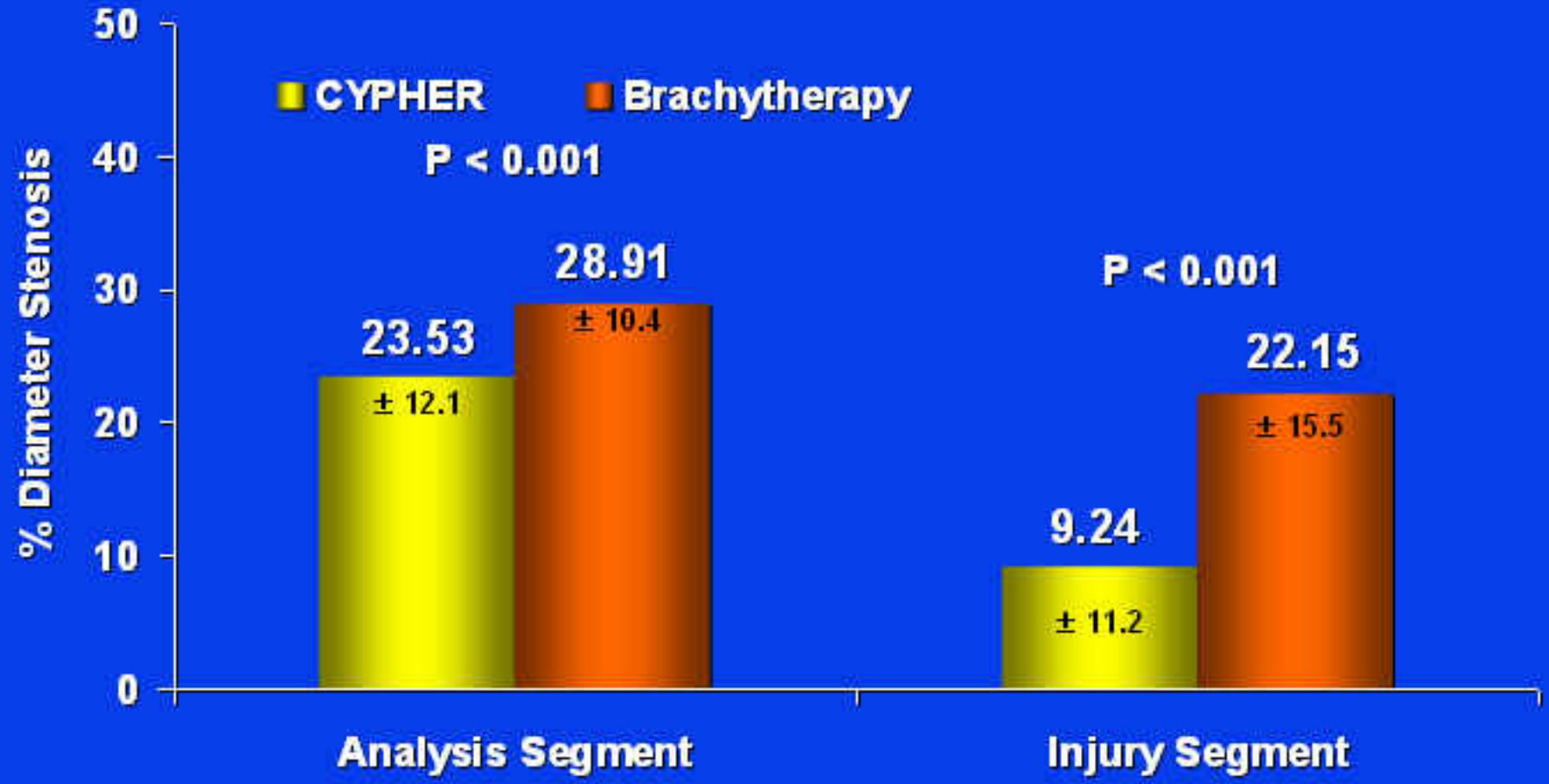
- To establish a more precise estimate of the objective performance criterion, applicable data from the Gamma I (N=131) and Gamma II (N=125) trials will be combined with the active control (brachytherapy) using Bayesian statistical methods
- The analysis will adjust for the following confounding variables:
  - reference vessel diameter (RVD)
  - post procedure minimum luminal diameter (MLD)
  - lesion length
  - history of diabetes
  - left anterior artery disease (LAD)
  - type of radiation treatment (Gamma versus Beta)
  - gender
- By adjusting for these variables, known differences between the trials will be accounted for, leaving the analysis susceptible to only unmeasured confounders

Primary Endpoint: TVF Through 9-Month Follow-Up

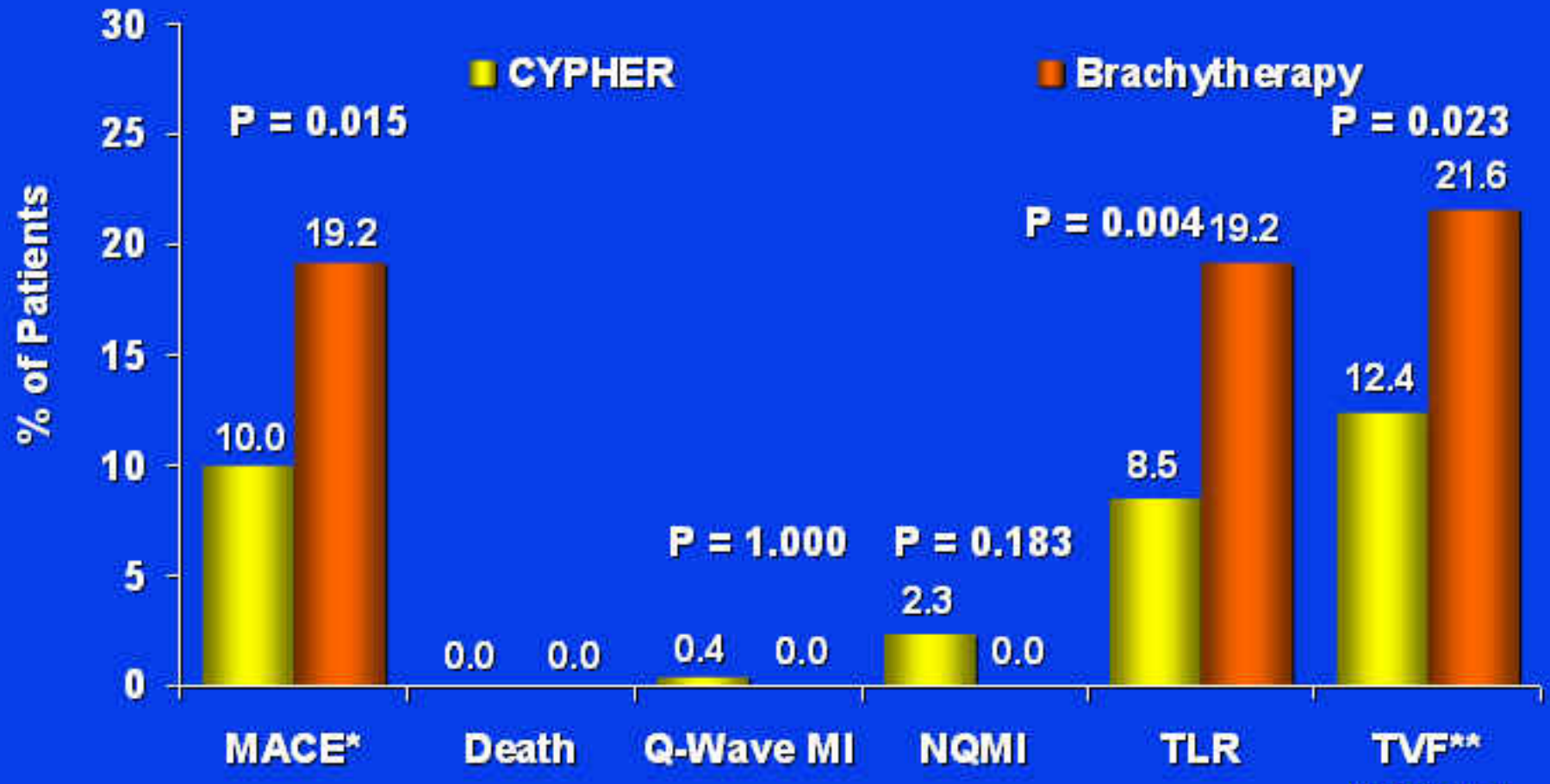


(TVR, MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel)

% Diameter Stenosis Post-Procedure



Clinical Outcomes Through 9-Months

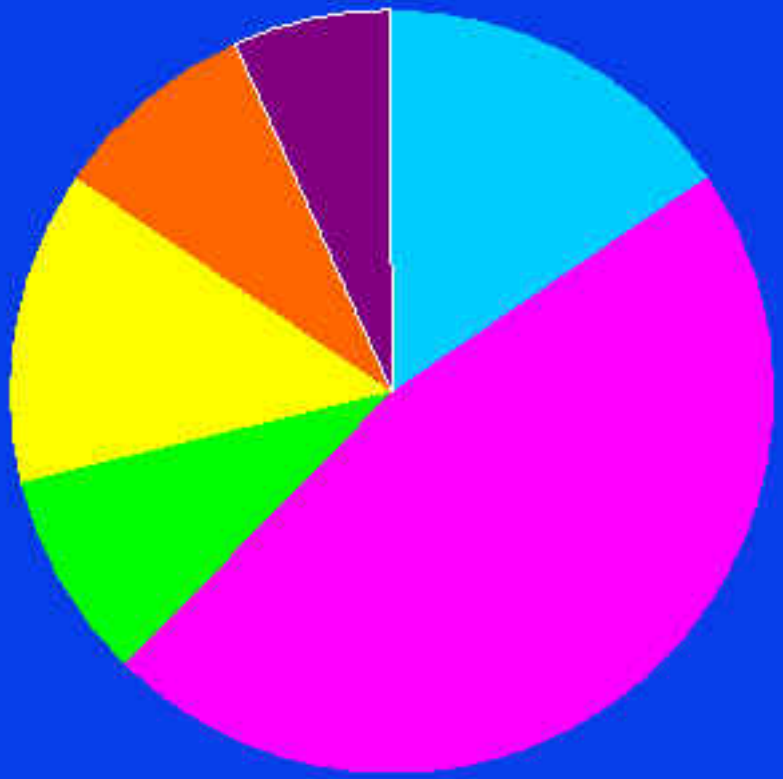


* Death, MI, emergent CABG, or TLR

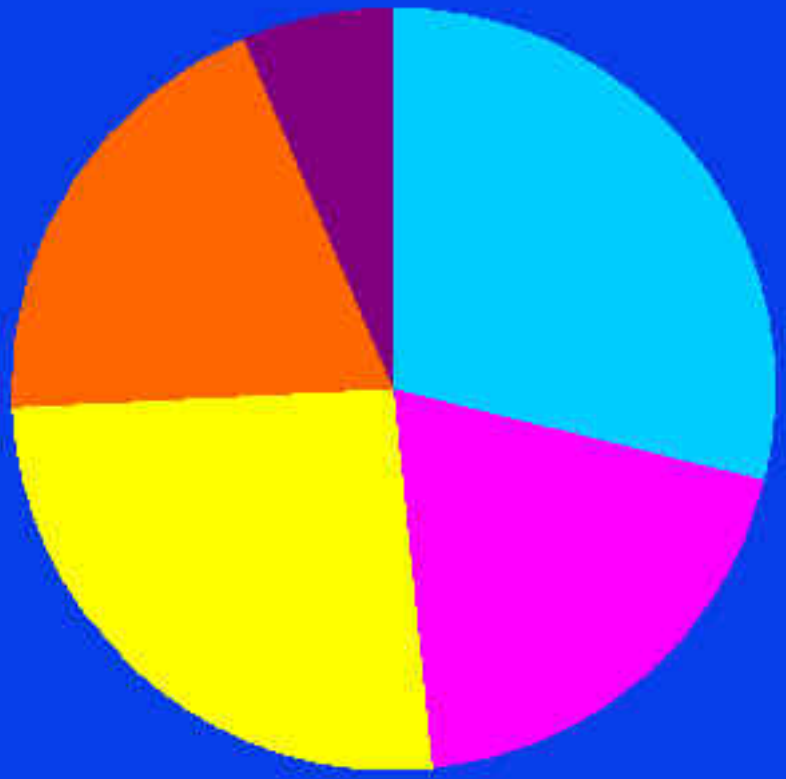
** TVR, MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel

Pattern of Restenosis at 6-Month Follow-Up

CYPHER (n = 45)



Brachytherapy (n = 31)



ISR Length, mm	10.73 ± 6.52	12.11 ± 6.29	p = 0.378

IVUS Analysis

6-Month F/U
(n = 16)

Post-Stent and 6-Month Follow-Up

	(n = 72)	(n = 33)	(n = 63)	(n = 23)
	SES Post	VBT Post	SES F/U	VBT F/U
Vessel Area (mm^2)	14.04	14.49	13.66	15.10
Vessel Volume (mm^3)	426.51	381.89	451.51	330.17
Mean Stent Area (mm^2)	5.45	7.03	6.44	8.15
Stent Volume (mm^3)	191.06	187.84	205.58	196.86
Mean Lumen Area (mm^2)	5.87	5.37	5.94	5.62
Minimal Lumen Area (mm^2)	4.86	3.84	4.38	3.98
Lumen Volume (mm^3)	190.65	134.51	190.71	133.34

Yellow indicates $p<0.05$ for difference between SES and VBT

Multivariate Predictors of TVF through 270 Days

Multiple Logistic Regression

All Patients	Coefficient	Standard Error	Odds Ratio	P-value
Modified ACC/AHA Score Classification (C vs. all others)	1.2973	0.3343	3.660	0.0001
Premature CAD in a first degree relative	- 0.7656	0.3741	0.465	0.0407
Treatment Group (CYPHER vs. Brachytherapy)	- 0.5305	0.3294	0.588	0.1073
SES Patients				
Modified ACC/AHA Score Classification (C vs. all others)	1.1466	0.4027	3.148	0.0044
Post-PCI Within-Injury MLD (mm)	- 0.7778	0.5055	0.459	0.1239

Predictors were chosen by stepwise linear regression using any entry criterion of 0.20 with a stay criterion of 0.10 (Significant p-value defined as $p<0.05$)

Multivariate Predictors of Net Gain through 270 Days

Multiple Logistic Regression

All Patients	Coefficient	Standard Error	P-value
Pre-PCI MLD (mm)	- 0.7508	0.0868	0.0000
Post-PCI Within-Analysis MLD (mm)	0.3726	0.1123	0.0010
Post-PCI Within-Injury MLD (mm)	0.2986	0.0987	0.0027
Prior CABG	- 0.2106	0.0846	0.0133
Diabetes Mellitus	- 0.1249	0.0614	0.0429
Gender (men)	0.1201	0.0612	0.0505
Pre-PCI RVD (mm)	0.1461	0.0975	0.1348
SES Patients			
Pre-PCI MLD (mm)	- 0.7229	0.1018	0.0000
Post-PCI Within-Analysis MLD (mm)	0.4482	0.1187	0.0002
Prior CABG	- 0.3033	0.0985	0.0023
Post-PCI RVD (mm)	0.2546	0.1282	0.0482

Predictors were chosen by stepwise linear regression using any entry criterion of 0.20 with a stay criterion of 0.10 (Significant p-value defined as $p<0.05$)

SISR

400 Patients with In-Stent Restenosis

Cypher Stent — **Vascular Brachytherapy**

2:1 Ratio

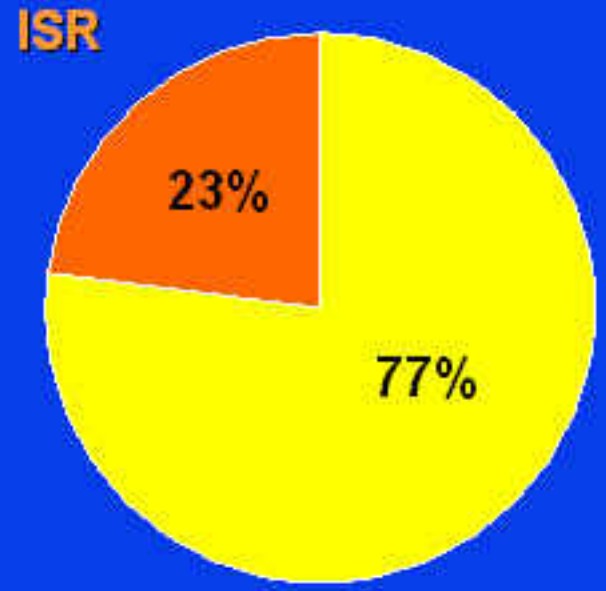
1° Endpoint: Target vessel failure at 9 months

2 ° Endpoint: Binary restenosis, TLR, TVR

Bare Metal Stents

- Revolutionized PCI
- Initially developed to treat AC/TC and were very successful
- Tested for prevention of restenosis and were also very successful
- Became predicate devices
- Did not eliminate restenosis and in fact, NIH was even increased vs conventional PTCA

German Cypher Registry
6,555 Patients



- ISR
  - 1,932 stents in 1,673 lesions
  - Success rate 98.9%

Mollmann H et al: Clin Res Cardiol 2008