

# PCI for In-Stent Restenosis



# ISR of BMS



# In-Stent Restenosis Patterns

## Pattern I : Focal



*Type IA: Articulation / Gap*



*Type IB: Margin*



*Type IC: Focal body*



*Type ID: Multifocal*

## Pattern II,III,IV : Diffuse



*Pattern II : Intra-stent*



*Pattern III: proliferative*

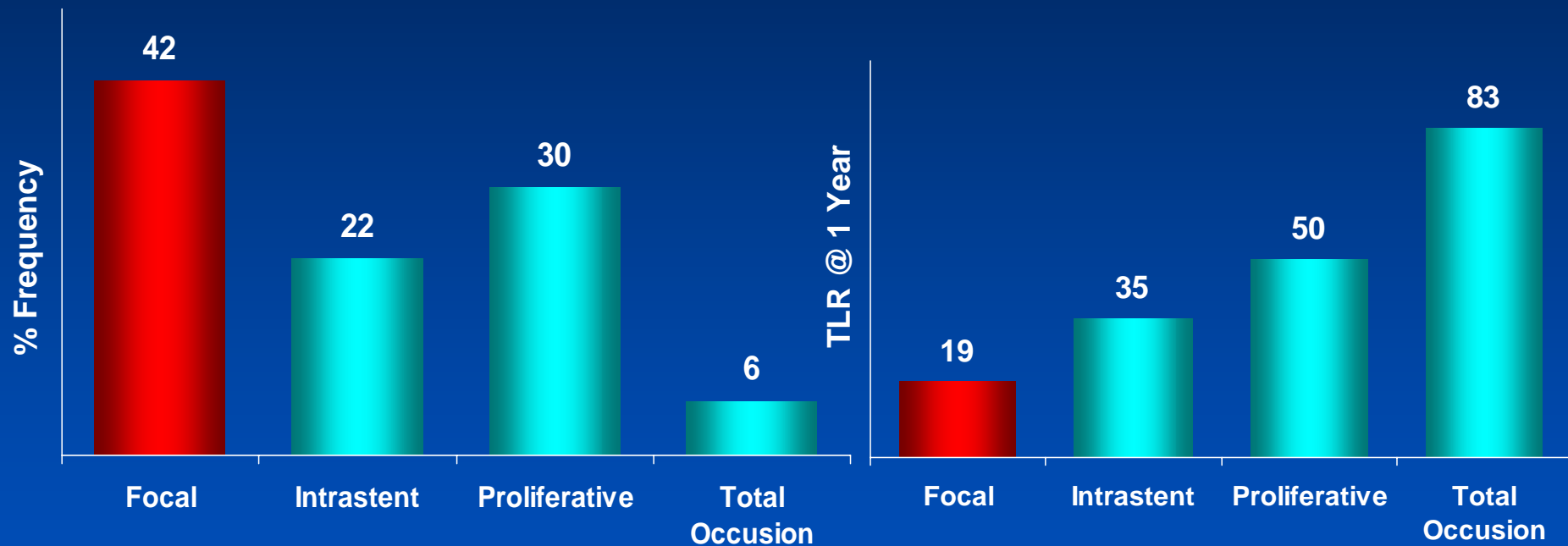


*Pattern IV : Total occlusion*

*Mehran et al. Circulation 1999;100:1872 -1878*

# Patterns of ISR

282 lesions



Predictors of TLR : diabetes, previous ISR and ISR patterns

*Mehran R et al. Circulation 1999;100:1872-78*

# Treatment of Bare Metal ISR

- Balloon angioplasty
- Cutting balloon angioplasty
- Rotablasting atherectomy
- Repeat stenting
- **Intracoronary brachytherapy**
- **Drug eluting stent**

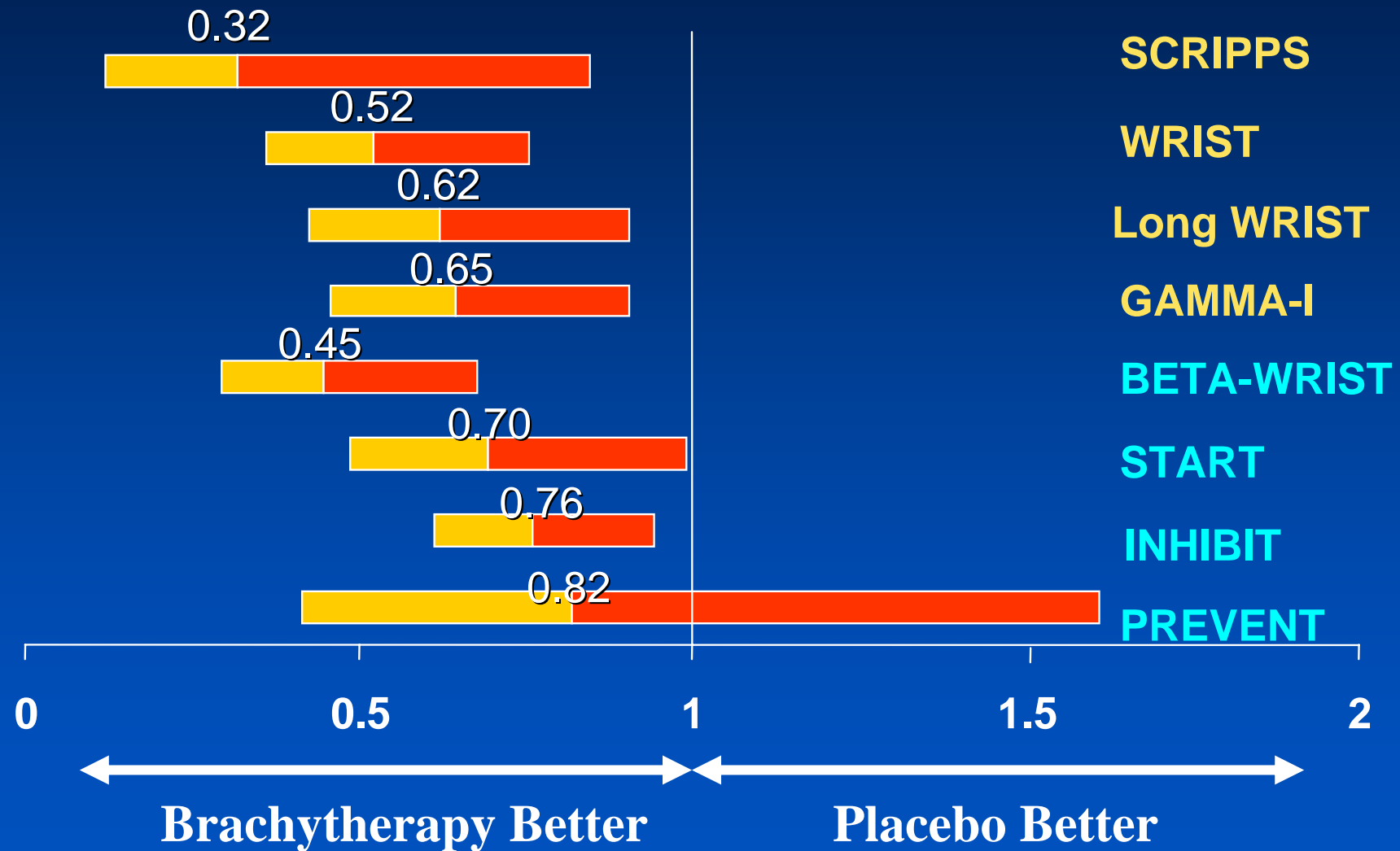
Not  
encouraging  
in diffuse ISR

# Intracoronary Brachytherapy

- Most effective therapy of in-stent restenosis before development of drug eluting stent
- Use of source train or balloon with beta or gamma radiation
- Inhibition of neo-intimal growth



# Risk Reduction of Brachytherapy



# Brachytherapy

## Reported Clinical Trials for ISR

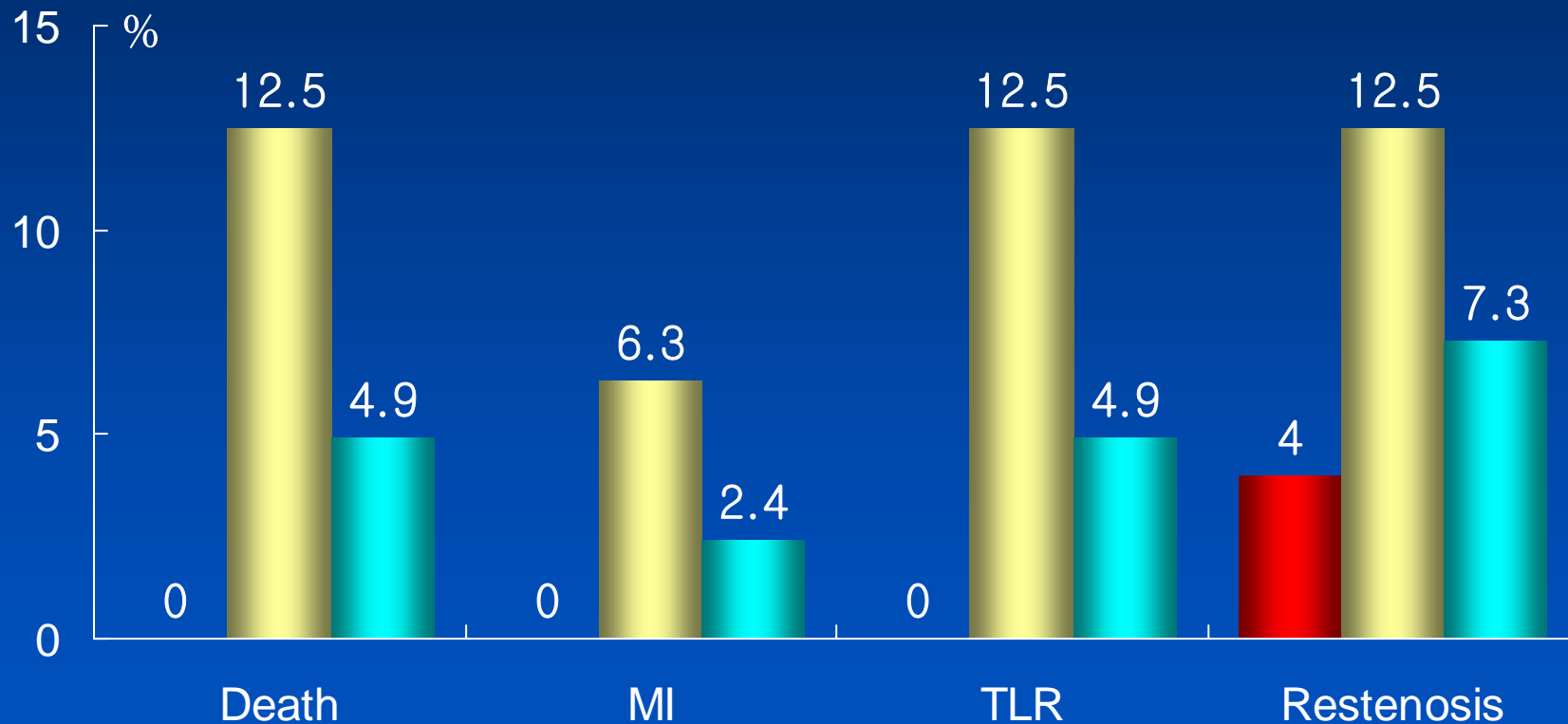
TRIAL	Source	Length (mm)	Pts (n)	Restenosis %	
				Placebo	Treated
SCRIPPS	192Ir	15.3	35	70.5	11.1
WRIST	192Ir	23.7	130	58.3	19
GAMMA 1	192Ir	20.2	252	50.5	21.6
GAMMA 2	192Ir	19	125		23
LONG WRIST	192Ir	32	120	71	32
B-WRIST	90Y	20.6	50		22
START	Sr/90	17	476	42.2	14.2
INHIBIT	P32	17	332	48	16
BRITE	P32	17	26		0



# First Study with SES

## 1-Year Clinical Event

■ Brazil (n=25) ■ Rotterdam (n=16) ■ Pooled data (n=41)

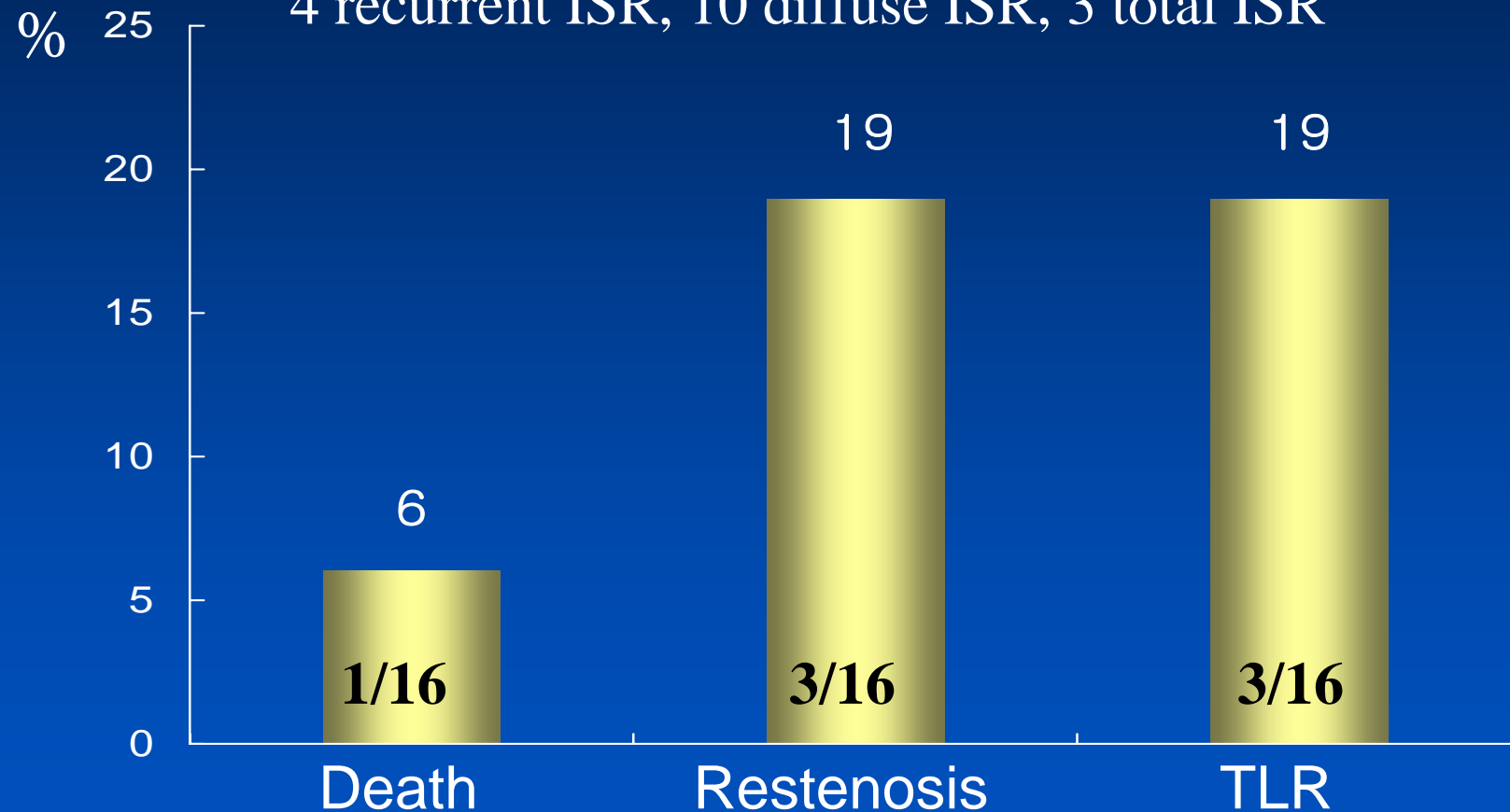


*K Tanabe, Circulation 2003;107*

# SES for Very Complex ISR

## 9-Month Results in 16 patients

4 recurrent ISR, 10 diffuse ISR, 3 total ISR



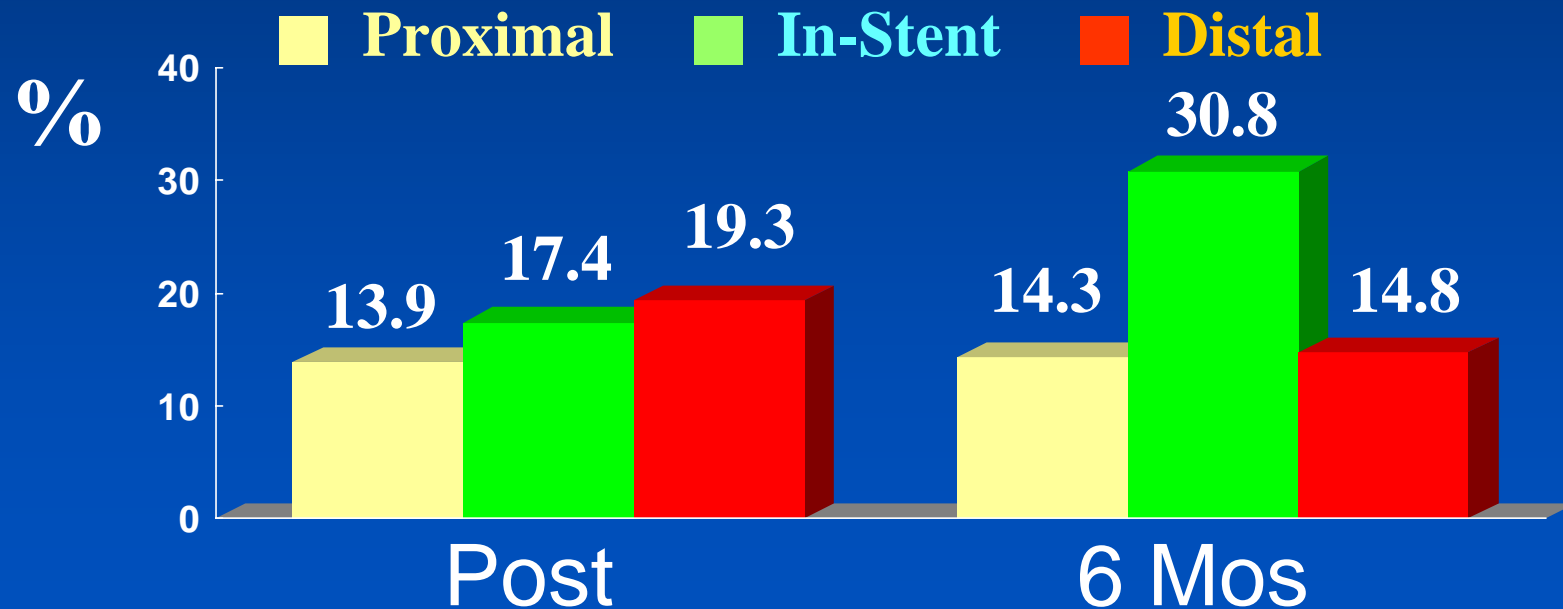
*Degertekin M, JACC 2003;41:184*

# TAXUS III for ISR

2 Clinical Centers (n=28 pts)

Re-Restenosis = 4 / 25 (16%)

## Percent diameter stenosis



*K Tanabe, Circulation 2003;107*

# ISR of BMS

## DES vs. Brachytherapy

# Treatment of IN-stent restenosis with Drug-Eluting stent versus intracoronary bEta-raDiation INDEED Study

Seung-Jung Park,<sup>1</sup> Seung-Wook Park,<sup>1</sup> Young-Hak Kim,<sup>1</sup>  
Seung-Whan Lee,<sup>1</sup> Cheol Whan Lee,<sup>1</sup> Myeong-Ki Hong,<sup>1</sup>  
Jae-Joong Kim,<sup>1</sup> Bon Kwon Koo,<sup>2</sup> Myoung Mook Lee,<sup>2</sup>  
for the INDEED Study investigators

<sup>1</sup> Asan Medical Center, University of Ulsan College of Medicine

<sup>2</sup> Seoul National University Hospital

# Study Algorithm

From March 2003 to July 2004

**Diffuse ISR (n=129)**

**Randomization (1:1)**

**Cutting balloon angioplasty**

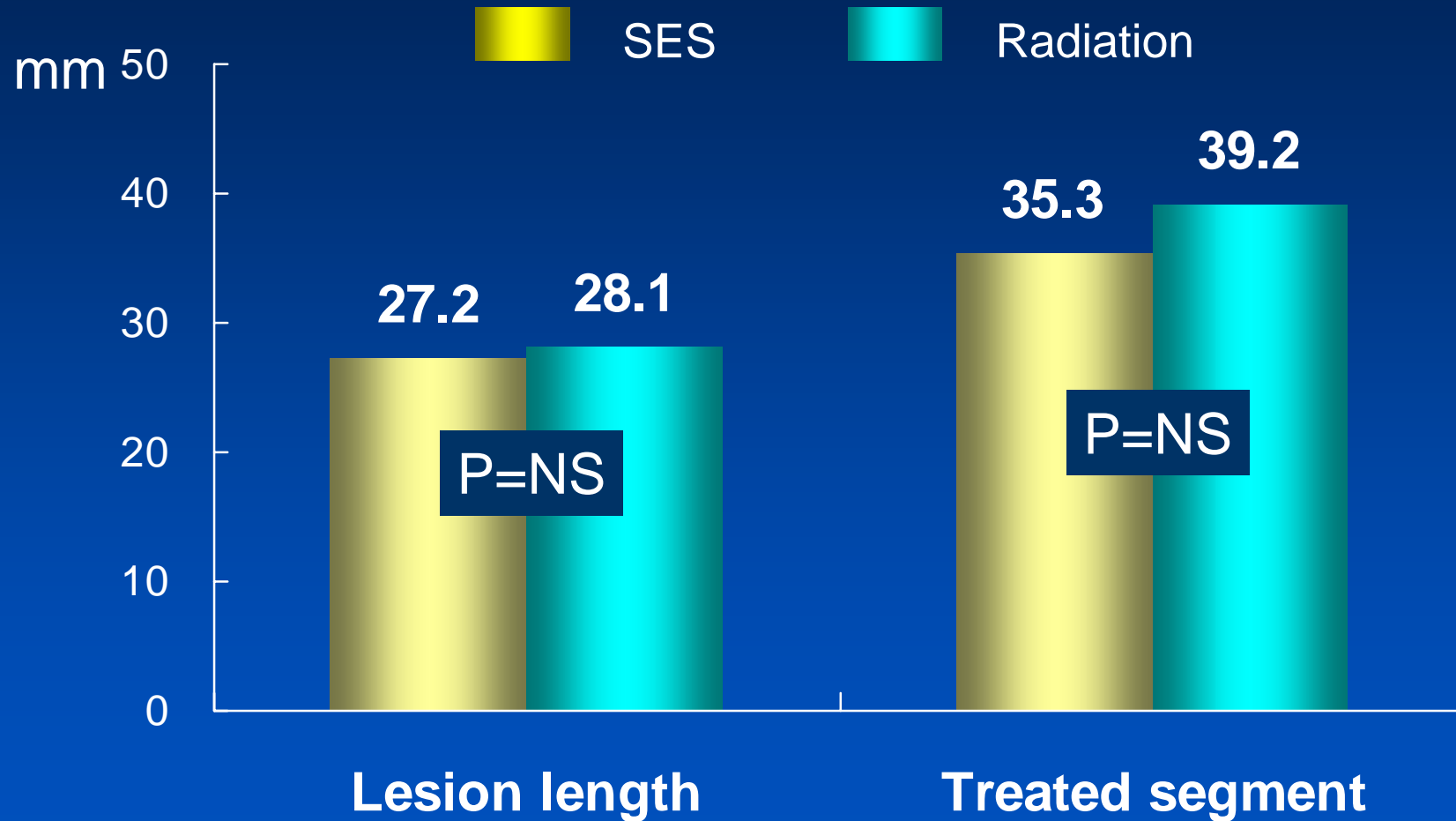
**Sirolimus-Eluting Stent  
(n=65, SES group)**

**\* Coronary Brachytherapy  
(n=64, RT group)**

6-month angiographic and  
1-year clinical follow-up

\* One patient failed to receive RT due to isotope spillage before RT

# Lesion Length & Treated Segment



INDEED

# QCA after Procedure

	SES (n=65)	RT (n=64)	<i>p</i>
<b>MLD, mm</b>			
Proximal edge	2.86±0.49	2.86±0.56	0.959
In-stent	2.49±0.47	2.20±0.47	0.0007
Distal edge	2.58±0.60	2.52±0.57	0.561
In-segment	2.30±0.55	2.10±0.48	0.034
<b>Acute gain</b>			
In-stent	1.72±0.57	1.39±0.49	0.0006
In-segment	1.52±0.59	1.29±0.50	0.0165

Values are given as n(%) and mean±SD





INDEED

# In-Hospital Outcomes

	SES	RT	P
Patients	65	64	
Death	0	0	1.0
Myocardial infarction	1 (1.5)	2 (3.1)	0.619
Q-MI	0	0	
Non-Q MI	1 (1.5)	2 (3.1)	
Stent thrombosis	0	0	1.0
TLR	0	0	1.0

Values are given as n(%)



INDEED

# QCA at Follow-up

	SES (n=49)	RT (n=54)	<i>p</i>
<b>F/U rate</b>	75%	84%	
<b>MLD, mm</b>			
Proximal edge	2.83±0.44	2.62±0.58	0.147
In-stent	2.29±0.63	1.78±0.75	0.0003
Distal edge	2.64±0.61	2.25±0.65	0.0024
In-segment	2.17±0.68	1.53±0.70	<0.0001

Values are given as n(%) and mean±SD



# QCA at Follow-up

INDEED

	SES (n=49)	RT (n=54)	<i>p</i>
<b>DS, %</b>			
Proximal edge	17.55±10.65	18.32±19.69	0.8280
In-stent	20.55±17.60	32.27±27.66	0.0112
Distal edge	13.35±12.98	18.35±21.18	0.152
In-segment	25.26±16.75	41.20±26.42	0.0004

Values are given as n(%) and mean±SD



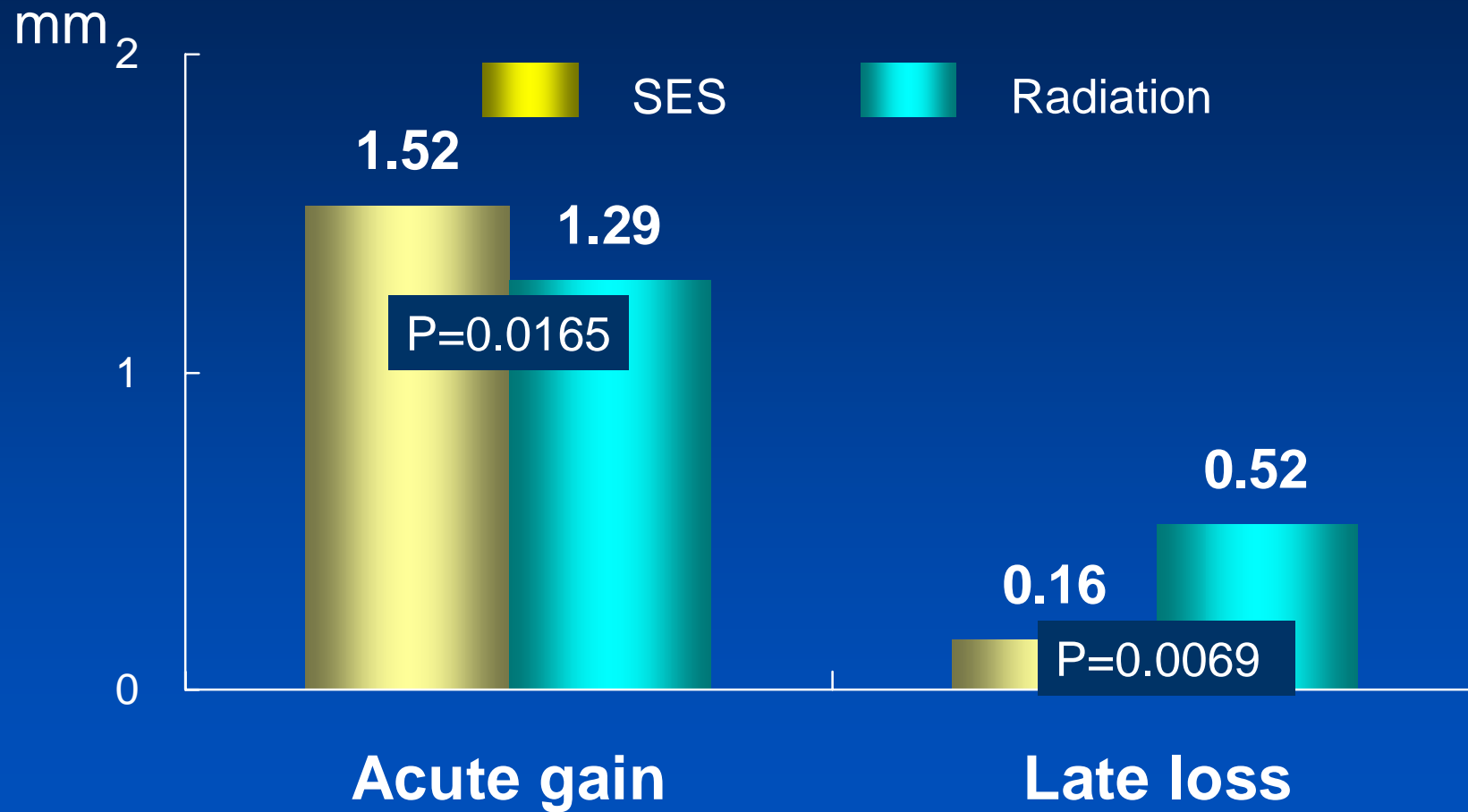
# QCA at Follow-up

INDEED

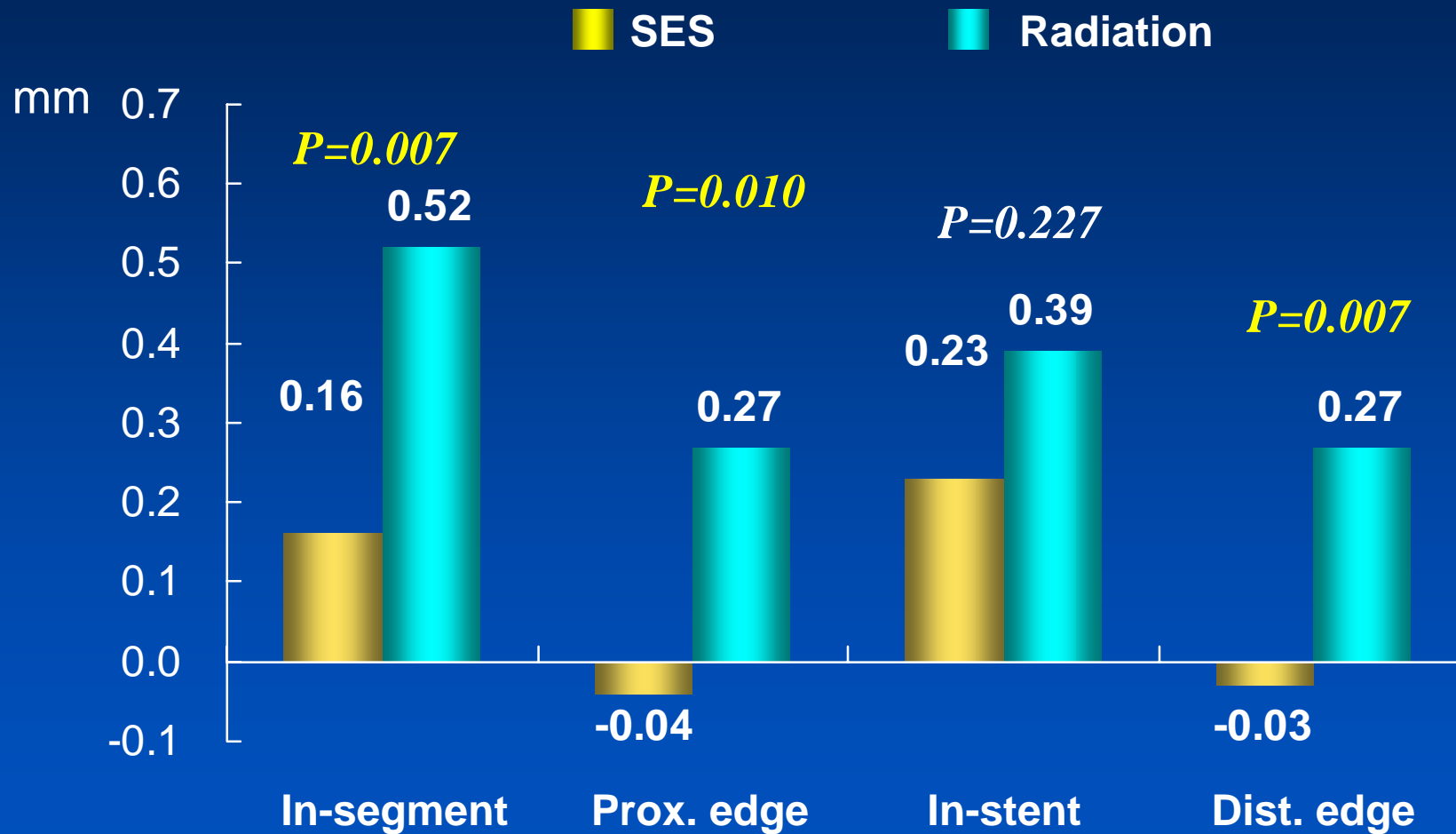
	SES (n=49)	RT (n=54)	<i>p</i>
<b>Late loss, mm</b>			
Proximal edge	-0.04±0.34	0.27±0.65	0.0095
In-stent	0.23±0.60	0.39±0.72	0.2269
Distal edge	-0.03±0.42	0.27±0.64	0.0057
In-segment	0.16±0.57	0.52±0.70	0.0069
<b>Loss index, In-segment</b>	0.13±0.60	0.43±0.82	0.0323
<b>Loss index, In-stent</b>	0.12±0.35	0.30±0.82	0.1480

Values are given as n(%) and mean±SD

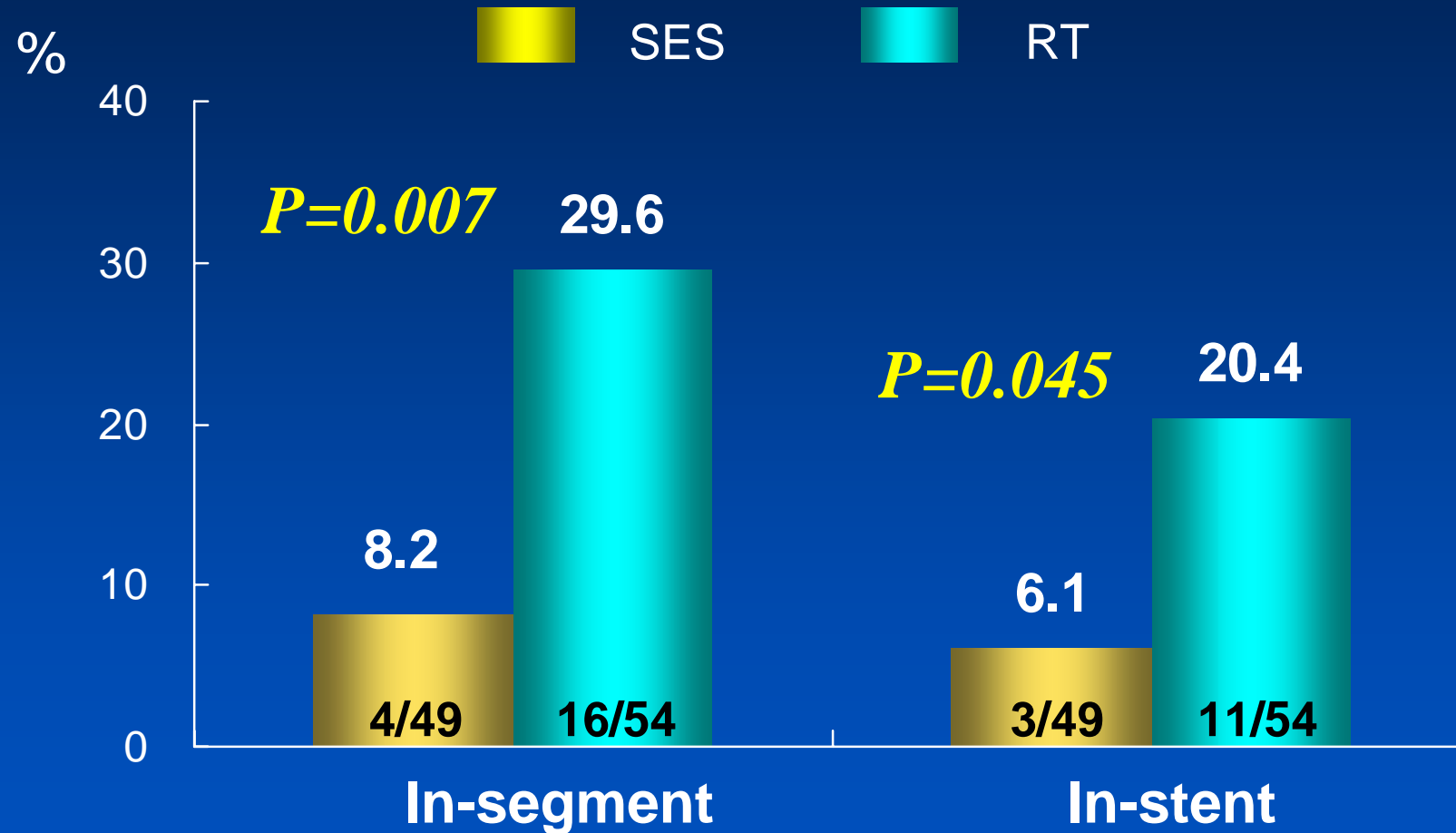
# Acute Gain & Late Loss In-segment



# Late Loss at 6 Months



# Restenosis Rates at 6 Months



# Clinical Outcomes at 1 Year

	SES	RT	P
Patients	65	64	
Death	2 (3.1)	0	0.496
Cardiac	1 (1.5)	0	
Non-cardiac	1 (1.5)	0	
MI	1 (1.5) *	0	1.0
Stent thrombosis	1 (1.5) **	0	1.0
TLR	3 (4.6)	12 (18.8)	0.014
Cardiac death, MI, and TLR	5 (7.7)	12 (18.8)	0.073

\* Acute STEMI due to the occlusion of non-target vessel

\*\* Late stent thrombosis, 6 months after the index procedure



# SES vs. RT

## SISR Study

From Feb 2003 to July 2004

**Bare metal ISR (n=374)**

Randomization (2:1)

**Cutting balloon angioplasty**

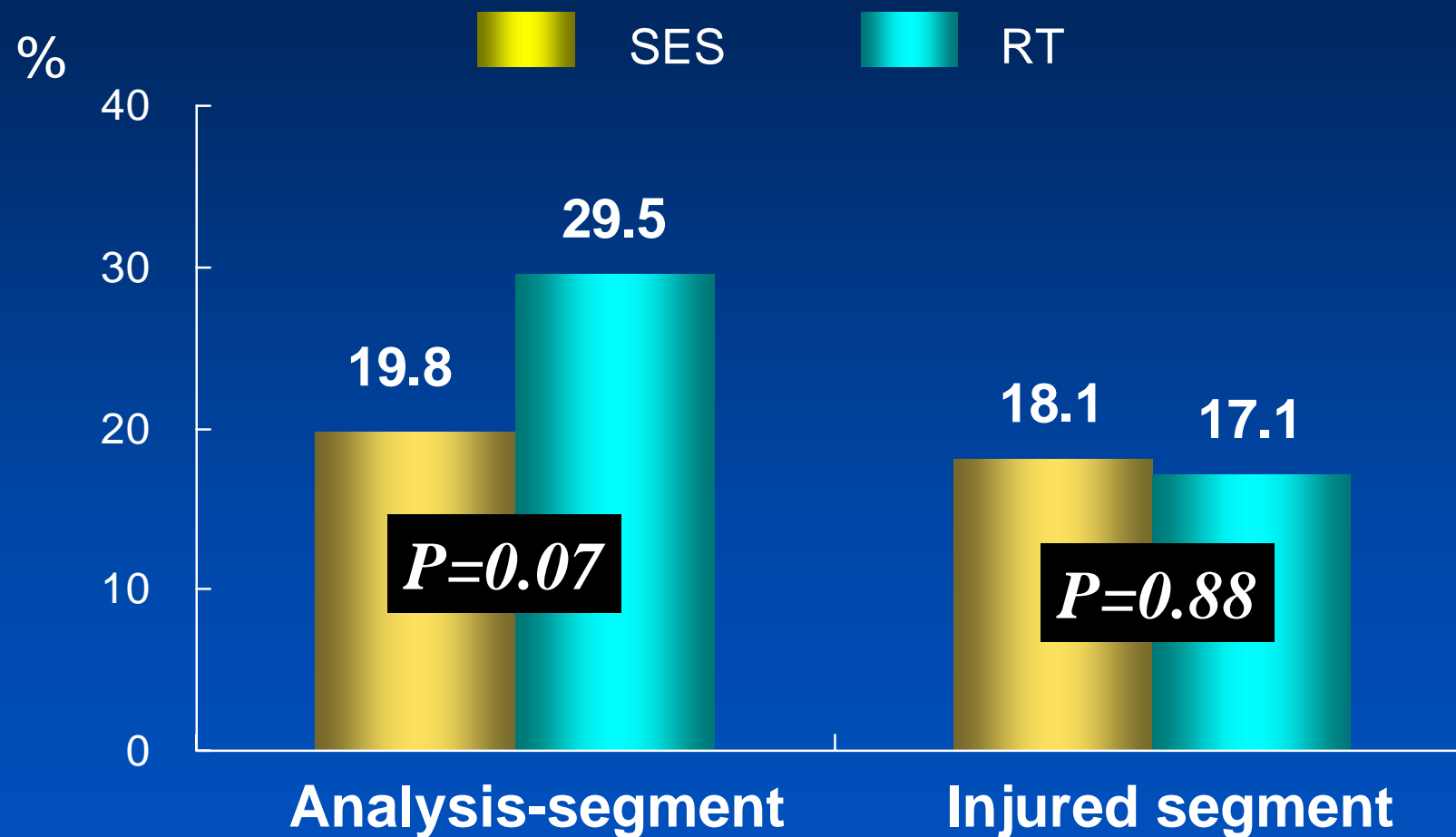
**Sirolimus-Eluting Stent  
(n=259, SES group)**

**Coronary Brachytherapy  
(n=125, RT group)**

9-month target vessel failure (cardiac death,  
myocardial infarction, target vessel revascularization)

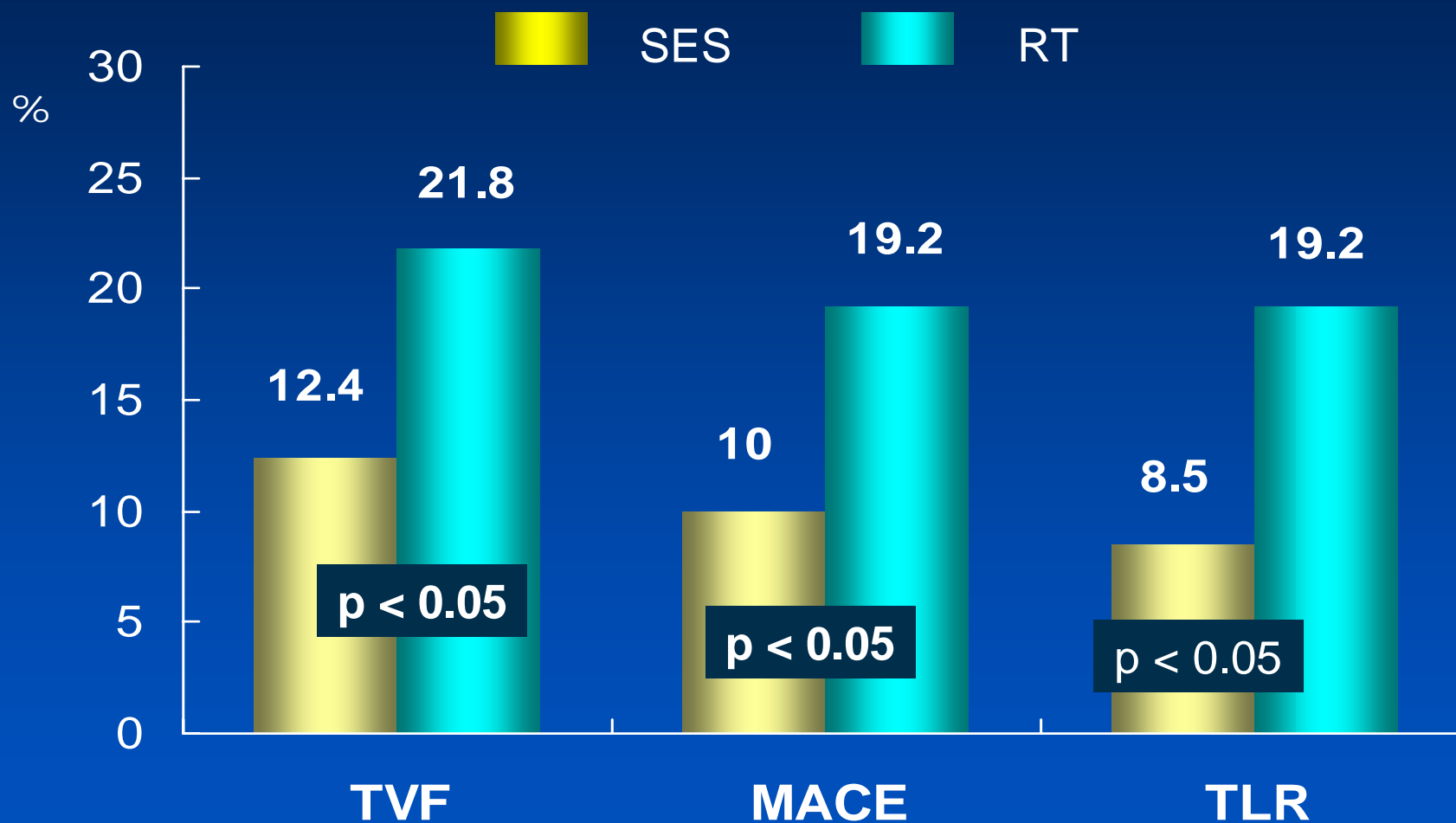
*Holmes D, et al. JAMA 2006;295:1307-9*

# Restenosis Rates at 6 Months



*Holmes D, et al. JAMA 2006;295:1307-9*

# 9-Month Clinical Outcomes



*Holmes D, et al. JAMA 2006;295:1307-9*

# PES vs. RT

## TAXUS V ISR Study

From June 2003 to July 2004

**Bare metal ISR (n=396)**

Randomization (1:1)

**Cutting balloon angioplasty**

**Paclitaxel-Eluting Stent  
(n=195, PES group)**

**Beta radiation  
(n=201, RT group)**

9-month ischemia driven target vessel revascularization

*Stone GW, et al. JAMA 2006;295:1253-1263*

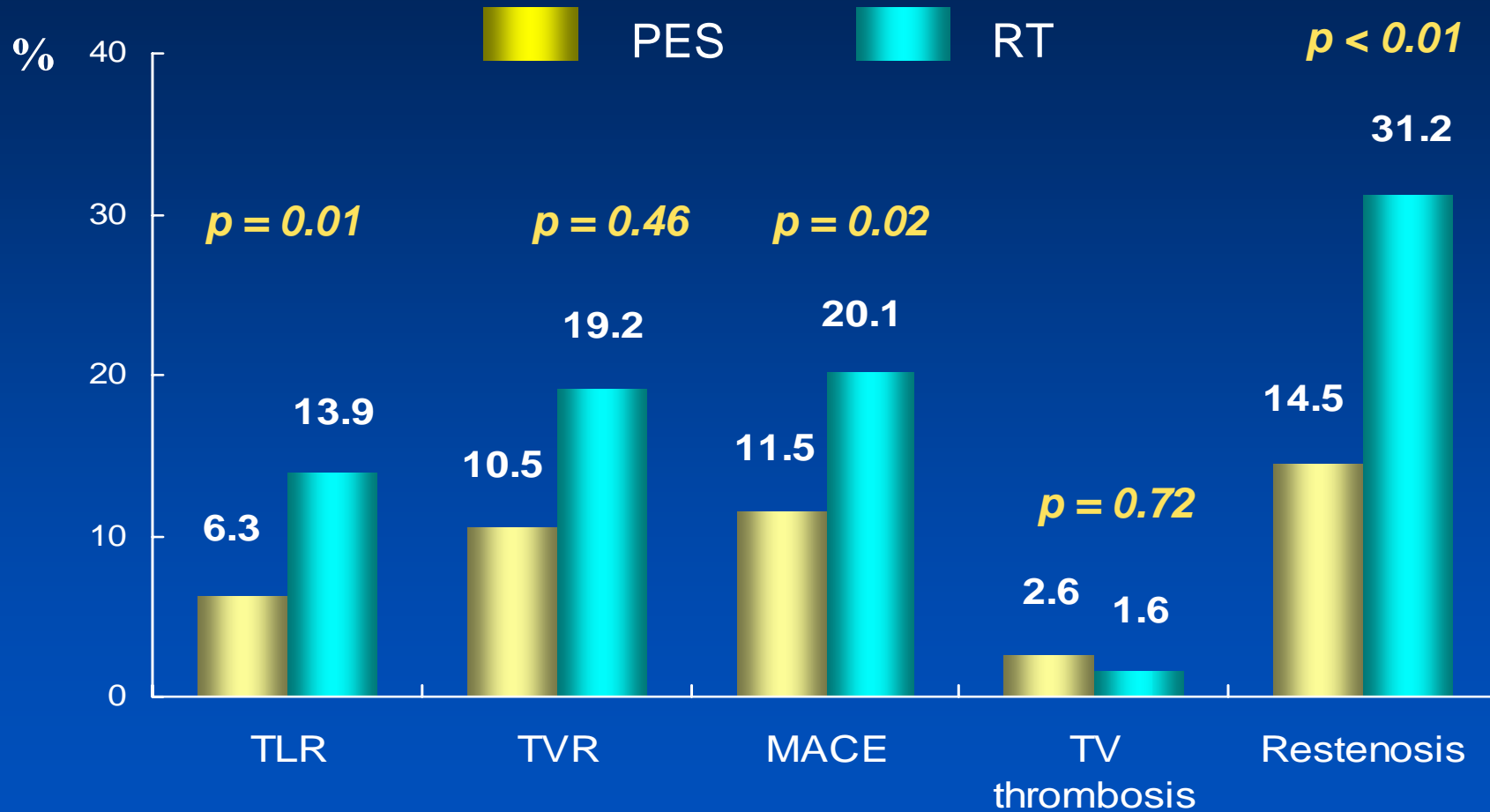


# Baseline Characteristics

	TAXUS (n=195)	RT (n=201)	P
Reference vessel, mm	2.58	2.61	0.29
Lesion length, mm	15.9	15.0	0.14
LAD lesion (%)	39.2	33.3	0.23
Type C lesion (%)	2.07	2.52	0.91
ISR pattern (%)			
- Focal	18.6	29	0.015
- Diffuse	60.8	47	0.006
- Proliferative	19.1	23.5	0.28
- Total occlusion	1.0	0.5	0.62

*Stone GW, et al. JAMA 2006;295:1253-1263*

# 9-Month Clinical Outcomes



Stone GW, et al. JAMA 2006;295:1253-1263

# Six-Month Angiographic and Long-Term Outcomes after Sirolimus-Eluting Stent Implantation for Diffuse In-Stent Restenosis: Comparison with Brachytherapy

Comparison of the 6-month and 2-year outcomes of sirolimus-eluting stent implantation versus  $\beta$ -radiation therapy with  $^{188}\text{Re-MAG}_3$ - filled balloon for diffuse ISR in a prospective manner.

# SES vs. Brachytherapy

Diffuse ISR (n=362)

Cutting or Rotablation or  
simple balloon

Sirolimus-Eluting Stent  
(n=120, SES group)

Historical control

\*  
Coronary Brachytherapy  
(n=242, RTx group)

Radiation dose of *15, 18 Gy at a  
depth of 1.0 mm* into the vessel wall

Six-month Angiography follow-up  
2-year Clinical follow-up including death, MI, TLR



# Baseline QCA Results

	SES	RTx	P
Patients	120	242	
Reference diameter, mm	2.98±0.52	2.91±0.43	0.154
Lesion length, mm	25.1±14.2	24.5±10.4	0.150
MLD, mm	0.74±0.61	0.73±0.40	0.380
DS, %	75.1±13.9	74.9±13.5	0.280

# QCA Results after Procedure

	SES	RTx	P
Patients	120	242	
MLD, mm	2.97±0.50	2.64±0.43	<0.001
DS, %	-0.5±14.3	8.32±14.0	<0.001
Acute gain, mm	2.23±0.62	1.91±0.54	<0.001

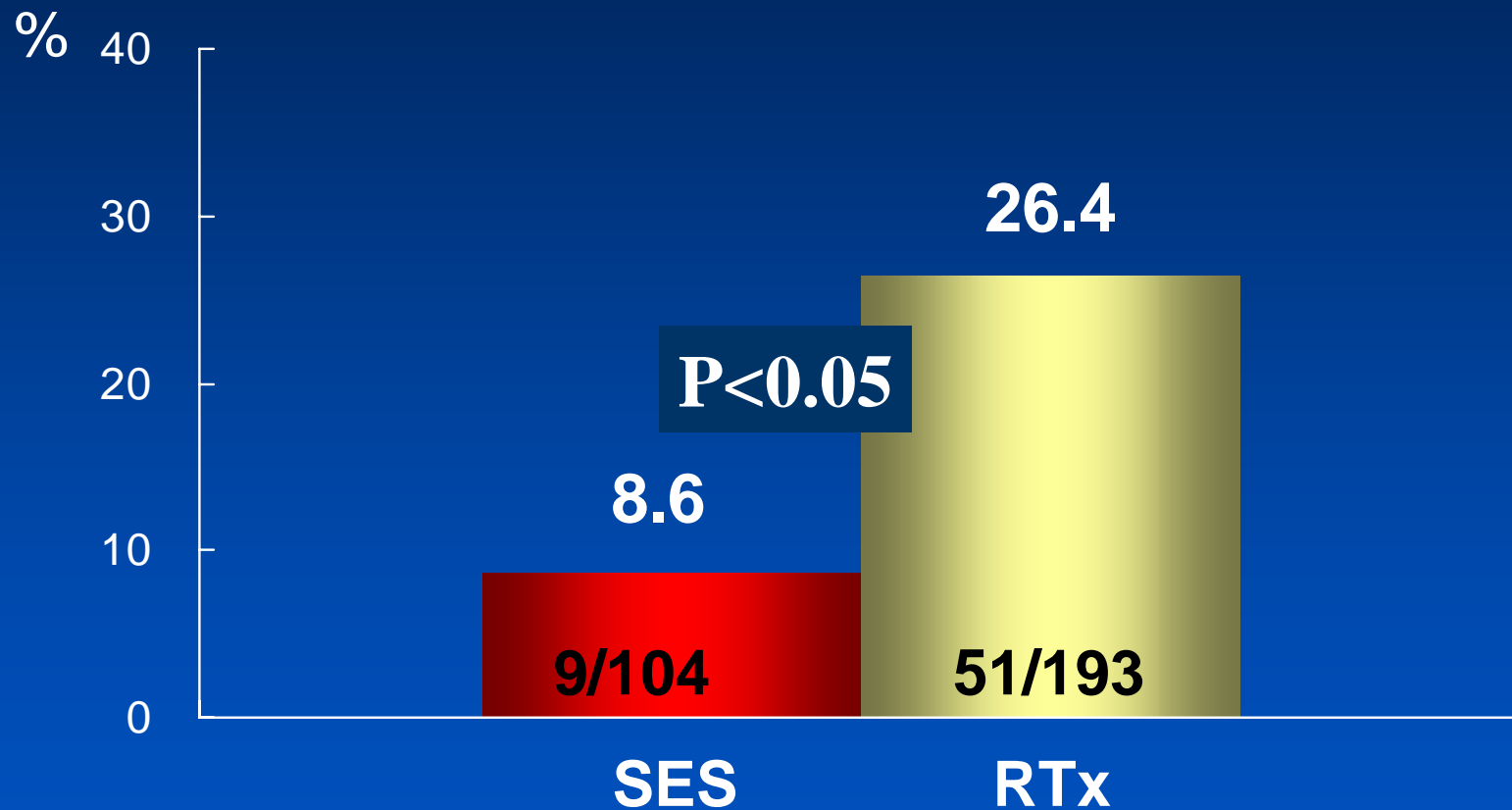
# In-Hospital Outcomes

	SES	RTx	P
<b>Patients</b>	<b>120</b>	<b>242</b>	
<b>Angiographic success</b>	<b>100 (100)</b>	<b>242 (100)</b>	<b>1.0</b>
<b>Death</b>	<b>0</b>	<b>0</b>	<b>1.0</b>
<b>Myocardial infarction</b>	<b>1 (0.8)</b>	<b>1 (0.4)</b>	<b>1.0</b>
<b>Q-MI</b>	<b>0</b>	<b>0</b>	
<b>Non-Q MI</b>	<b>1 (0.8)</b>	<b>1 (0.4)</b>	
<b>Stent thrombosis</b>	<b>0</b>	<b>0</b>	<b>1.0</b>
<b>TLR</b>	<b>0</b>	<b>0</b>	<b>1.0</b>

# QCA at Follow-up

	SES	RTX	P
Angio F/U rate	104/120(86%)	193/242(80%)	
Reference, mm	2.98±0.52	2.91±0.43	0.154
MLD, mm	2.48±0.77	1.97±0.79	<0.001
DS, %	16.34±24.9	31.34±28.64	<0.001
Late loss, mm	0.50±0.55	0.67±0.81	0.042

# Restenosis Rate at 6 Months

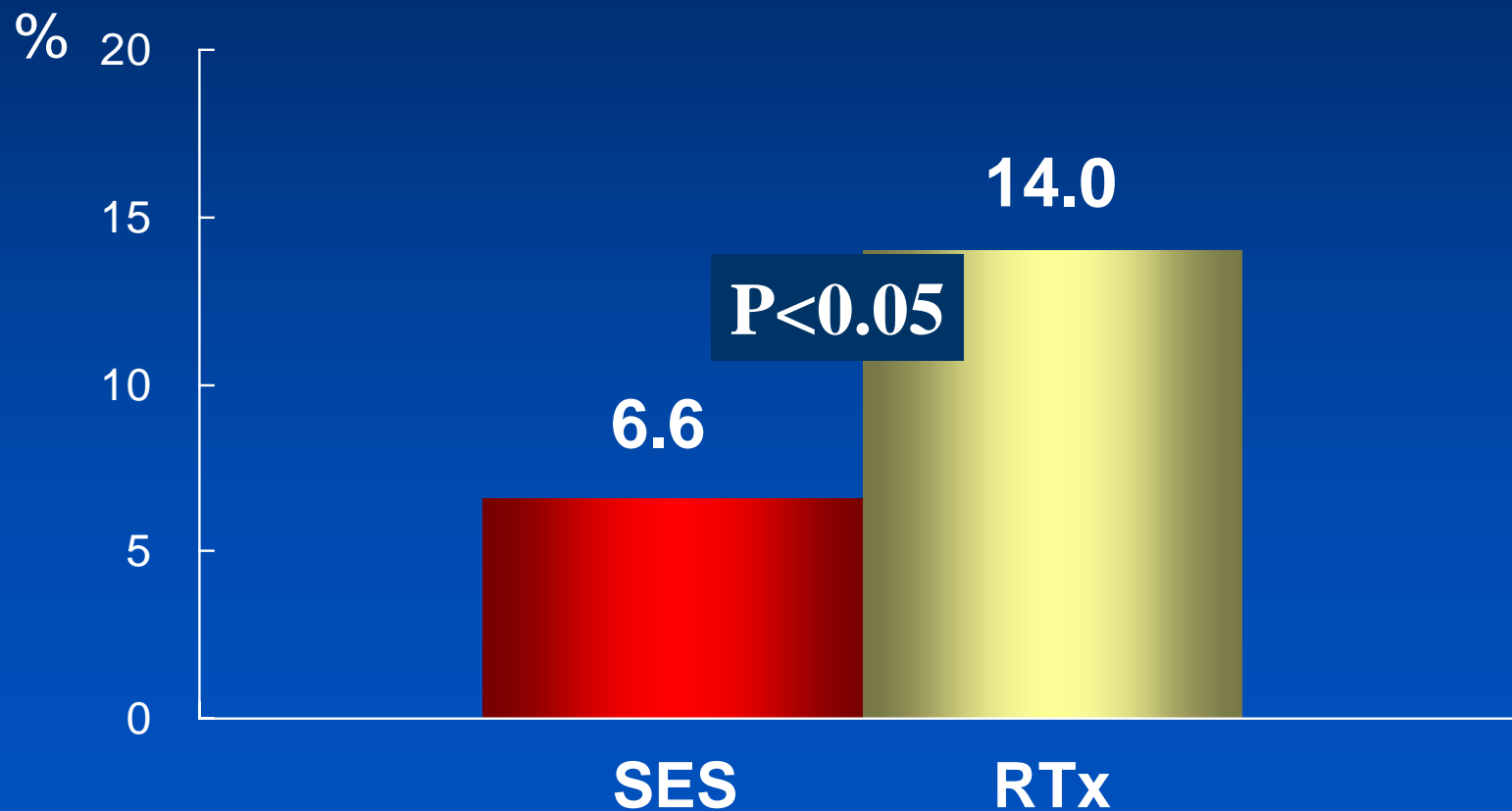


# Clinical Outcomes at 2 years

	SES	RTx	P
Patients	120	242	
Death	0.8%	0.4%	NS
MI	0.8%	0.4%	NS
<b>TLR</b>	<b>4.6%</b>	<b>13.2%</b>	<b>&lt;0.05</b>
One-year	4.6%	9.9%	<0.05
Two-year	4.6%	13.2%	<0.05

# Two-Year Clinical Outcomes

**MACE including death, MI, TLR**



# ISR of BMS

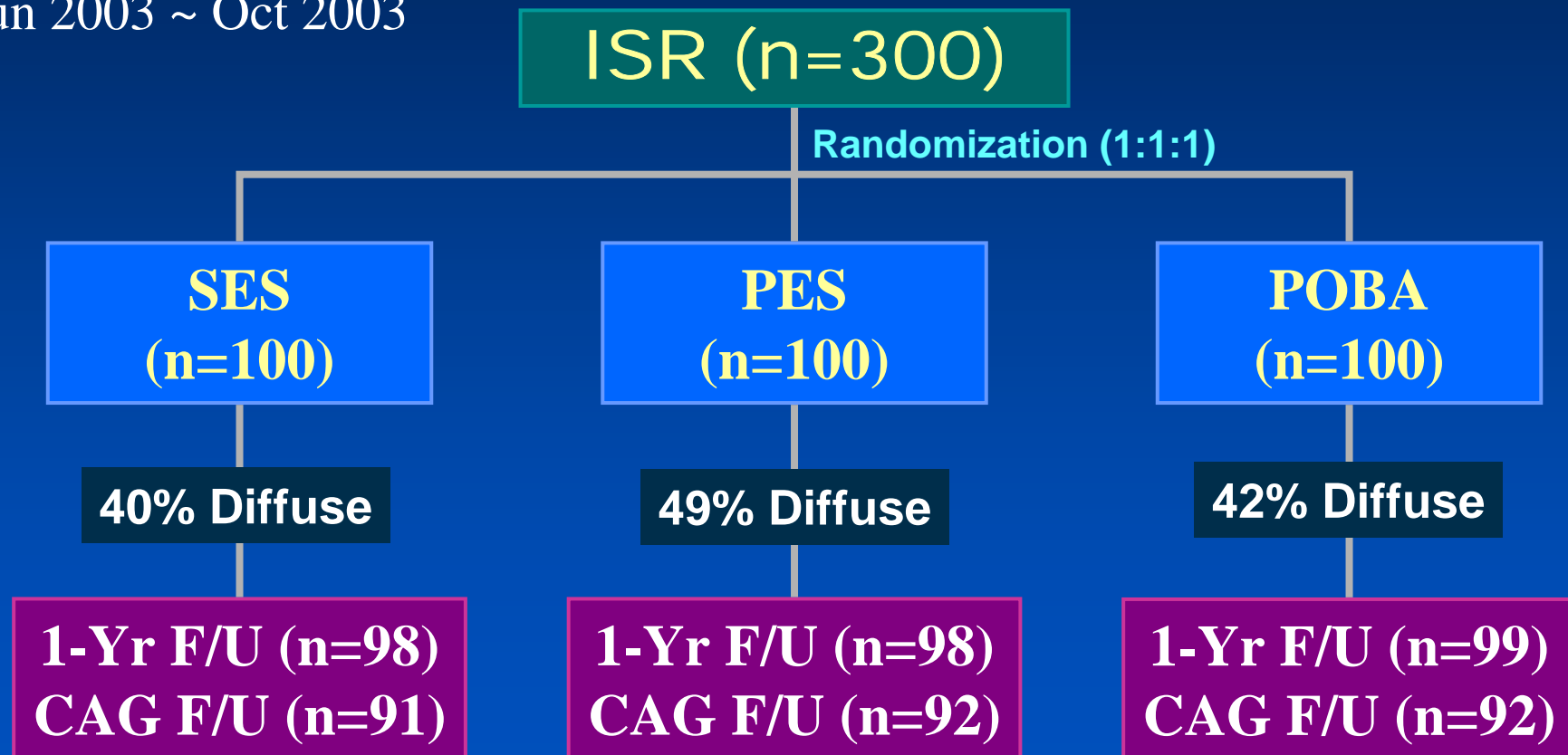
## SES vs. PES



# SES vs PES vs POBA for ISR

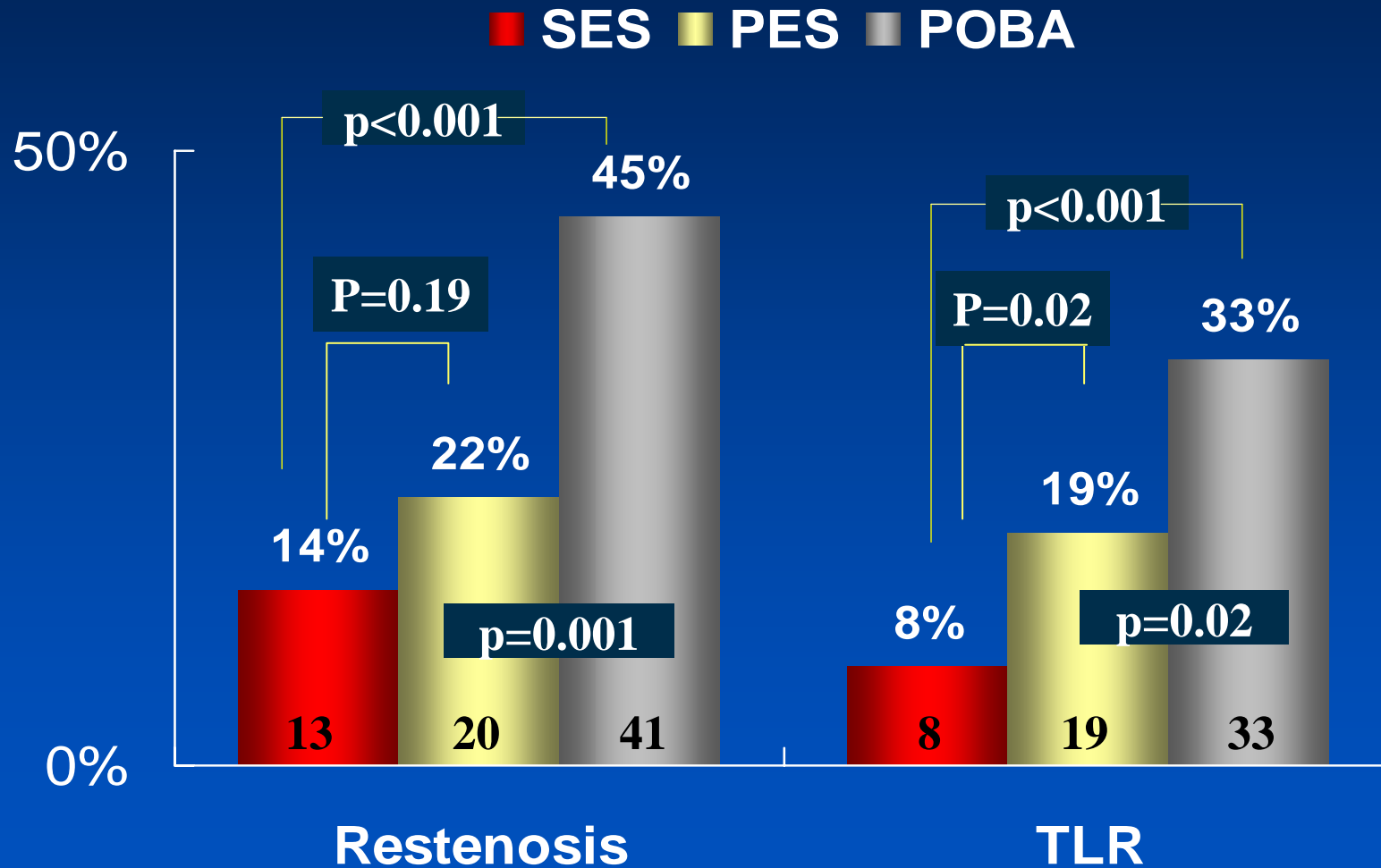
## ISAR-DESIRE study

Jun 2003 ~ Oct 2003



*A Kastrati et al. JAMA 2005;293:165*

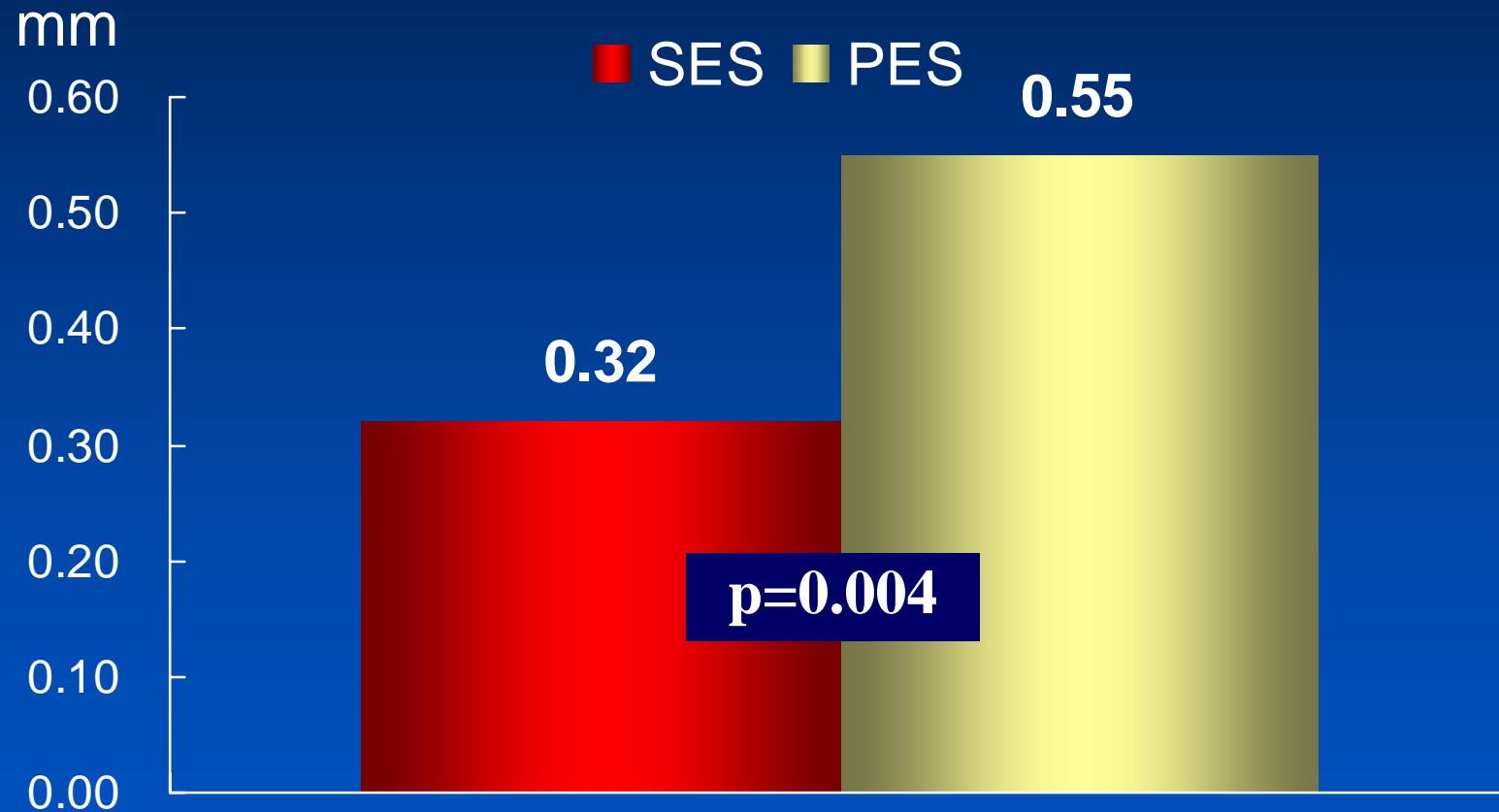
# Restenosis and TLR Rates



*A Kastrati et al. JAMA 2005;293:165*

# SES vs PES

## In-segment Late loss of SES and PES



Late loss

*A Kastrati et al. JAMA 2005;293:165*

# Conclusions

- The superiority of DES for bare-metal ISR is derived from the greater acute gain and similar to or lower late loss than that of brachytherapy.
- Drug-eluting stent has become the first-line therapy for bare-metal ISR replacing the brachytherapy.

# Conclusions

- Among the DESs, the SES may be more effective in reducing the recurrent restenosis and improving clinical outcomes in treatment of bare-metal ISR.
- The superiority of SES over brachytherapy for treatment of bare-metal ISR was maintained to 2 years.

# ISR of DES

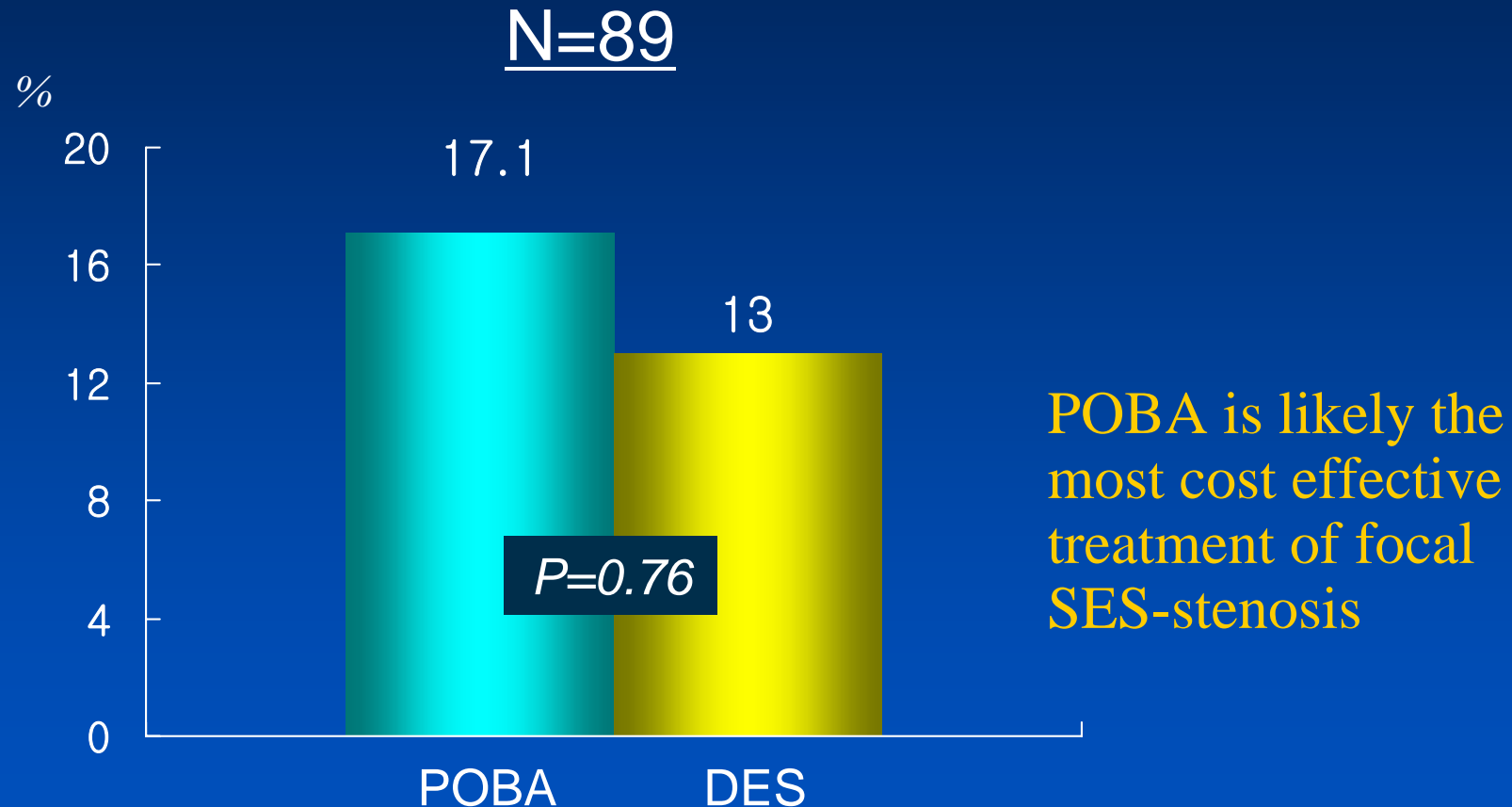
# Treatment of DES failure

Very little information about the results of ...

- Balloon angioplasty
- Cutting balloon angioplasty
- Repeat stenting
- Debulking
- Intracoronary brachytherapy
- Drug eluting stent

# Focal SES Restenosis

## Target lesion revascularization



*Melzi G, et al. Am J Cardiol 2005;96(suppl 7A): 188H*



# Brachytherapy for DES Restenosis

## RESCUE registry

### 6-month clinical follow-up

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All MACE	2 (4.0%)
Death	0 (0)
Q-wave MI	0 (0)
Non Q-wave MI	2 (4.0%)
TVR	2 (4.0%)
TLR	2 (4.0%)
Subacute thrombosis	0 (0)
Late thrombosis	0 (0)

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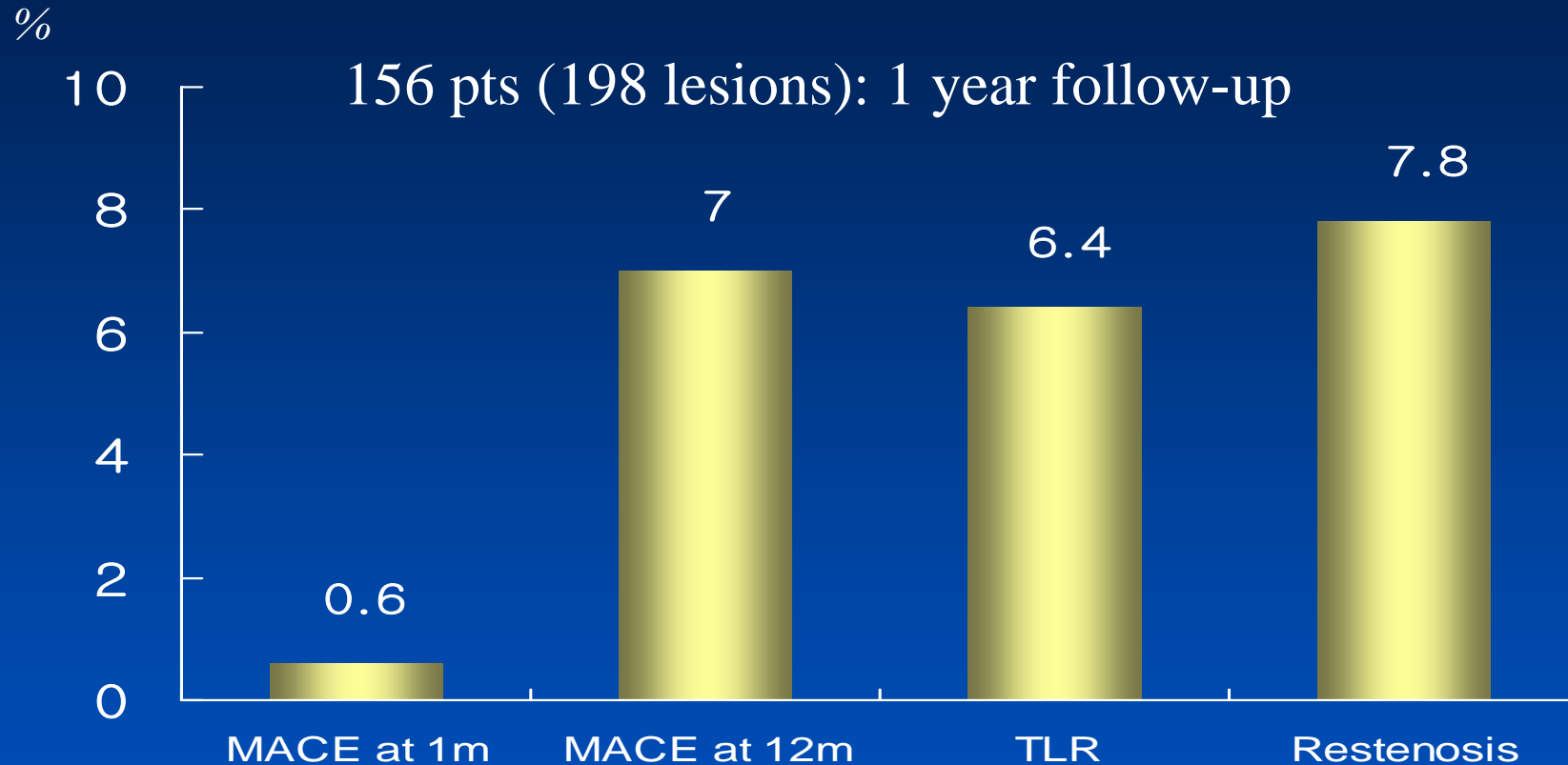
**RT as adjunct therapy to PCI for ISR of a DES is safe.**

*Torguson R, et al. Circulation 2005;112 (suppl 17): II-519*



# SES for SES Restenosis

## Asian Multicenter Registry



**The use of SES in SES-ISR was safe with low complication and low incidence of restenosis.**

*Nakamura S, et al. Circulation 2005;112(suppl 17A): II-736*

# Patterns of Cypher Restenosis

## SIRIUS

	Cypher	BMS	p
Number of ISR	31	128	
Focal	26 (84%)	55 (43%)	<0.001
Diffuse	1 (3.2%)	46 (35.9%)	<0.001
Proliferative	2 (6.5%)	17 (13.3%)	0.372
Total	2 (6.5%)	10 (7.8%)	1.00
Length of ISR, mm	9.1	14.8	<0.001
Aneurysm	2 (0.6%)	4 (1.1%)	0.686

Popma JJ et al. Circulation 2004;110:3773

# Patterns of Taxus Restenosis

## TAXUS-IV

	Taxus	BMS	p
Number of ISR	16	65	
Focal	63 %	31 %	0.04
Diffuse	19 %	58 %	<0.001
Proliferative	6 %	8 %	0.11
Total	13 %	3 %	1.00
Length of ISR, mm	9.8	15.3	0.01

Stone GW et al. New Engl J Med 2004;350:221

# TLR for SES Restenosis in SIRIUS

27 TLRs (5%) from 533 patients

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Bypass surgery	4 (14.8%)
Repeat PCI	23 (85.2%)
BMS	20 (87.0%)
Balloon	2 (8.7%)
Brachytherapy	1 (4.3%)
Recurrent TLR for 2 years	<b>6 (26%)</b>
BMS	2
Balloon	1
Brachytherapy	3

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Moses JW et al. Am J Cardiol 2004;supple 6A:130E



# Registry of Repeat PCI for SES Restenosis

## Lesion characteristics at index procedure

24 pts (27 lesions)

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De novo lesion	70%
Balloon restenosis	4%
In-stent restenosis	15%
Brachytherapy failure	11%

*Lemos PA, et al. Circulation 2004;109: 2500-2502*



# Registry of Repeat PCI for SES Restenosis Methods of PCI

24 pts (27 lesions)

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Balloon dilatation	11%
Bare-metal stenting	4%
Repeated SES implantation	44%
PES implantation	41%
Mean lesion length, mm	11.2 (6.6-17.1)
Total length of repeat stenting, mm	17(8-30)

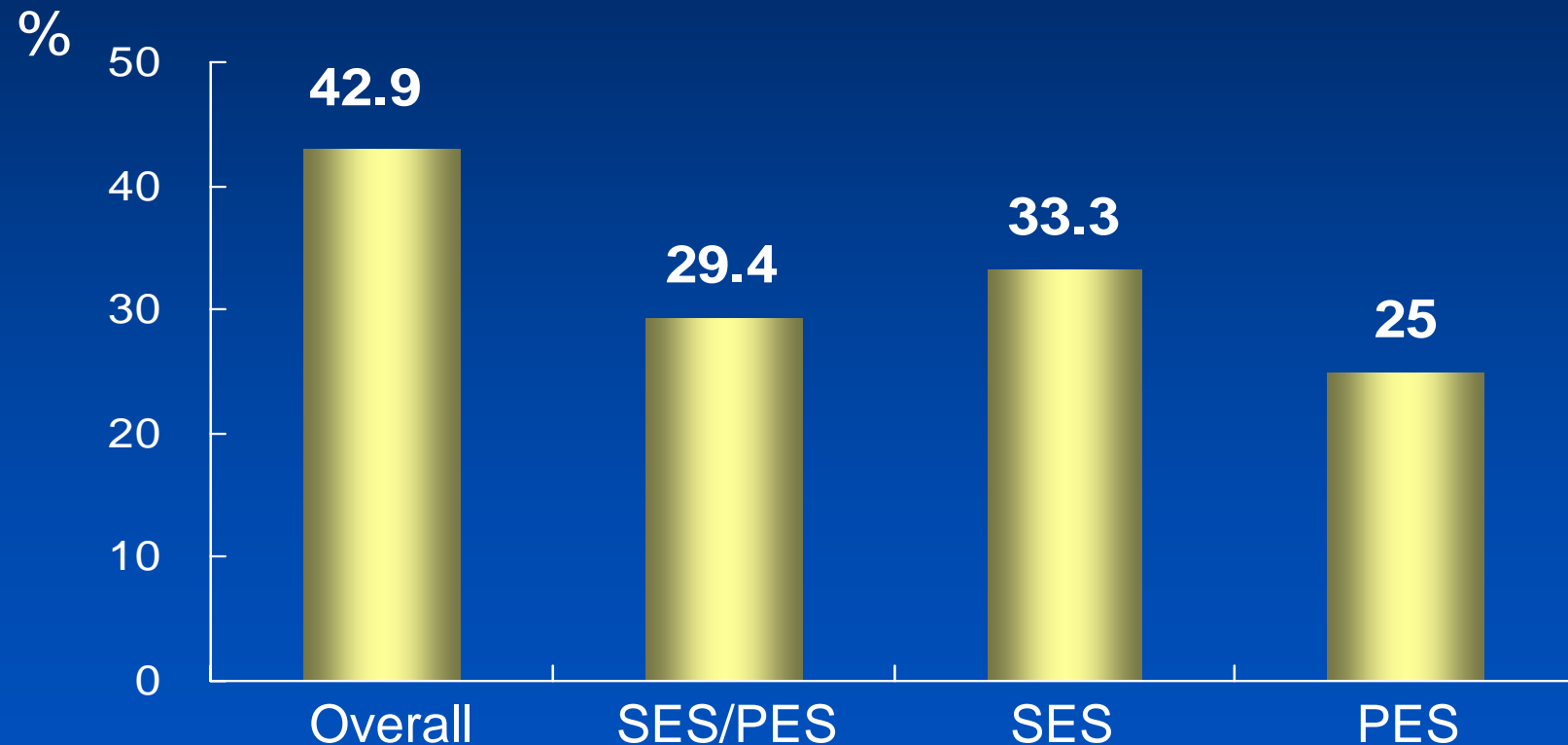
*Lemos PA, et al. Circulation 2004;109: 2500-2502*



# Registry of Repeat PCI for SES Restenosis

## Restenosis Rates (median 281 days)

(TLR: 20.8%, Event-free survival : 70.2% during 279 days)



*Lemos PA, et al. Circulation 2004;109: 2500-2502*



# Registry of Repeat PCI for SES Restenosis

## Predictors of recurrent restenosis

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Hypercholesterolemia	69% vs. 0%, p<0.01
Previous angioplasty at index procedure	67% vs. 11%, p=0.02
Failed brachytherapy	100% vs. 33%, p=0.06
SES failure treated with balloon dilatation	100% vs. 33%, p=0.06
Needing treatment before 6 months from index procedure	100% vs. 25%, p<0.01

*Lemos PA, et al. Circulation 2004;109: 2500-2502*



# Repeat PCI for DES ISR

## AMC Registry

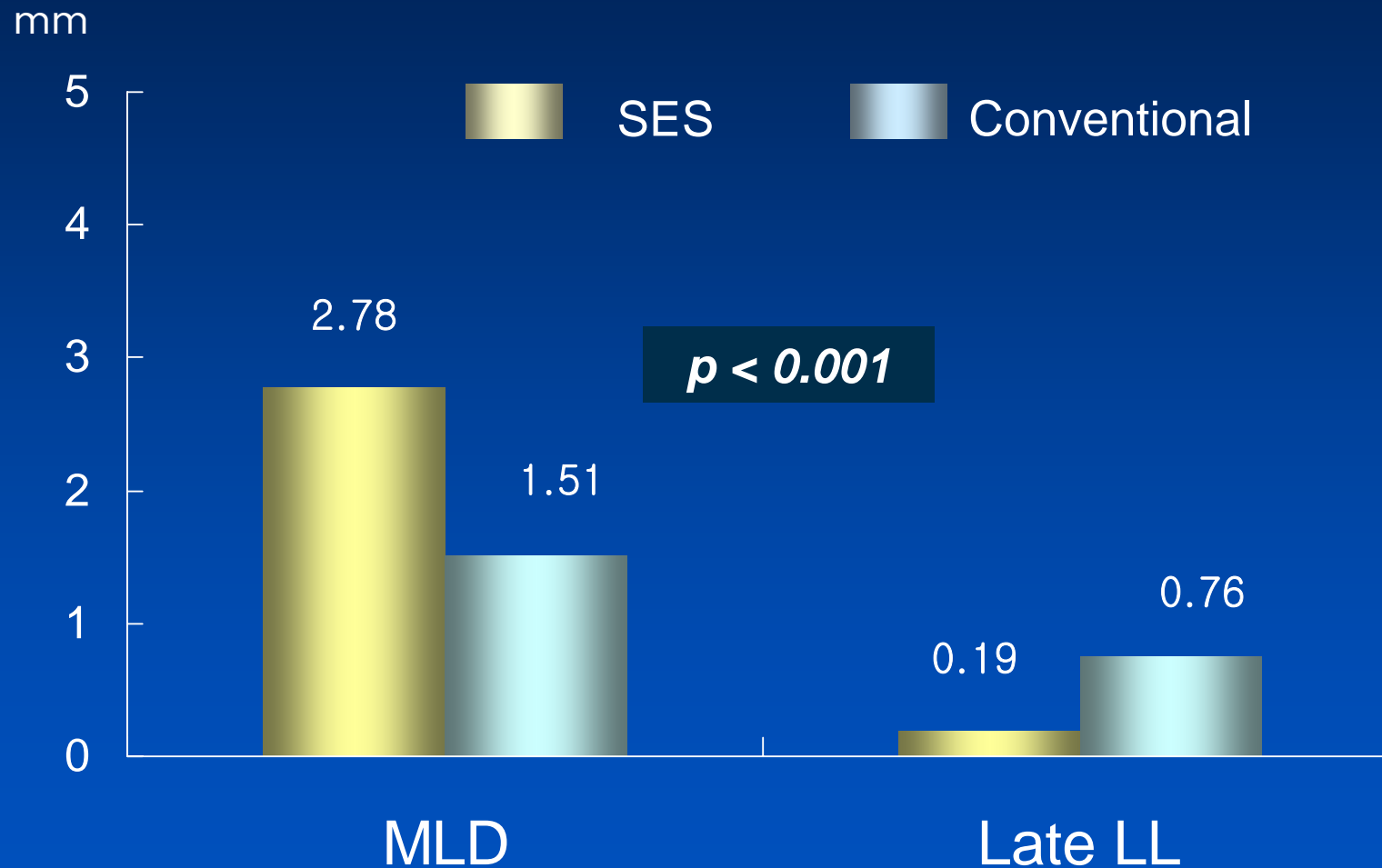
	SES (n=33)	Conventional (n=25)	p
CTO (> 3m)	2.60	2.57	1.000
ISF of BMS	12.4	12.3	0.690
Ostial	0.91	0.95	0.222
Bifurcation stenting	2.52	2.07	0.387
Use of SES	14 (42.4%)	13 (52%)	0.596
Location			0.801
LM	2 (6.1%)	1 (4.0%)	
LAD	23 (69.7%)	15 (60.0%)	
LCX	1 (3.0%)	1 (4.0%)	
RCA	7 (21.2%)	8 (32.0%)	
Total stent length (mm)	32.2 ± 15.6	40.2 ± 20.4	0.107

Conventional treatment: cutting balloon in 11 lesions and brachytherapy in 14 lesions

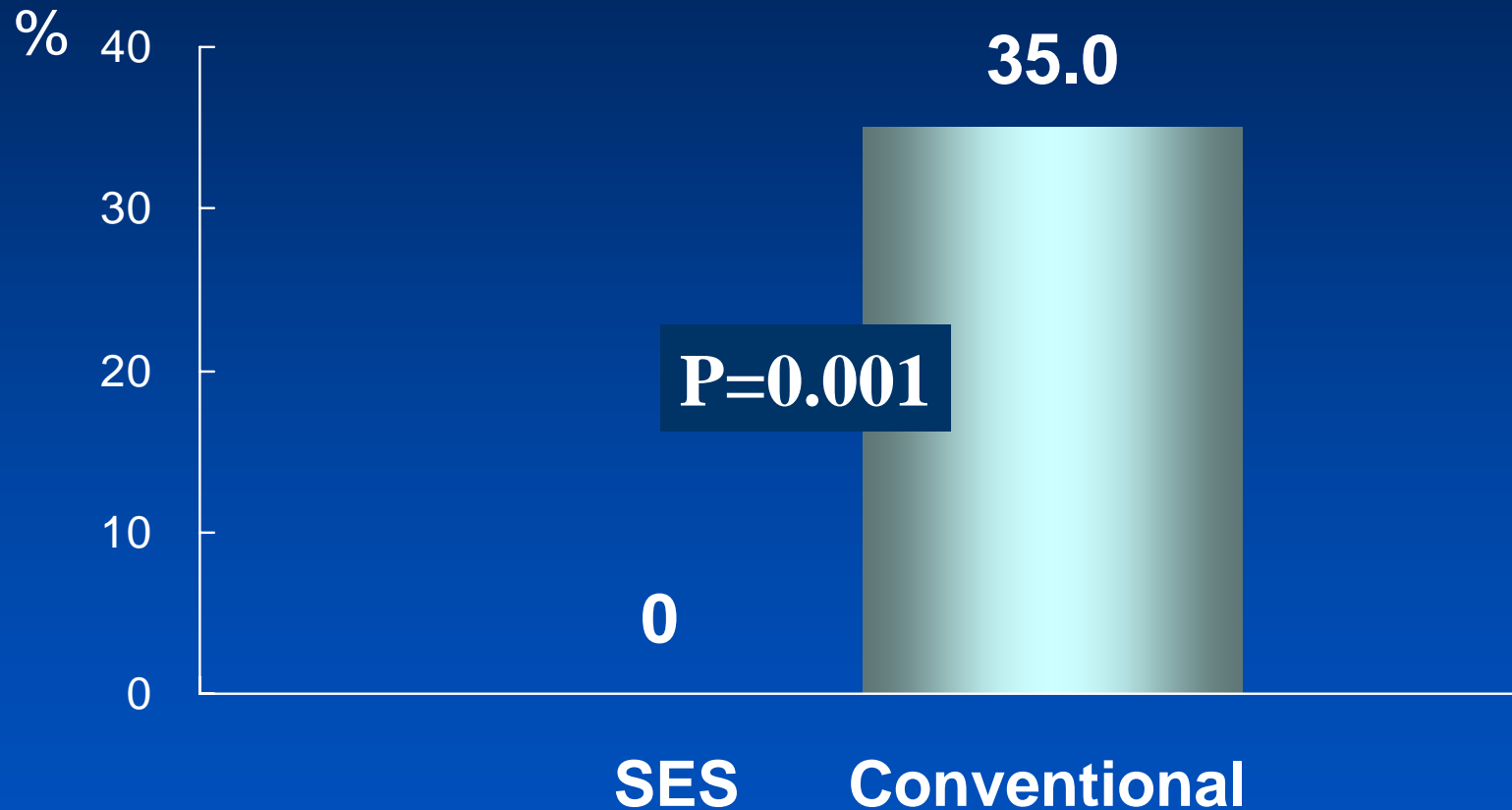
# Angiographic Characteristics

	SES (n=33)	Conventional (n=25)	p
ISR classification			
Focal	18 (54.9%)	9 (36.0%)	0.161
Diffuse	5 (15.2%)	8 (32.0%)	0.203
Proliferative	7 (21.2%)	7 (28.0%)	0.550
Total	3 (9.1%)	1 (4.0%)	0.627
Location of restenosis			
Edge	25 (75.8%)	9 (36.0%)	0.002
Intra-stent	17 (51.5%)	25 (100.0%)	< 0.001
LL, mm	14.0 ± 8.2	15.3 ± 10.8	0.606
RVD, mm	2.92 ± 0.45	2.81 ± 0.31	0.300
MLD, mm			
Before procedure	0.95 ± 0.43	0.98 ± 0.42	0.800
After procedure	2.93 ± 0.45	2.21 ± 0.31	< 0.001
Acute gain, mm	1.98 ± 0.50	1.22 ± 0.48	< 0.001

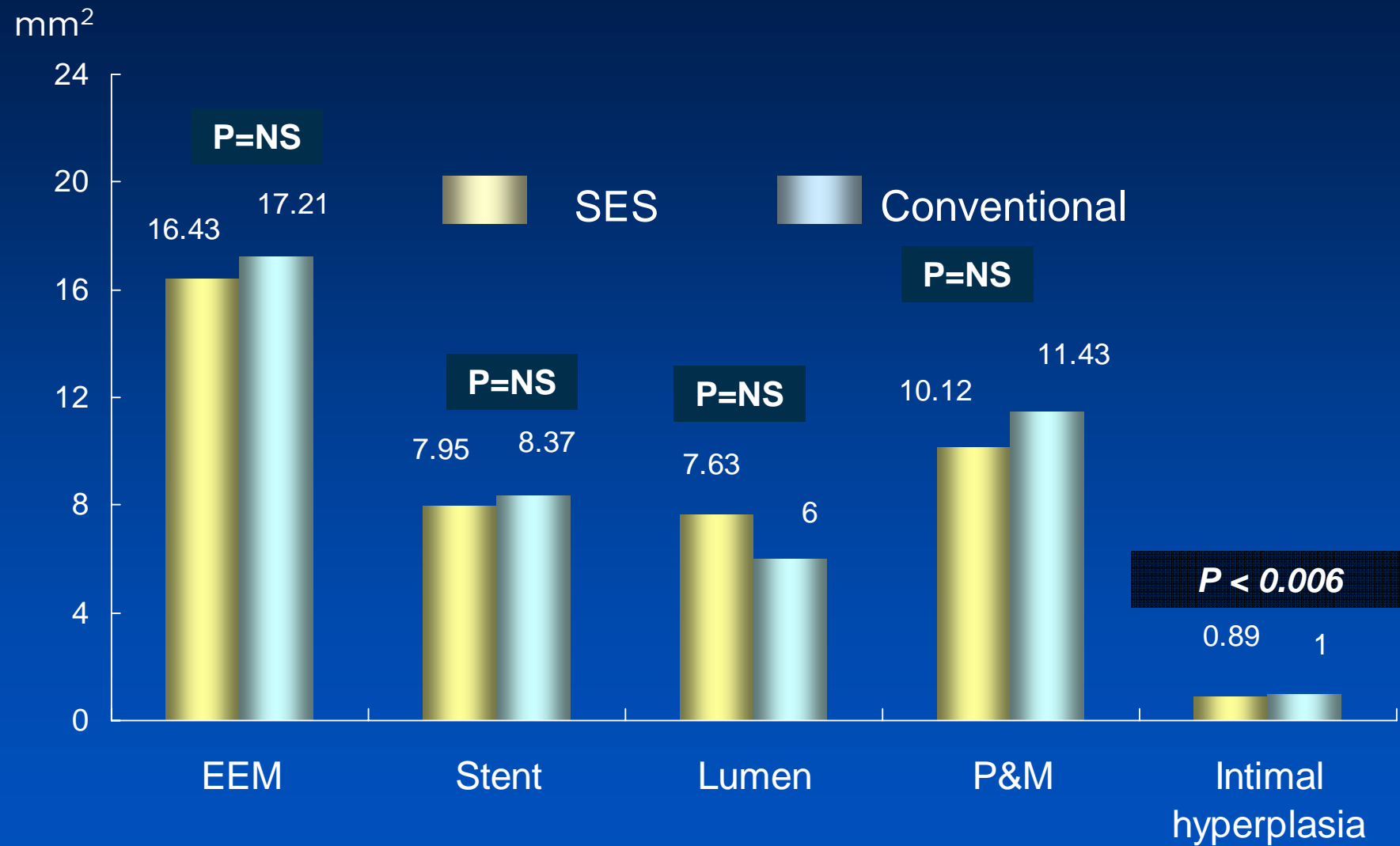
# Follow-up MLD and Late Loss



# Restenosis Rate at 6 Months



# Outcomes of IVUS Follow-up



# Subgroup Analysis of Recurrent Restenosis Rates

Variables	SES	Conventional	P value
<b>Used stent at the index procedure</b>			
Sirolimus-eluting	0/12 (0%)	2/11 (18.2%)	0.217
Paclitaxel-eluting	0/15 (0%)	5/9 (55.6%)	0.003
<b>Location of restenosis</b>			
Edge	0/22 (0%)	4/7 (57.1%)	0.001
Intra-stent	0/12 (0%)	7/20 (35.0%)	0.029
<b>Pattern of restenosis</b>			
Type I	0/16 (0%)	3/8 (37.5%)	0.028
Type II, III, and IV	0/11 (0%)	4/12 (33.3%)	0.093

# Conclusions

- The effective treatment of ISR within DES has not been sufficiently studied.
- Up to now, the effectiveness of conventional angioplasty for the focal ISR after DES may be acceptable and comparable to repeat DES implantation.



# Conclusions

- Repeat DES treatment with same or different antiproliferative agents appears to be effective treatment option for DES failure
- Further larger trial is needed for delineating the role of DES, conventional treatment or brachytherapy for treatment of DES failure.