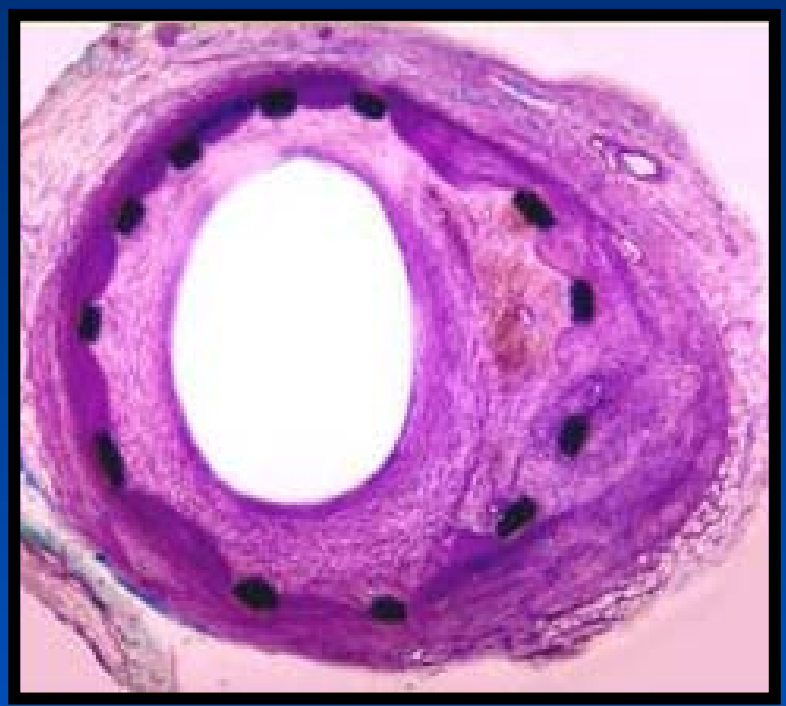
In-Stent Restenosis

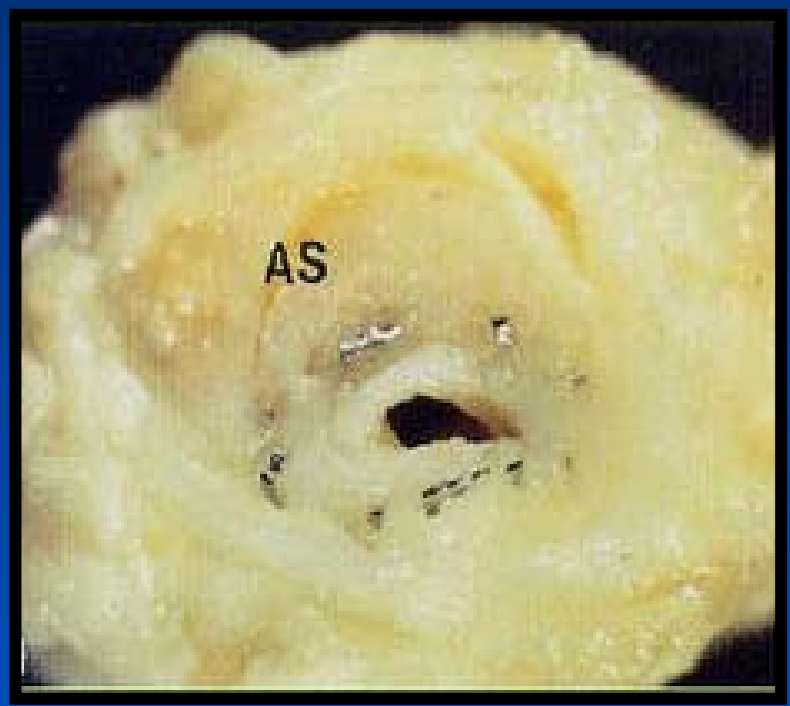
Can we kill it ?

However, In-stent Restenosis

is the most serious problem (20-25%)

More than 150,000 lesions will need treatment because of in-stent restenosis.





Varying Prevalence Rates of Restenosis with Bare Metal Stents

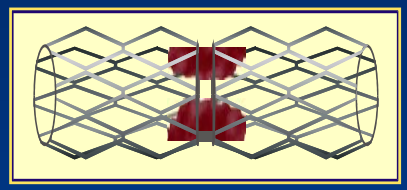
Non-Diabetic	Lesion length			
Post-procedure In-stent MLD	10 mm	15 mm	20 mm	25 mm
2.5 mm	27%	30%	33%	37%
3.0 mm	17%	19%	22%	25%
3.5 mm	10%	12%	14%	16%
4.0 mm	6%	7%	8%	10%

Diabetic	Lesion length			
Post-procedure In-stent MLD	10 mm	15 mm	20 mm	25 mm
2.5 mm	35%	39%	43%	46%
3.0 mm	23%	26%	30%	33%
3.5 mm	15%	17%	19%	22%
4.0 mm	9%	10%	12%	14%

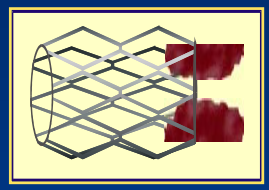
AHA 1998, CDAC K. Ho. et al.

Patterns of ISR

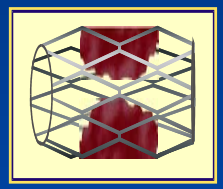
FOCAL



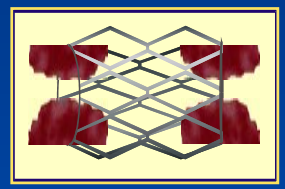
Articulation or Gap



Margin

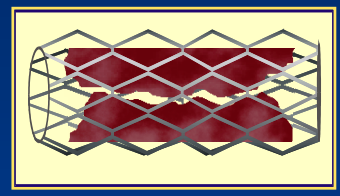


Focal Body

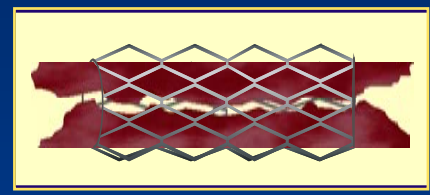


Multifocal

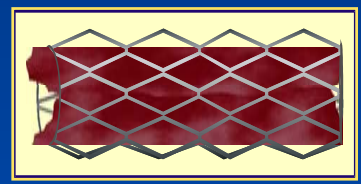
DIFFUSE



Intra-stent



Proliferative

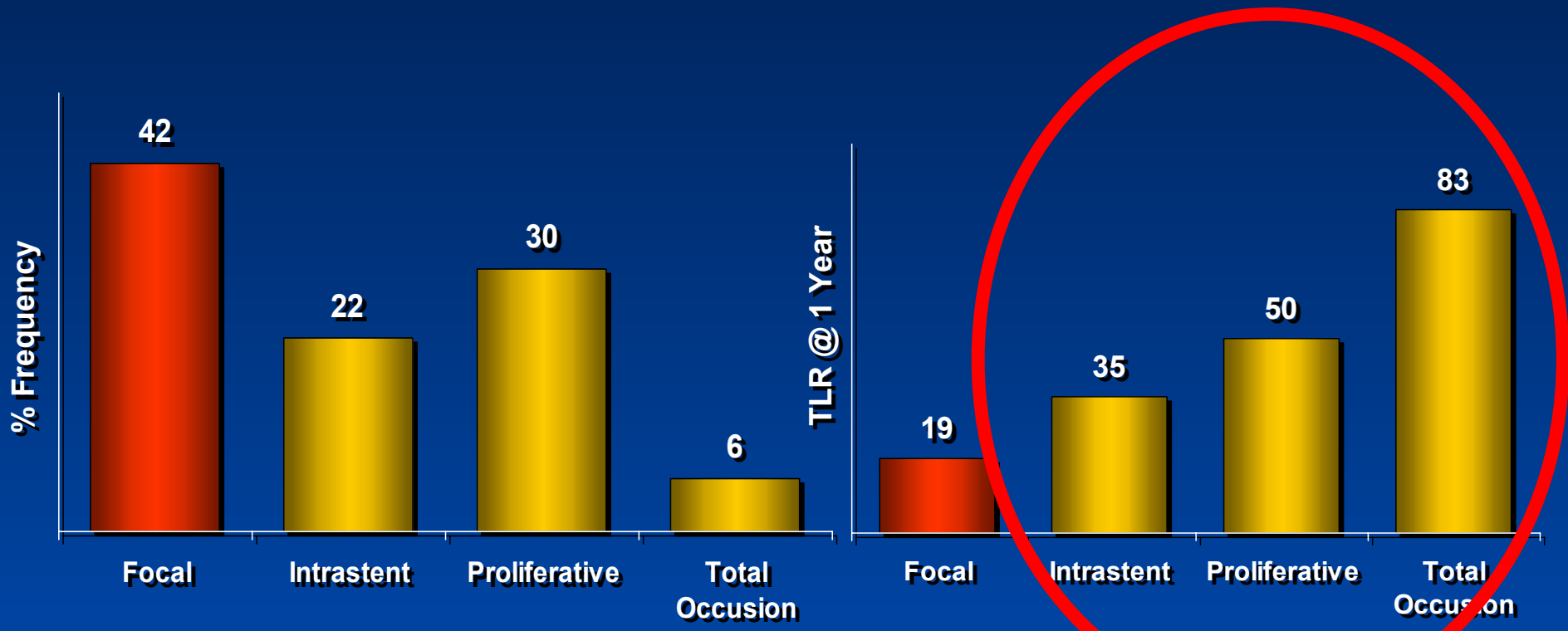


Total Occlusion

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

Patterns of ISR

282 lesions



Predictors of TLR : diabetes, previous ISR and ISR patterns

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

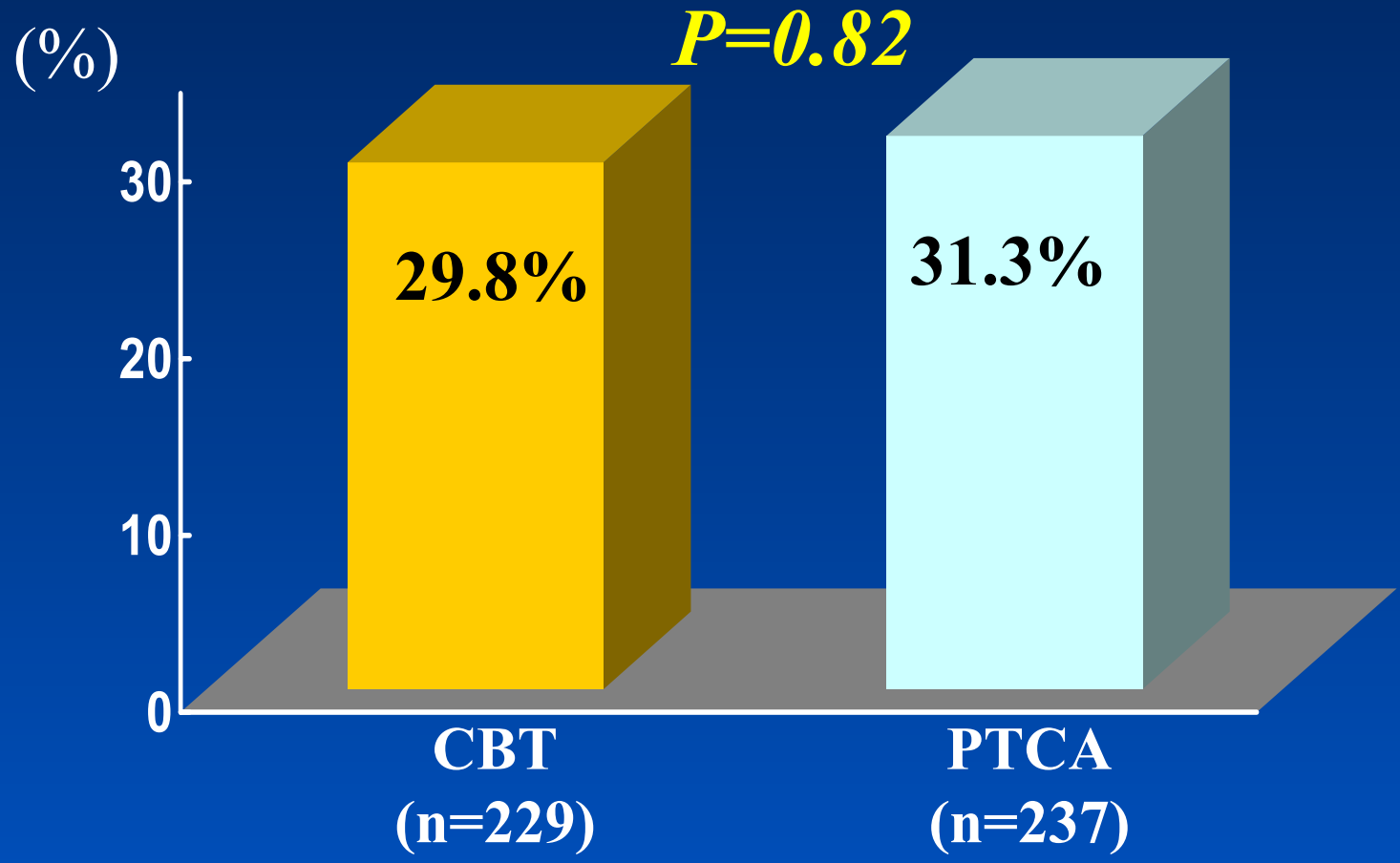
Treatment of ISR

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

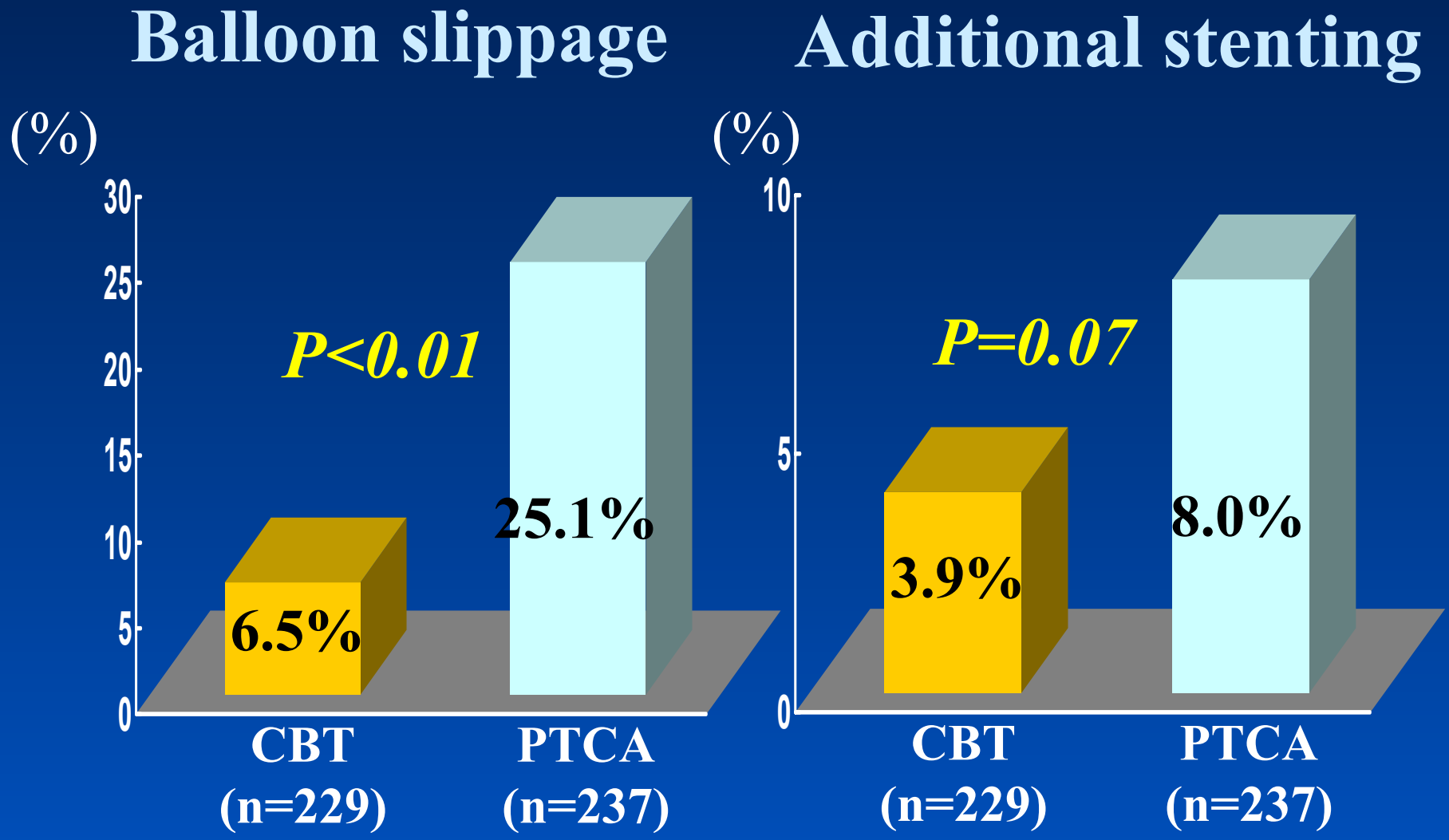
Not encouraging in diffuse ISR

Cutting Balloon Without RT

Binary Restenosis

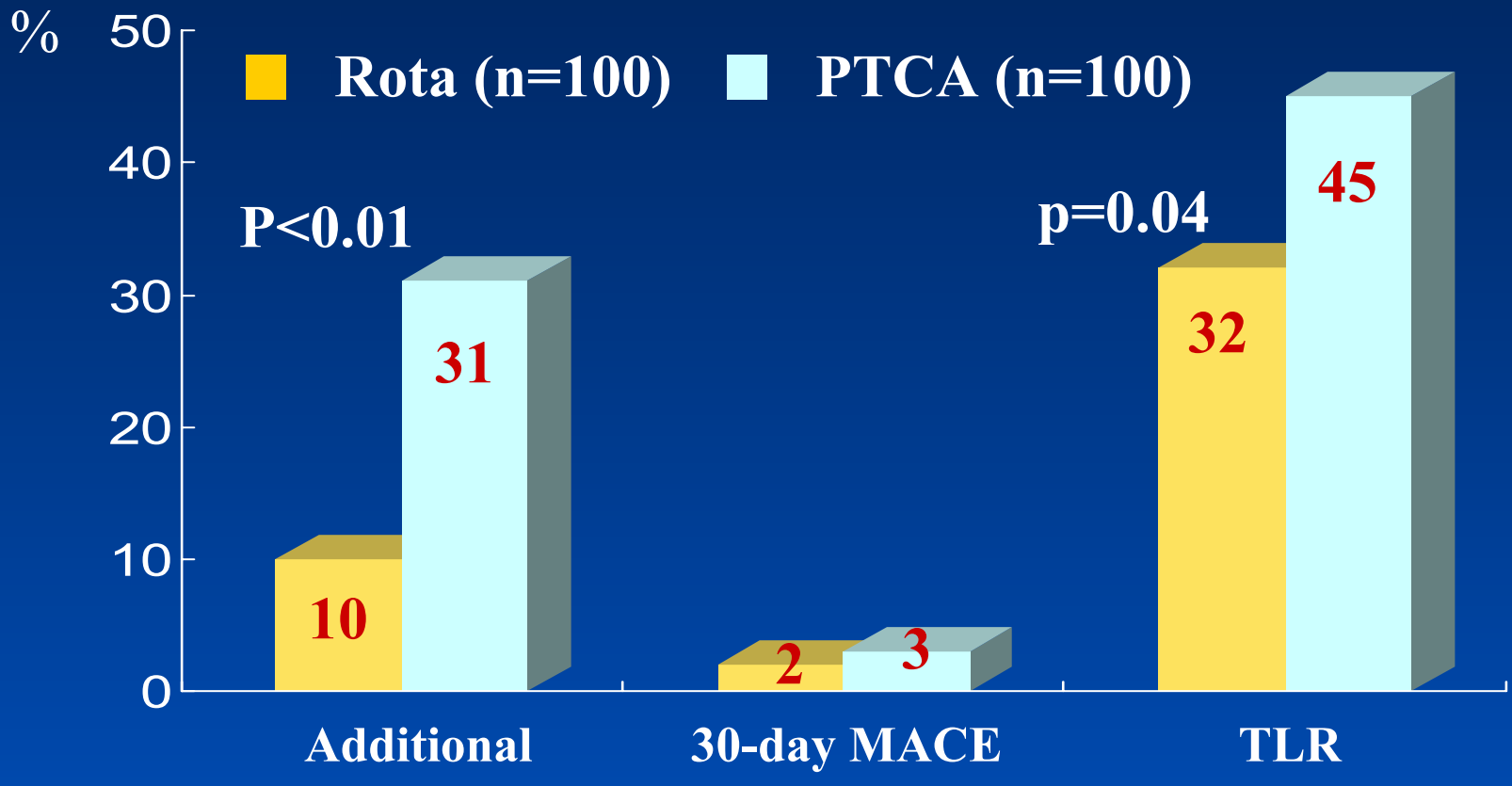


Cutting Balloon Without RT



Rota vs. PTCA for Diffuse ISR

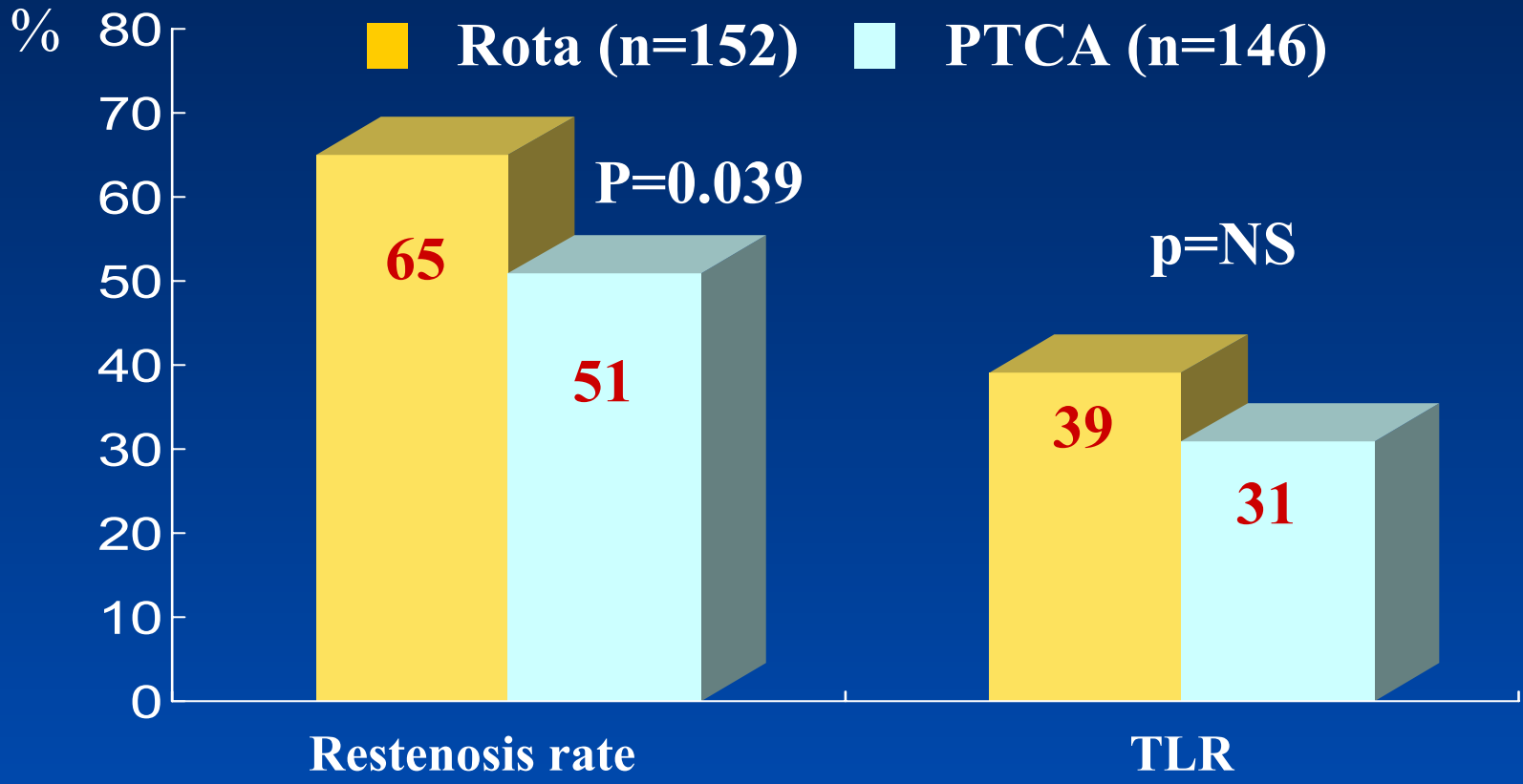
Small benefit of rotablation over balloon PTCA



Sharma SK et al. JACC. 2001;37(2):55A

Rota vs. PTCA for Diffuse ISR

Inferiority of rotablation compared to balloon PTCA

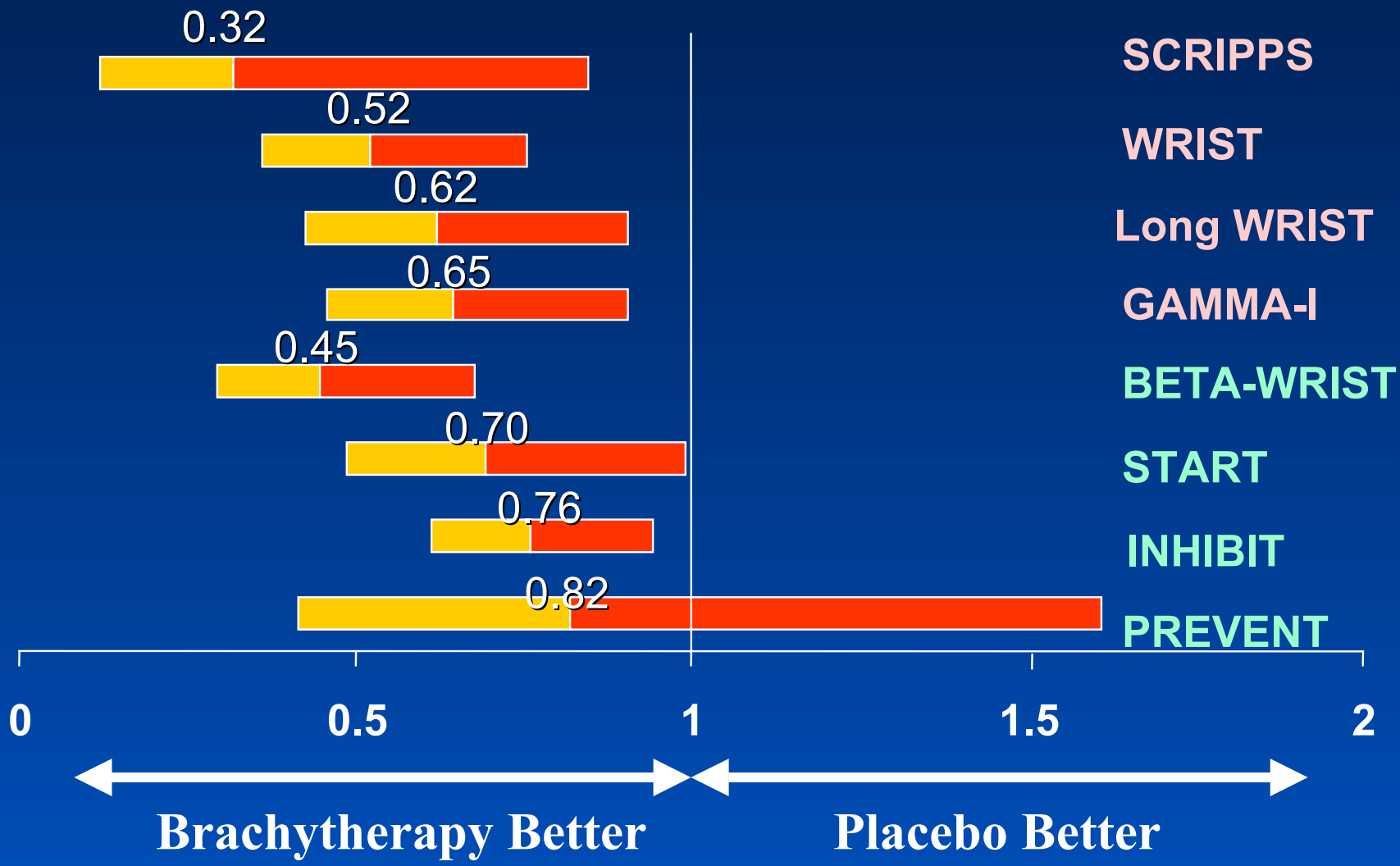


Dahl J et al. Circulation 2002;105:583

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



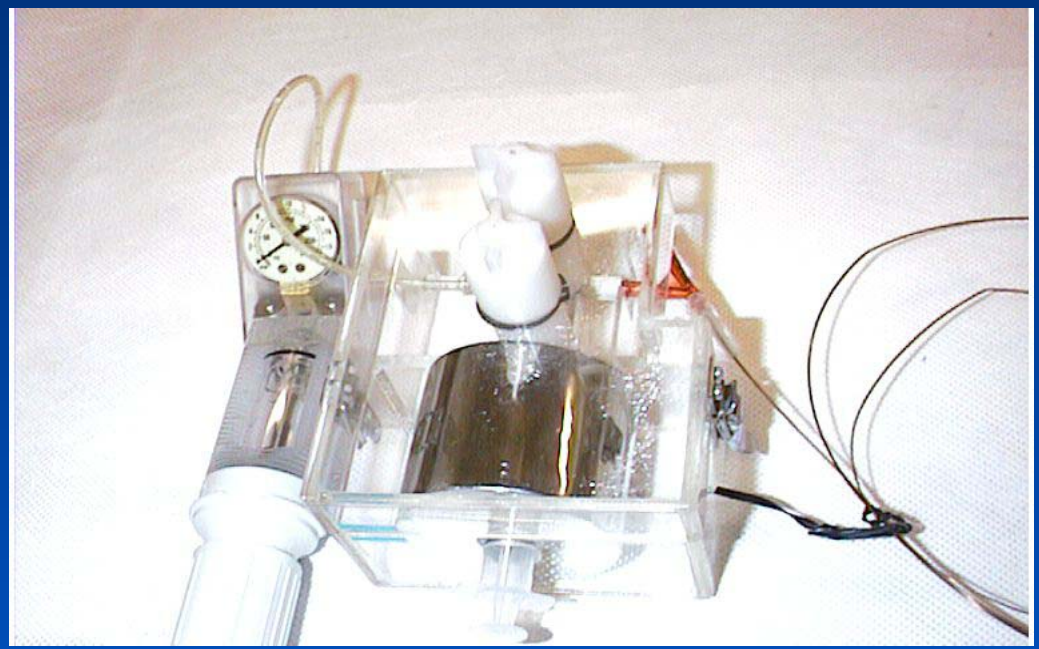
Brachytherapy

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

Why ^{188}Re-MAG_3 balloon ?

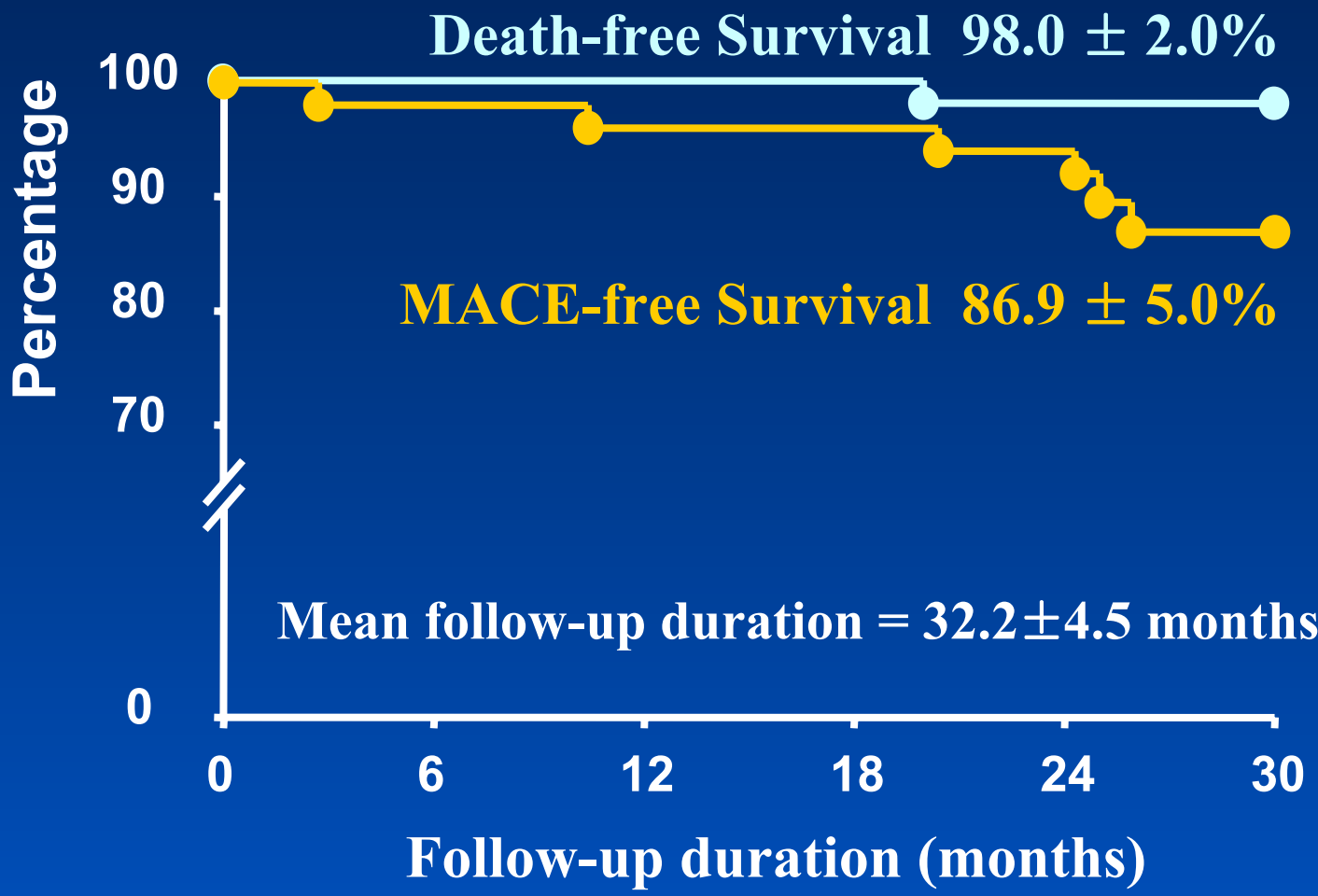
- Cost-effective
- No additional shielding
- Obtained from a Generator



Why ^{188}Re-MAG$_3$ balloon ?

- Centering, Angled lesion
- Beta source with High energy (Max 2.12 MeV)
- Short Half-life ($T_{1/2}$ = 17 hrs)
- Negligible radiation exposure
- Very safe

Death & Event-Free Survival after Rotablation and Beta-Radiation with ^{188}Re



Effective Pretreatment Methods Before Beta Radiation

Performed Studies in AMC

- Robating atherectomy

  vs. Simple balloon

- Cutting balloon angioplasty

  vs. Simple balloon

Rotablation vs. Simple Balloon

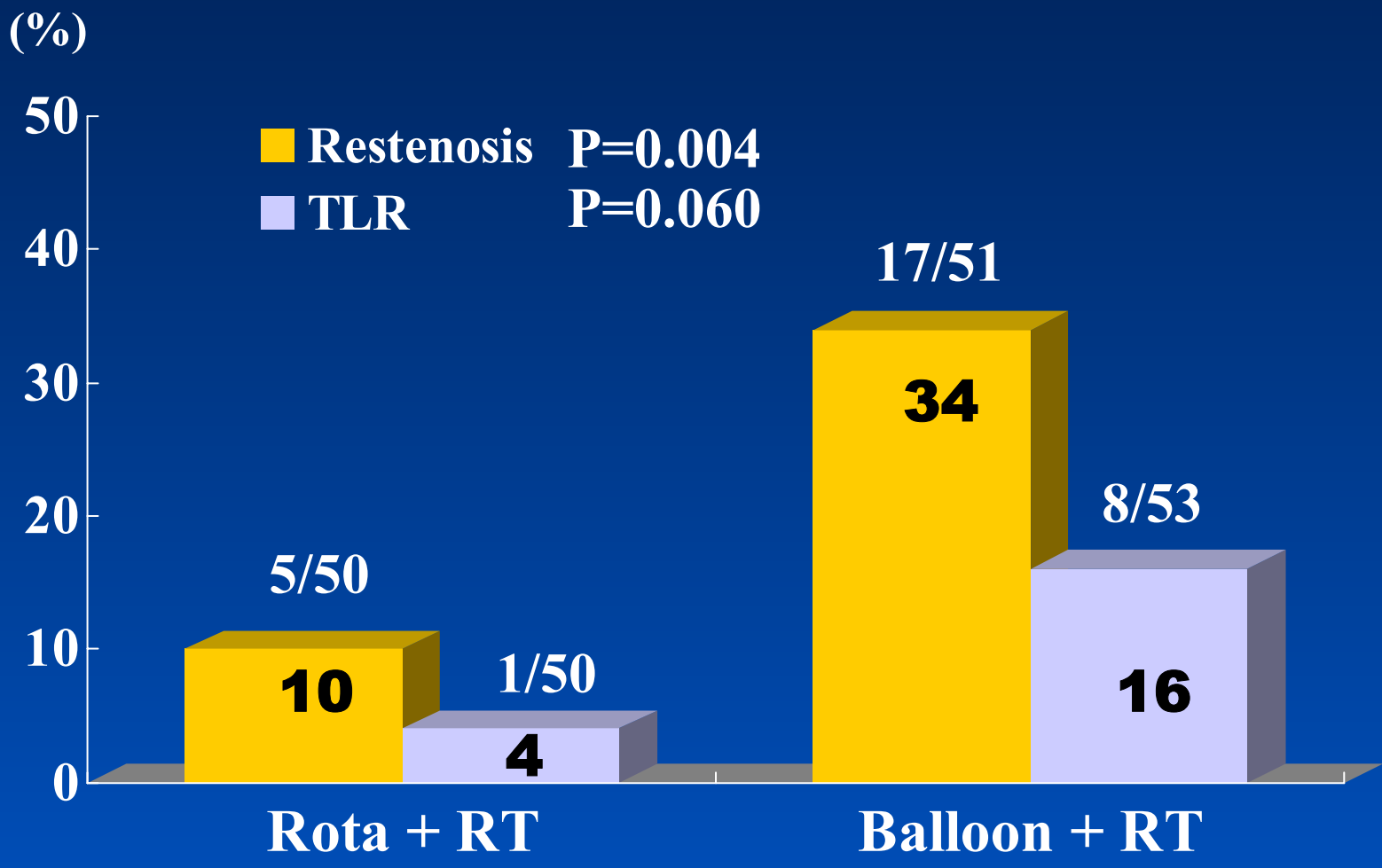
First 50 consecutive patients have been performed rotablation prior to radiation,

- ***Rota+RT N=50***

and the remaining 53 consecutive patients received balloon + radiation strategy.

- ***Balloon+RT N=53***

6-Month Restenosis Rate & TLR
Rota vs. Balloon



Rotablation vs. Cutting Balloon

Patients with diffuse in-stent restenois in a native coronary artery (n=113)

Randomization

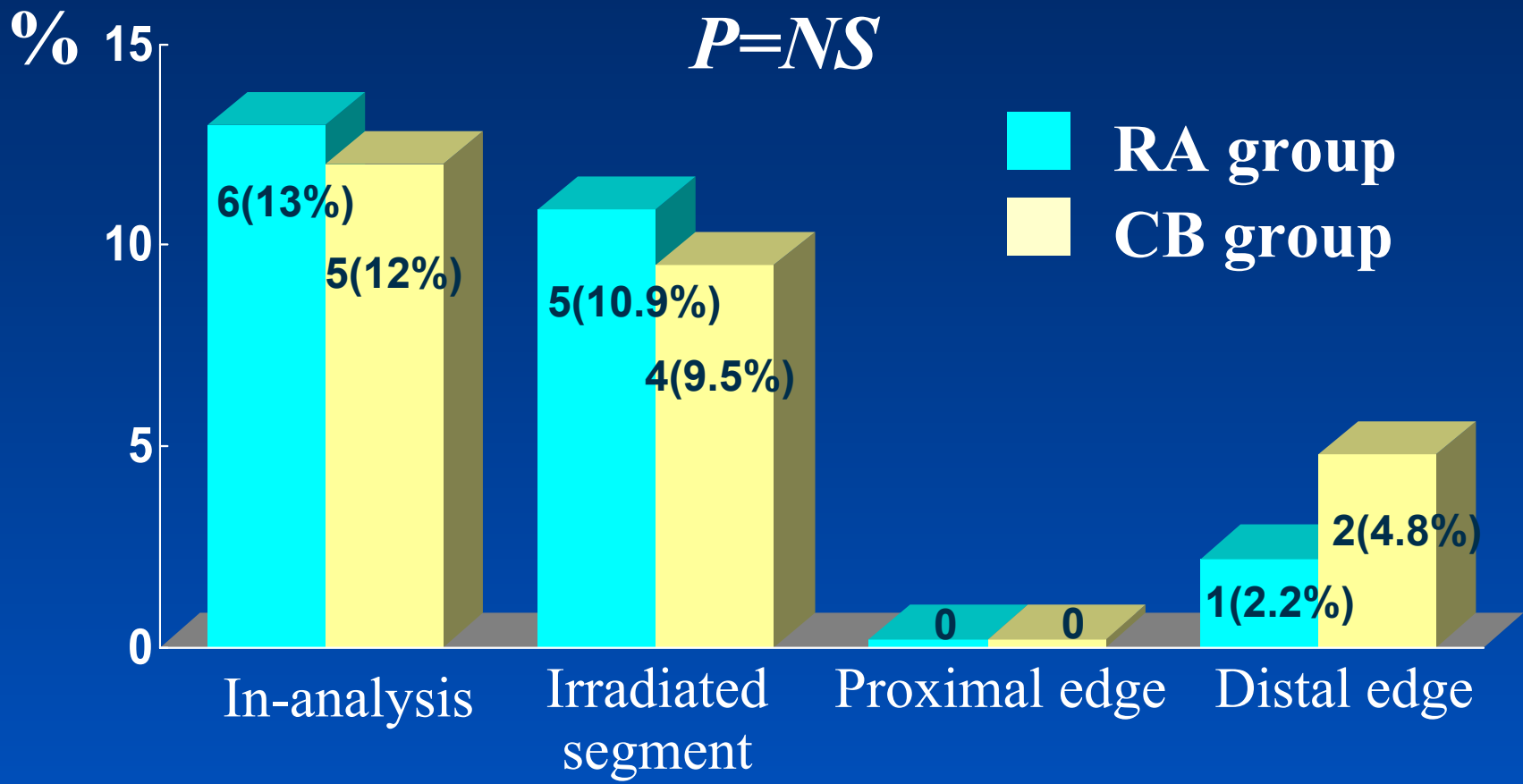
Rotational atherectomy ± PTCA (n=58, RA group)

Cutting balloon angioplasty (n=55, CB group)

Beta-radiation therapy using ^{188}Re-MAG$_3$-Filled Balloon

Angiographic Restenosis

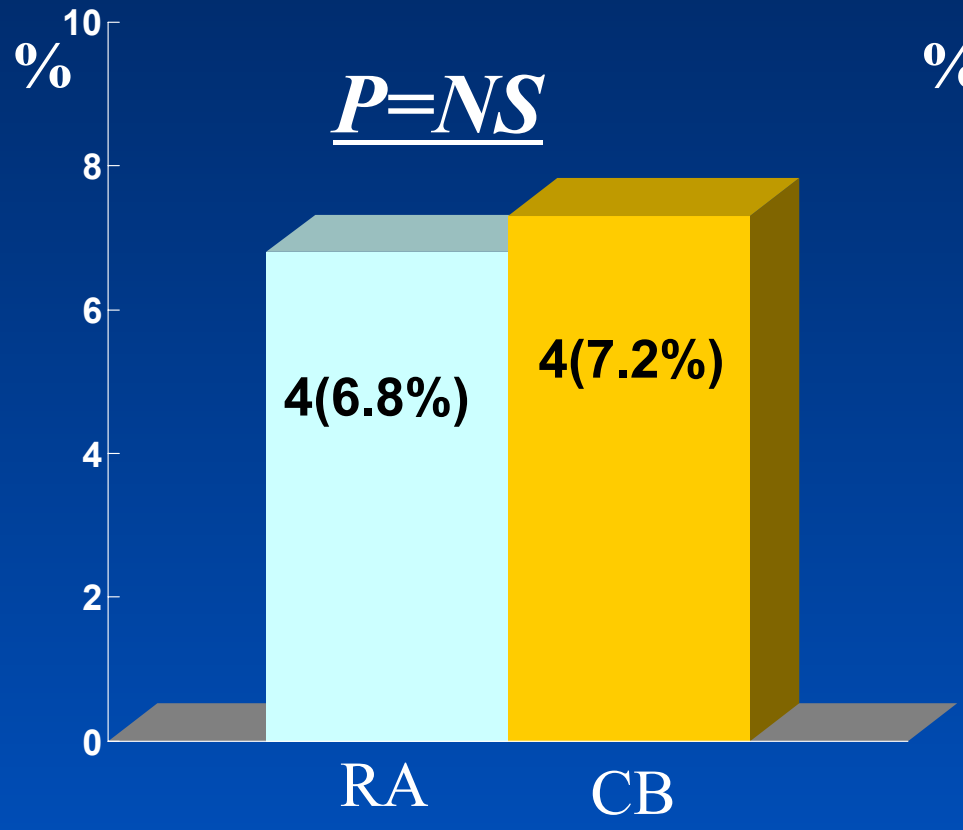
Rota vs. Cutting

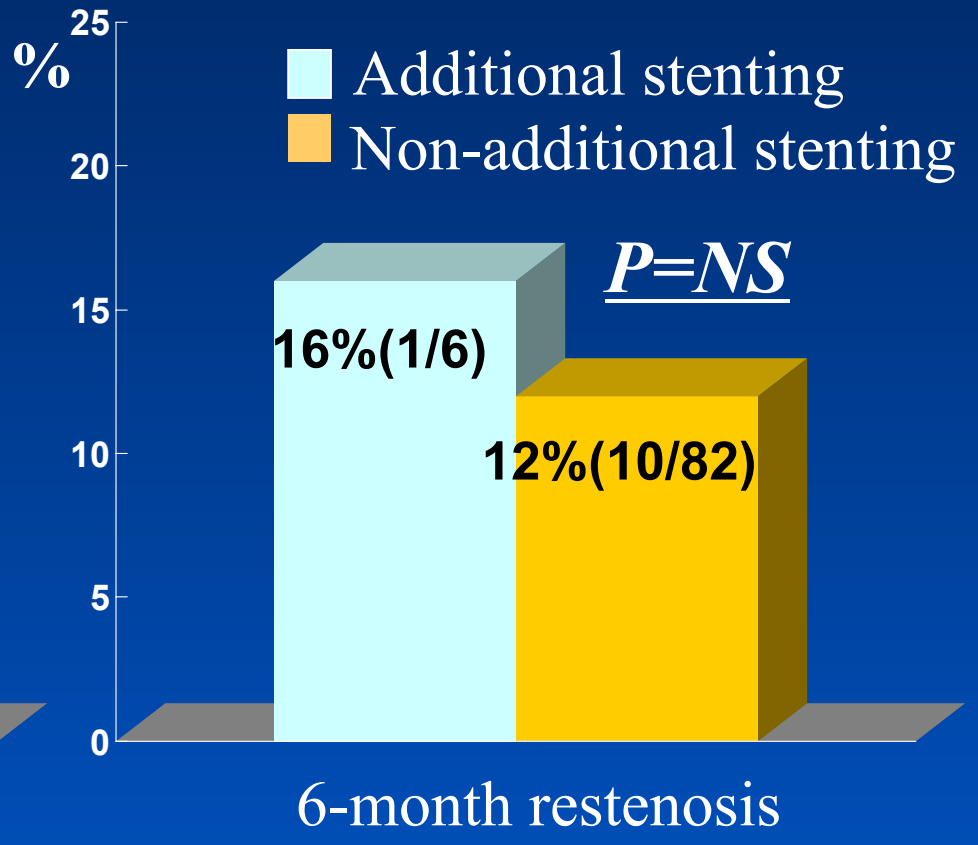


Additional Stenting

Rota vs. Cutting

RA group (3: dissection, 1:hematoma)
CB group (3: angiographic optimization, 1: dissection)





9-Month Clinical Outcome

Rota vs. Cutting

	RA group (n=58)	CB group (n=55)	*p*
Stent thrombosis	0	0	NS
MI	0	0	NS
TLR	2(3.4%)	2(3.6%)	NS
PCI	2(3.4%)	2(3.6%)	
CABG	0	0	
Death	0	0	NS

Drug Eluting Stent

We expect that

It may be an alternative of brachytherapy for ISR

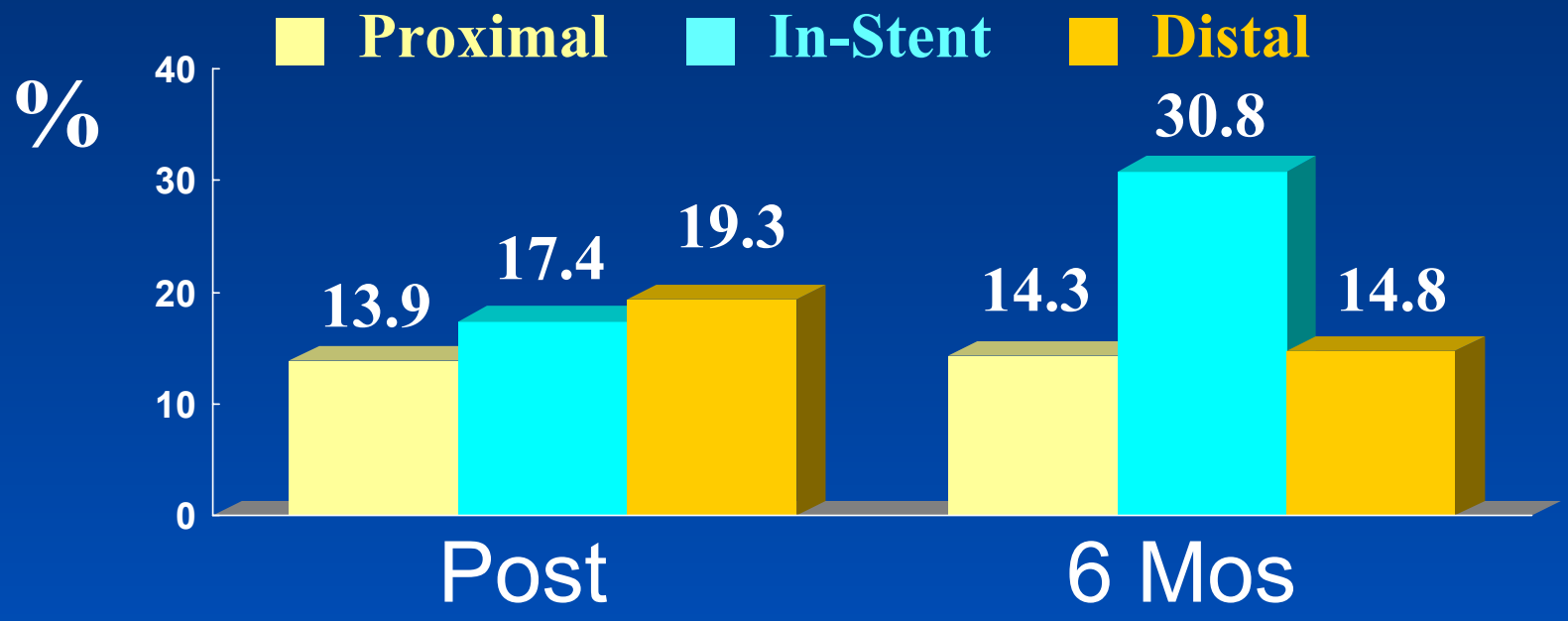
Pilot Studies of Drug Eluting Stent Implantation for In-Stent Restenosis

TAXUS III for ISR

2 Clinical Centers (n=28 pts)

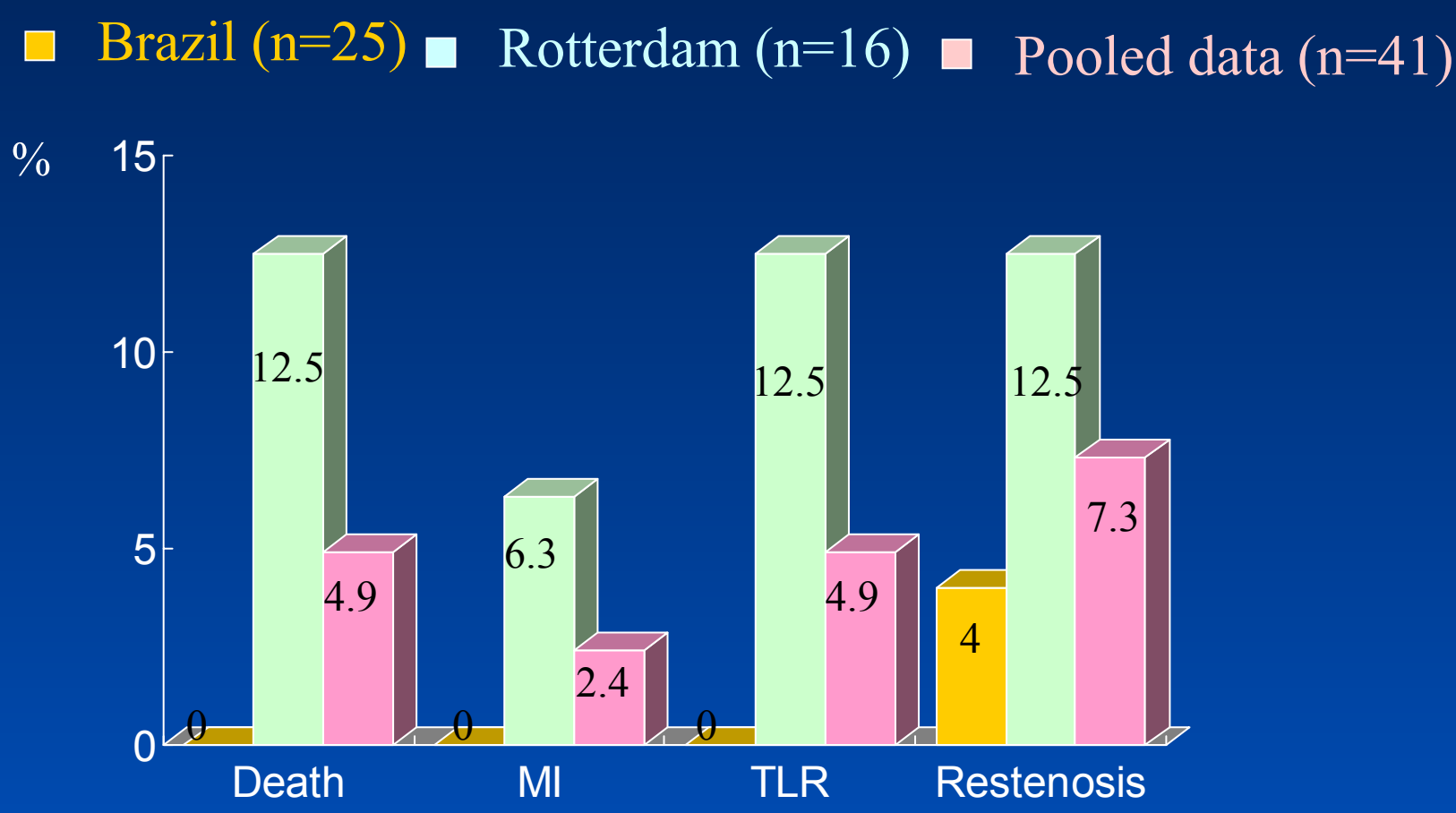
Re-Restenosis = 4 / 25 (16%)

Percent diameter stenosis



K Tanabe, Circulation 2003;107

First Study with Cypher
1-Year Clinical Event

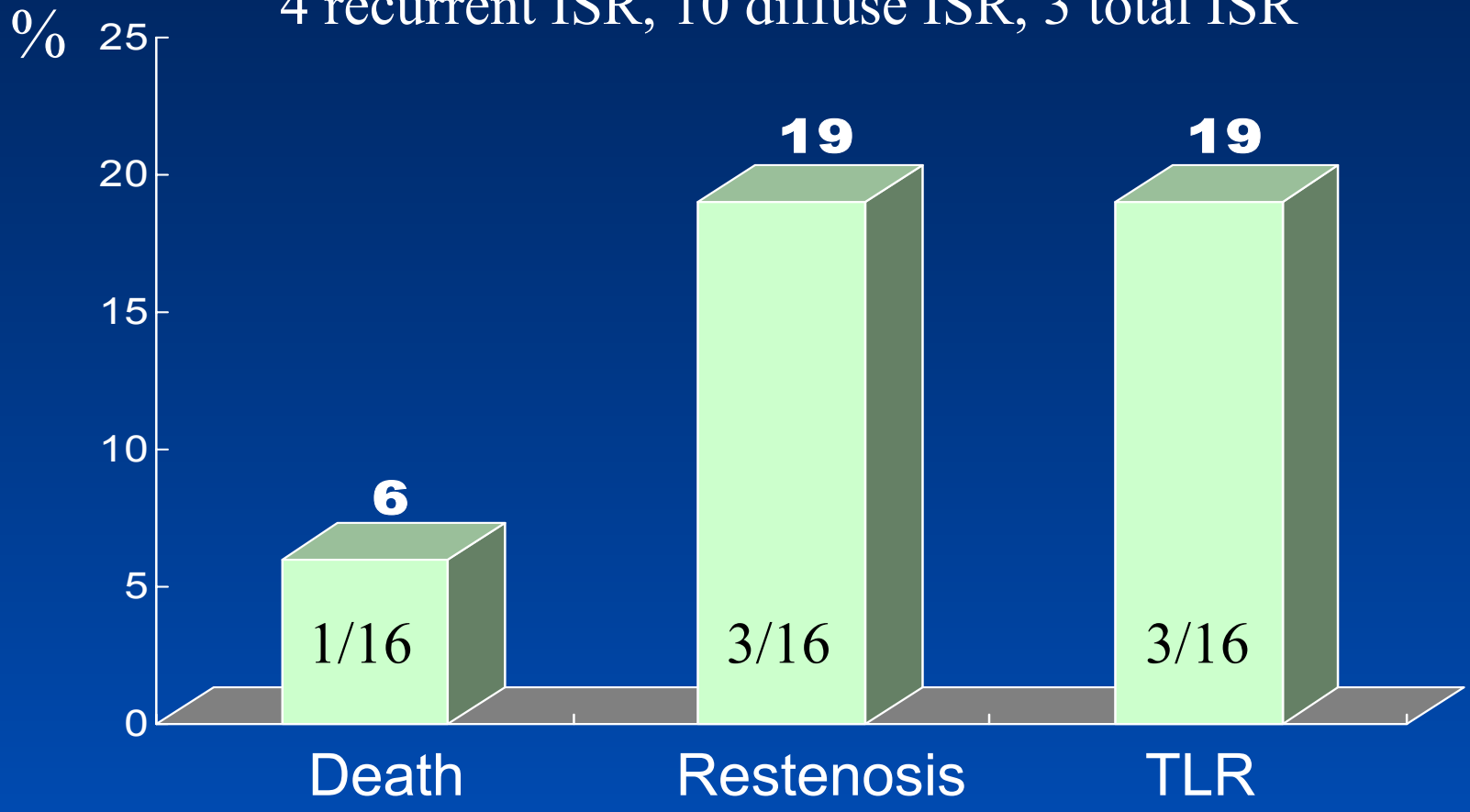


K Tanabe, Circulation 2003;107

Cypher 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

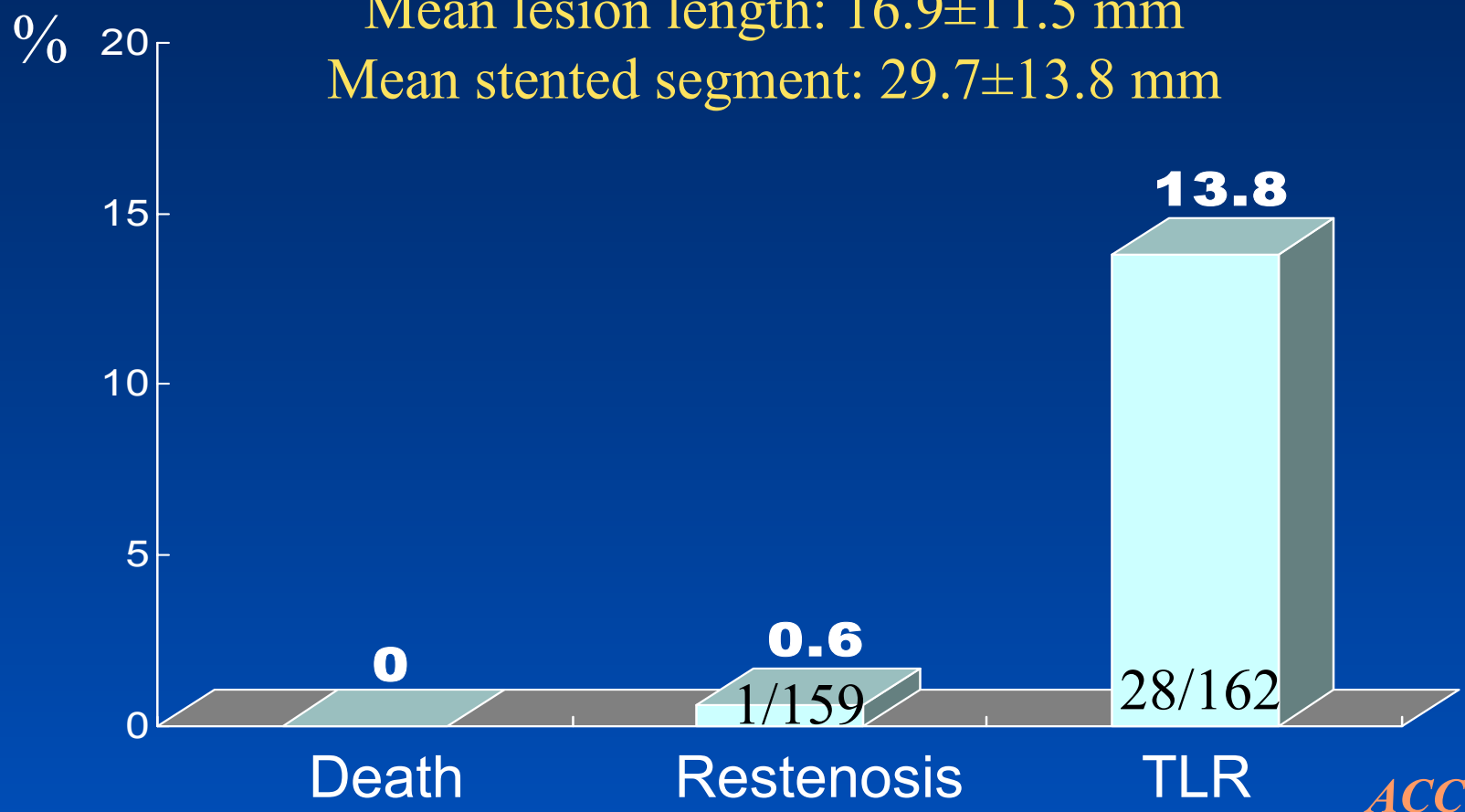
Cypher for ISR in Milan

Immediate and mid-term results

206 ISR, 159 patients

Mean lesion length: 16.9±11.5 mm

Mean stented segment: 29.7±13.8 mm



ACC 2004

In-Stent Restenosis in AMC

Total : 108 lesions with Cypher Implantation

Focal	26 (24 %)
Diffuse	63 (58 %)
Proliferative	16 (15 %)
Total occlusion	3 (3 %)

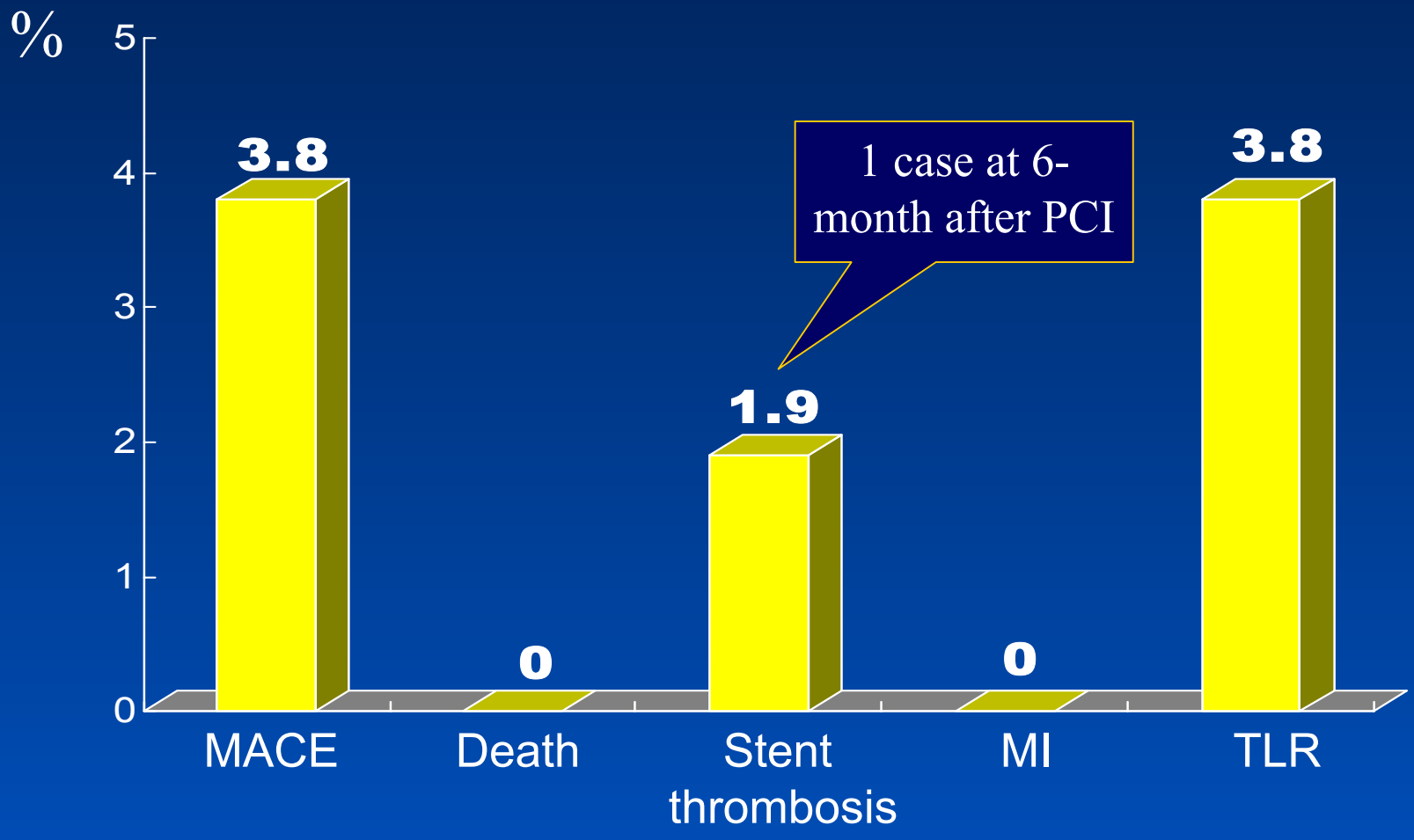
Lesion length : 18.3 ± 13.4 mm

6-Month QCA Results

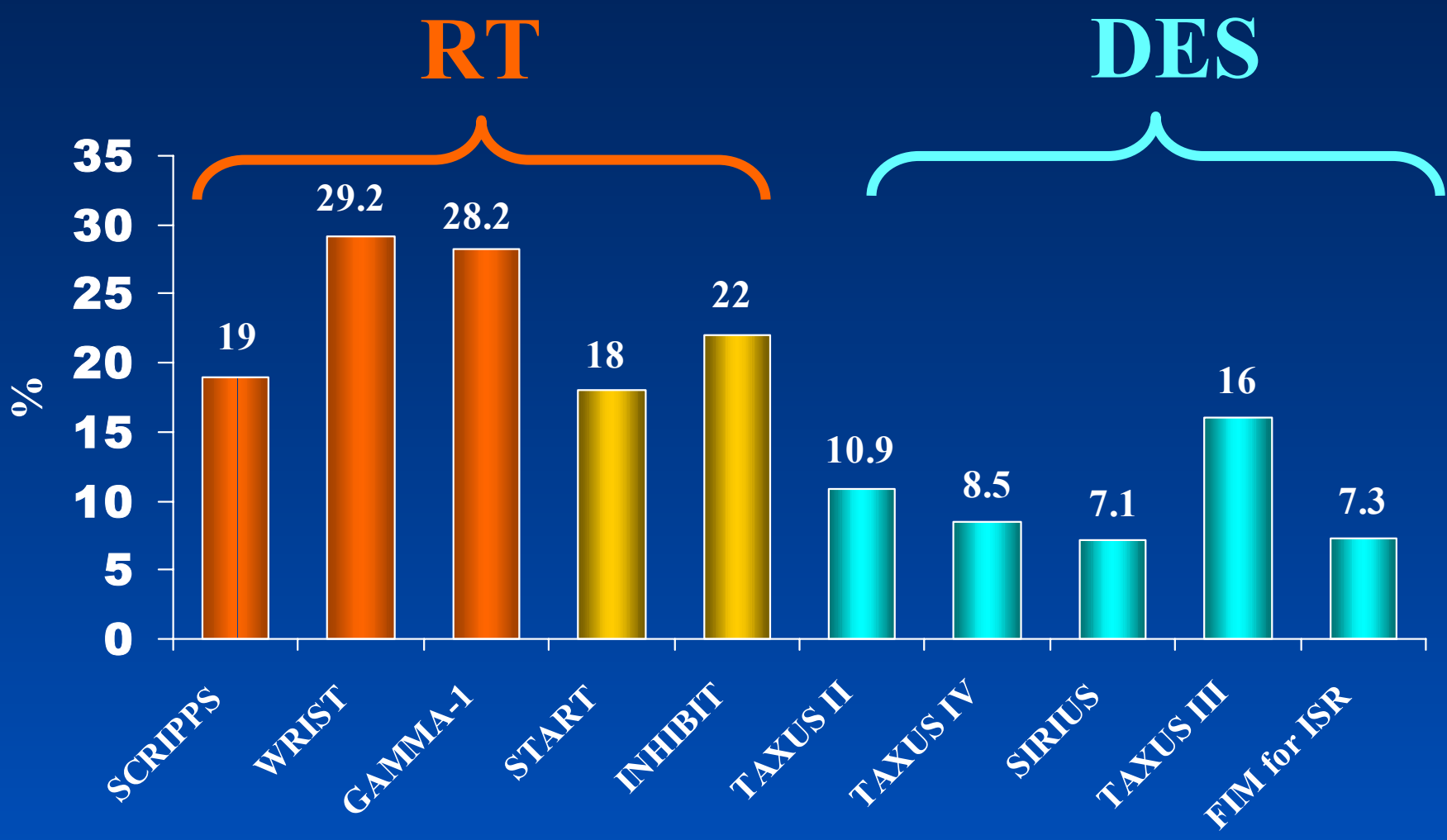
6-month follow-up	52 / 69 eligible lesions (75%)
Reference vessel (mm)	2.77 ± 0.48
MLD (mm)	2.40 ± 0.66
Late loss (mm)	0.55 ± 0.42
Diameter stenosis (%)	12.8 ± 21.7
Binary restenosis (%)	2 (4%)
Focal	1
Diffuse	1

6-Month Clinical Results

Total 53 eligible patients



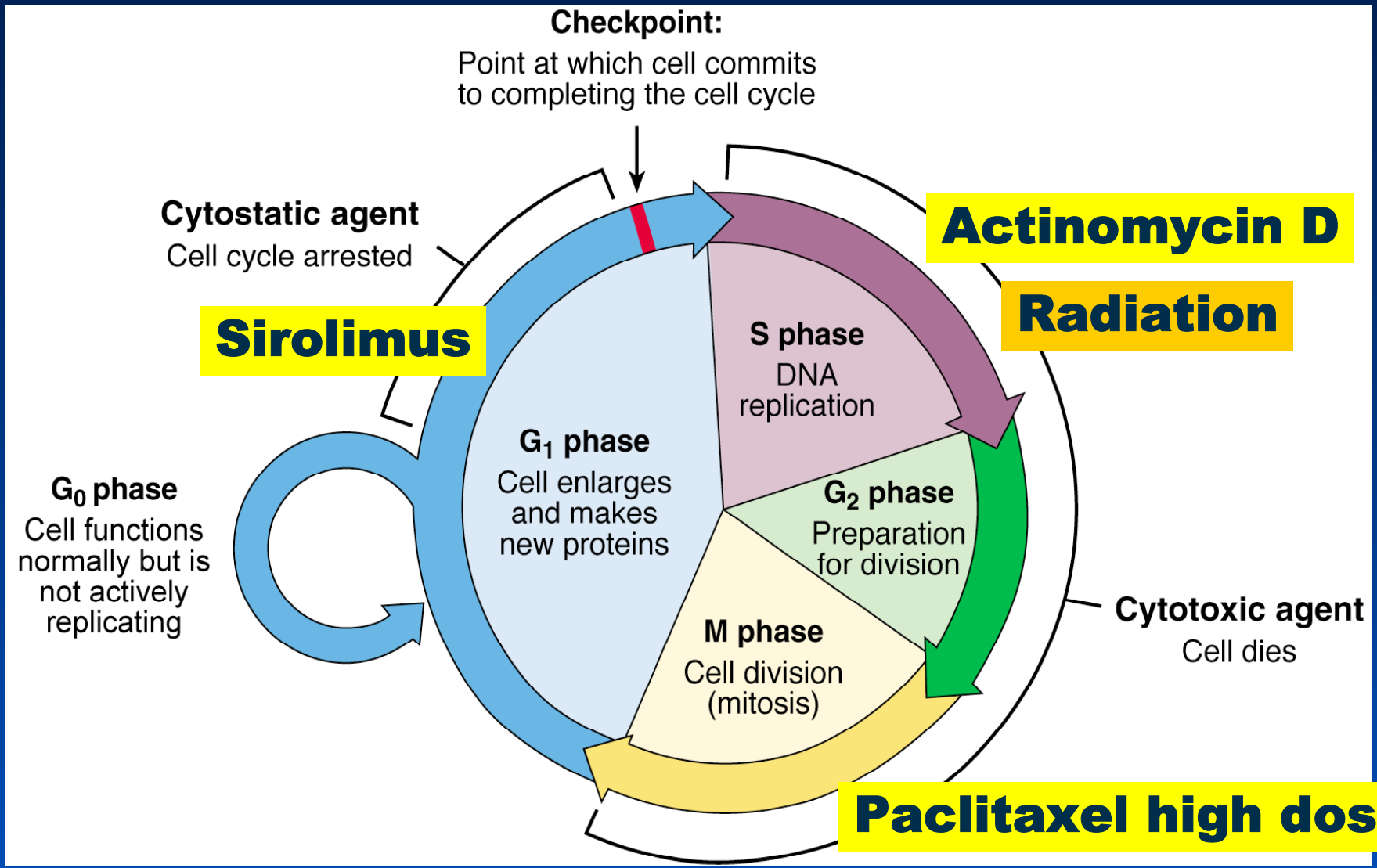
Comparison of MACE



RT vs. DES

Who will be a winner ?

Cytostatic ? Cytotoxic ?

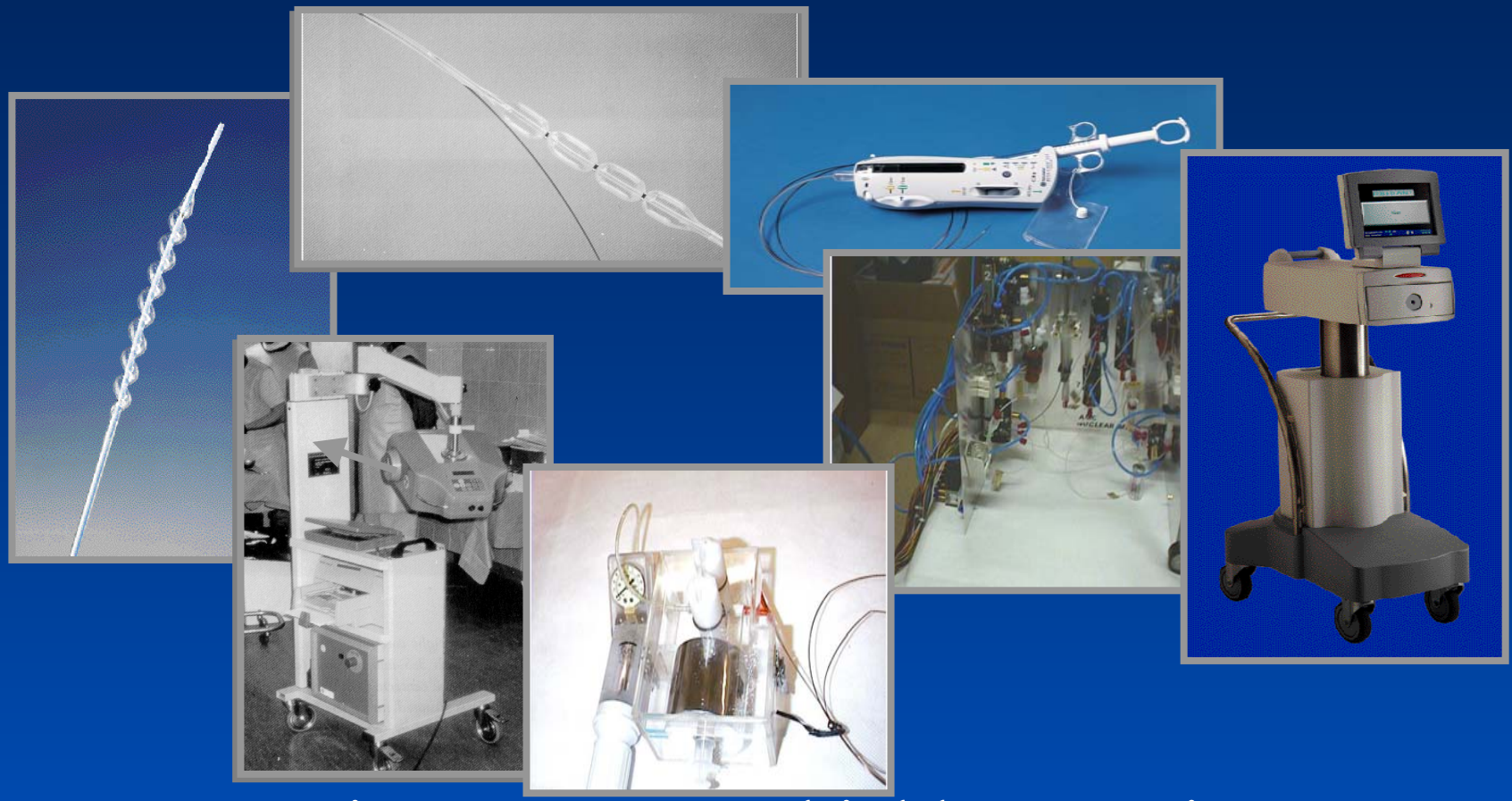


RT vs. DES

Theoretical Issues

- **Technical consideration**
- **Late thrombosis**
- **Edge effect**
- **Late catch-up**

DES is more user-friendly DES than RT



Source train, generator, shielder… …in RT

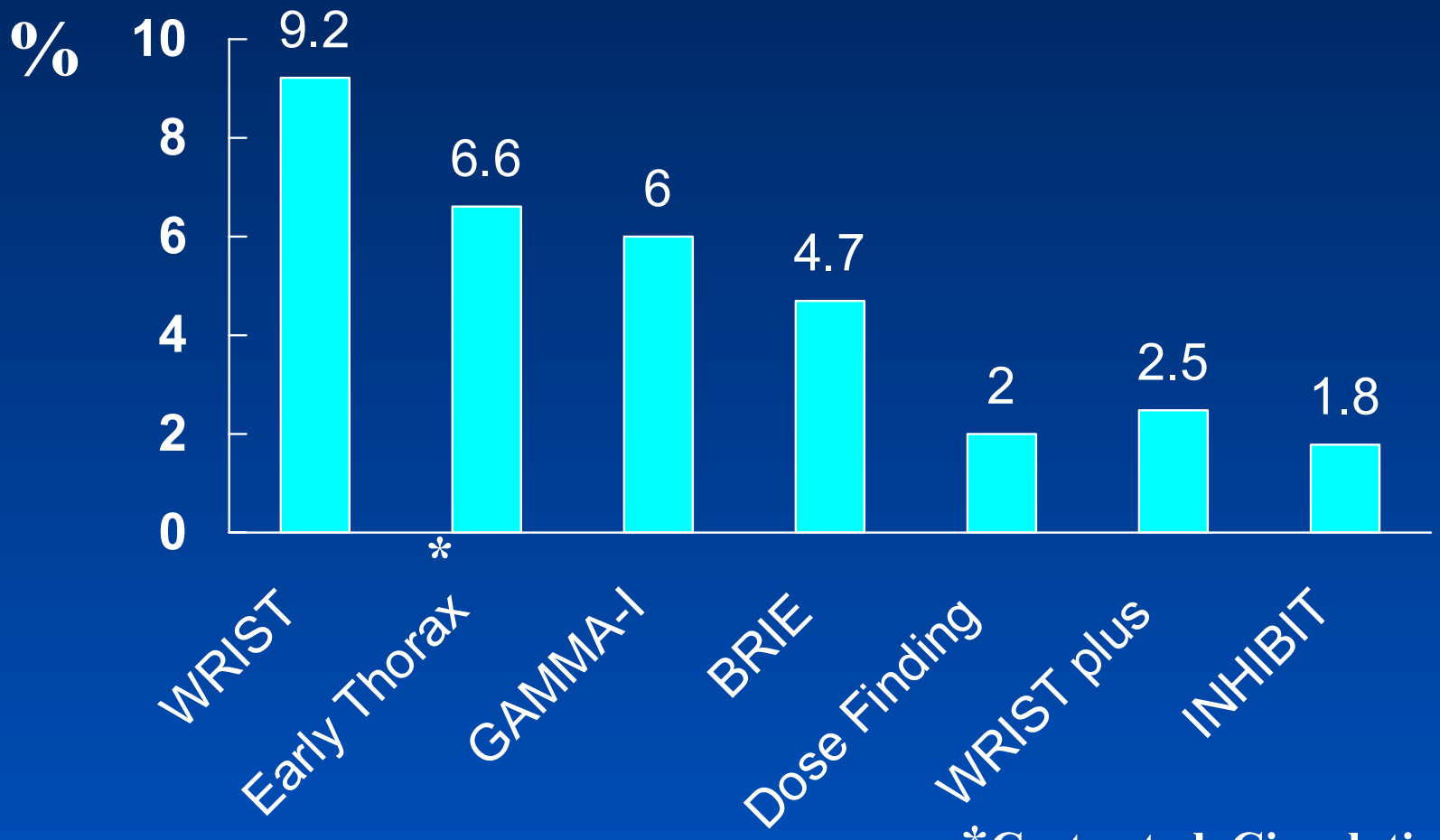
RT vs. DES

Theoretical Issues

- Technical consideration
- Late thrombosis
- Edge effect
- Late catch-up

Brachytherapy

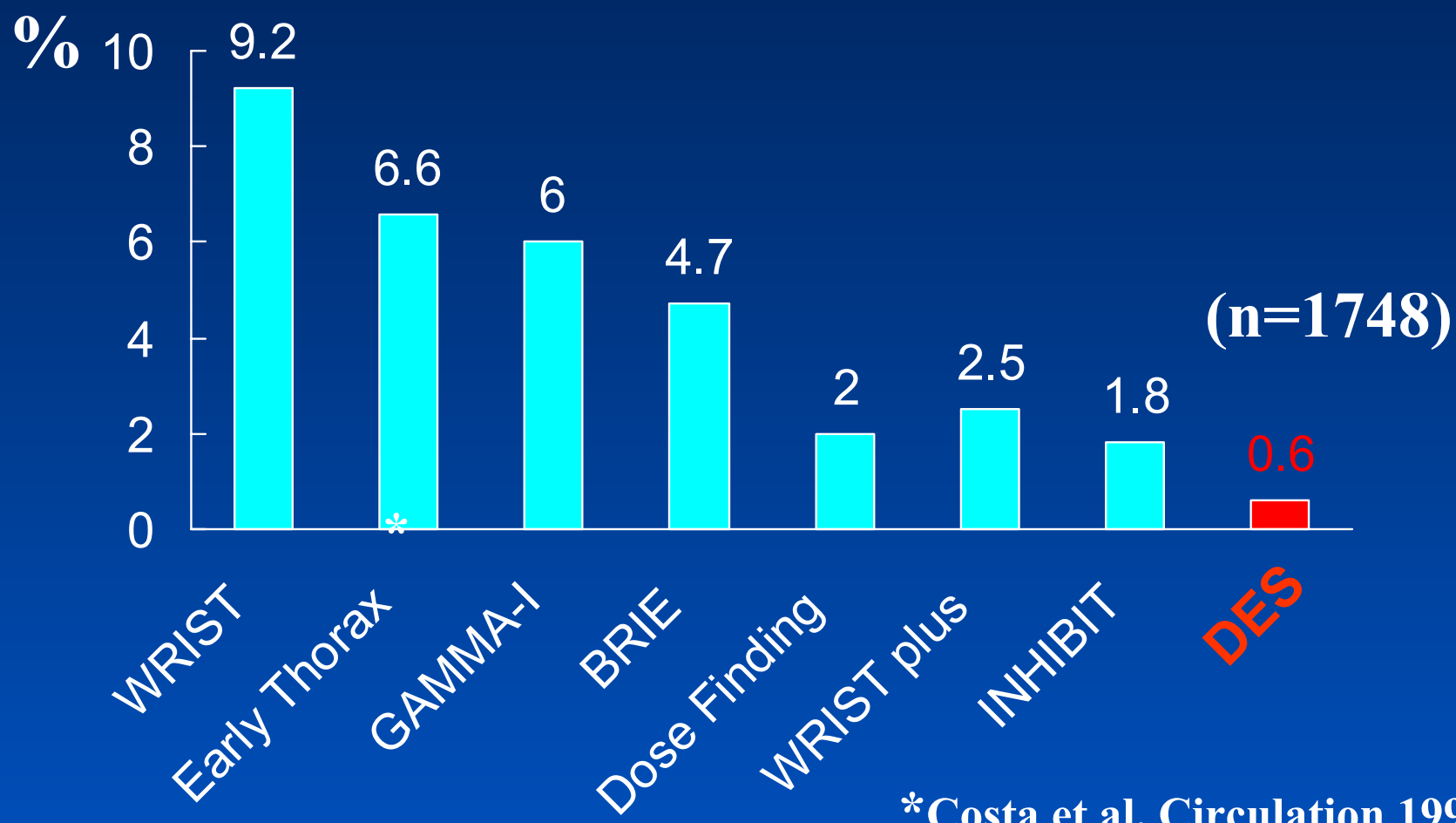
Late Thrombotic Occlusion



*Costa et al. Circulation 1999

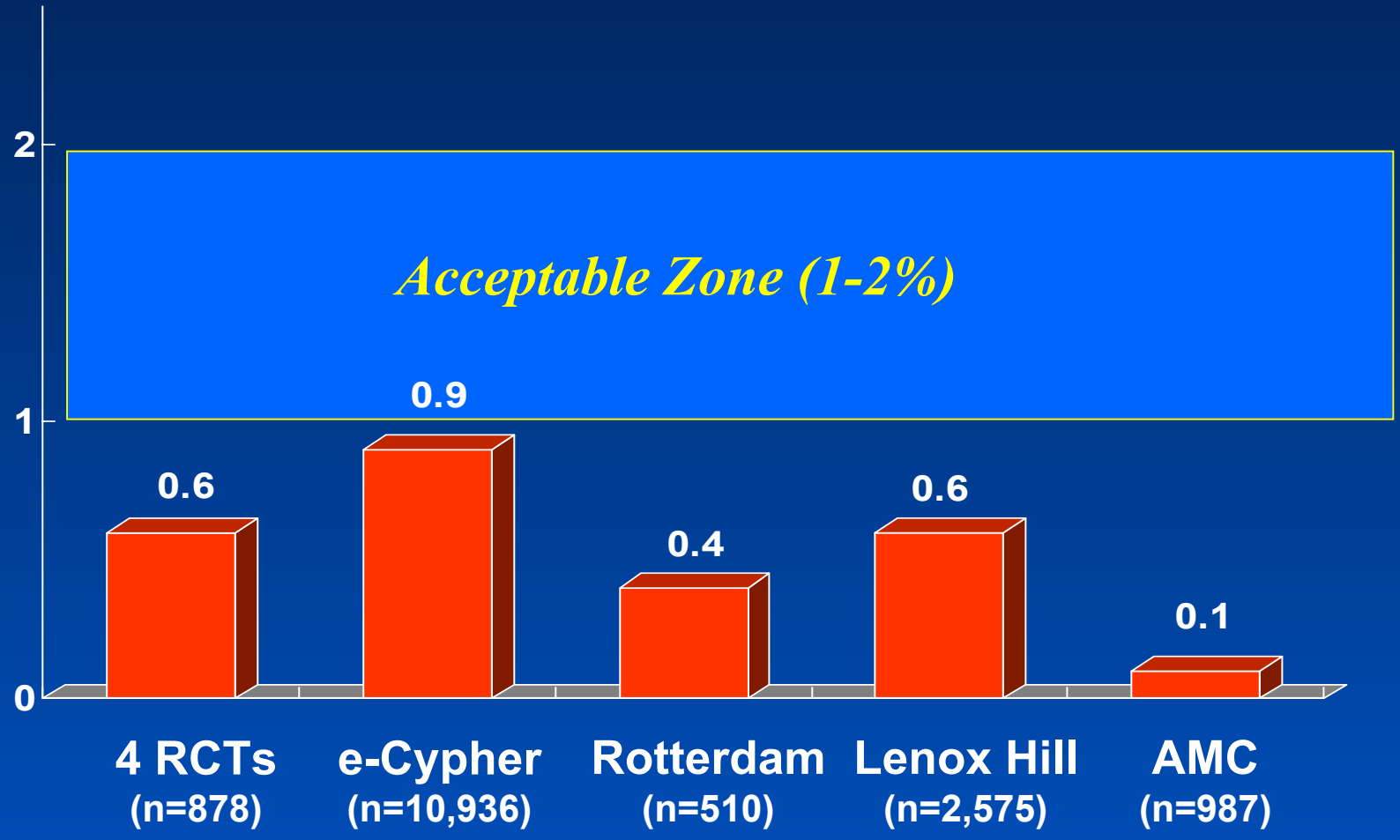
Pooled Data of DES in US

Late Thrombotic Occlusion



*Costa et al. Circulation 1999

Cypher™ Stent Thrombosis



Taxus™ Stent Thrombosis

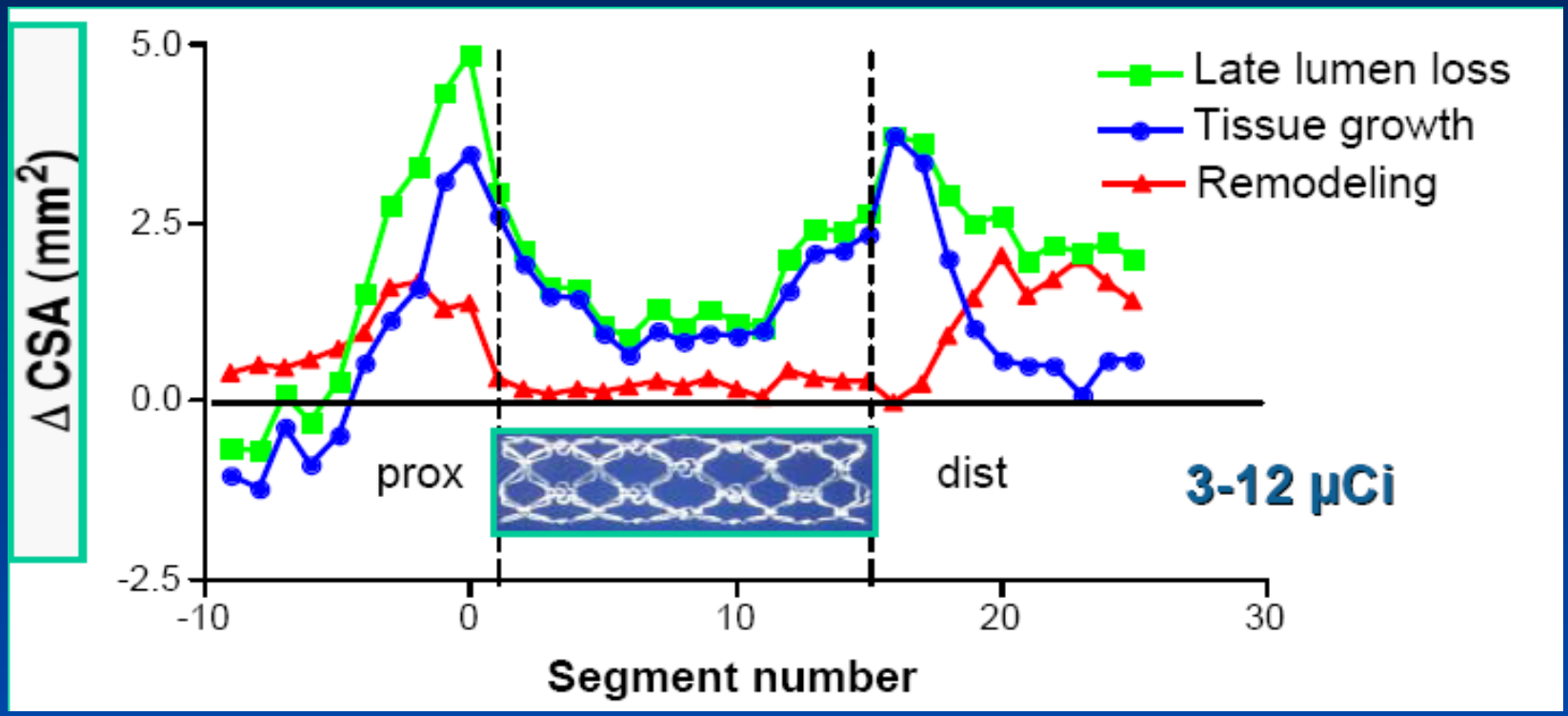
RT vs. DES

Theoretical Issues

- Technical consideration
- Late thrombosis
- **Edge effect**
- Late catch-up

Brachytherapy

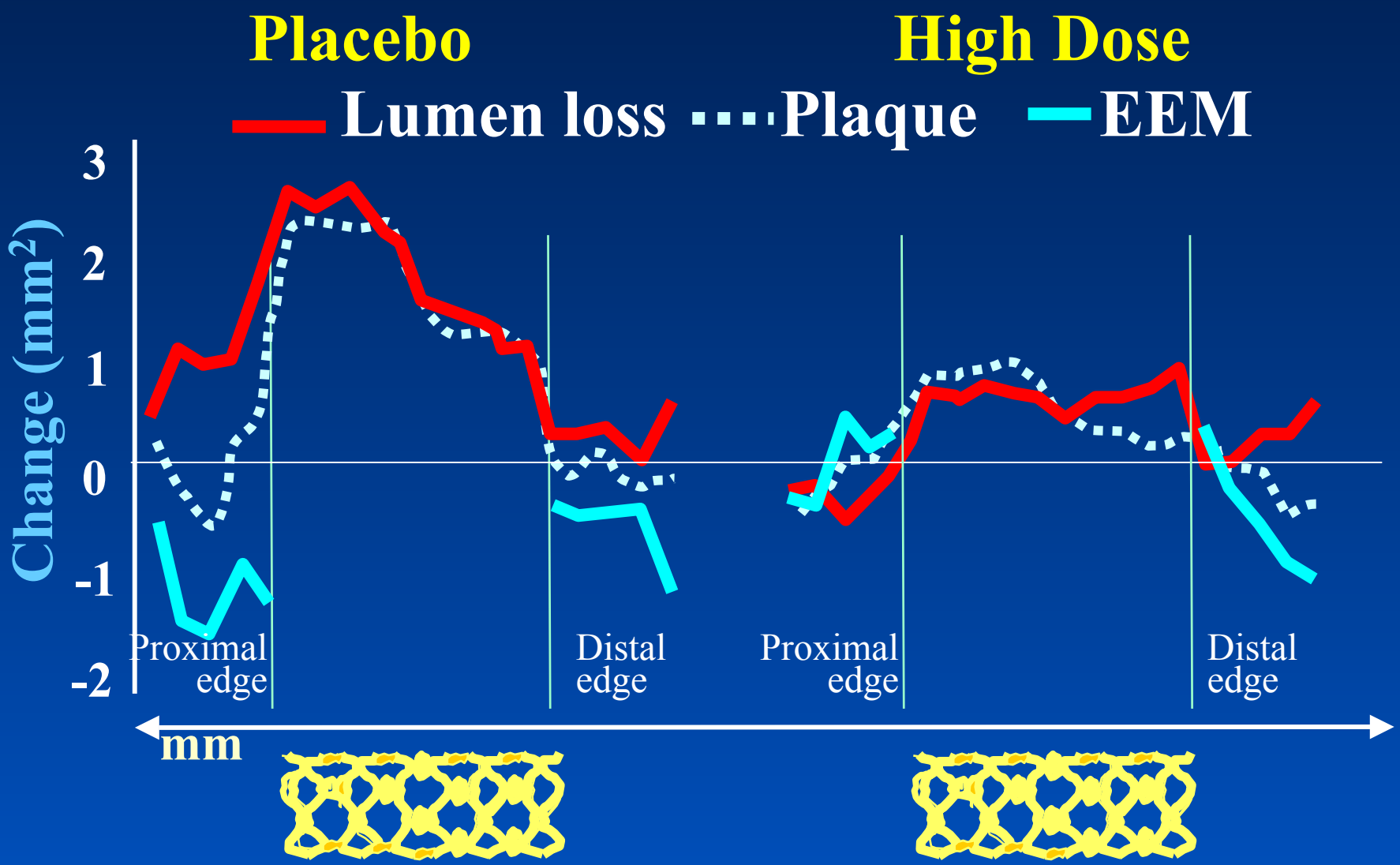
Tissue Growth at Both Edges



Abiero, Colombo et al. 1999

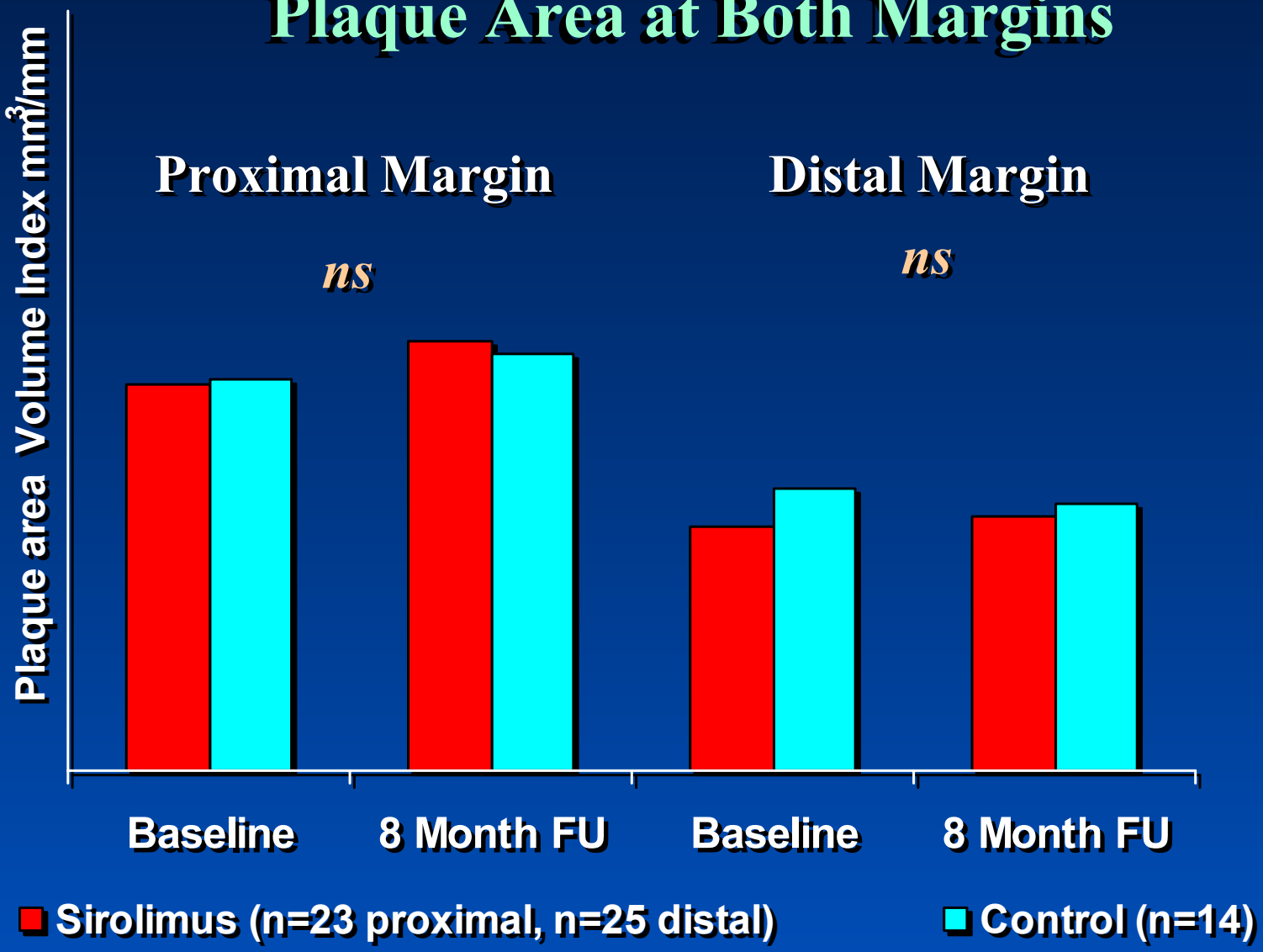
ASPECT

Paclitaxel Elutng Stent

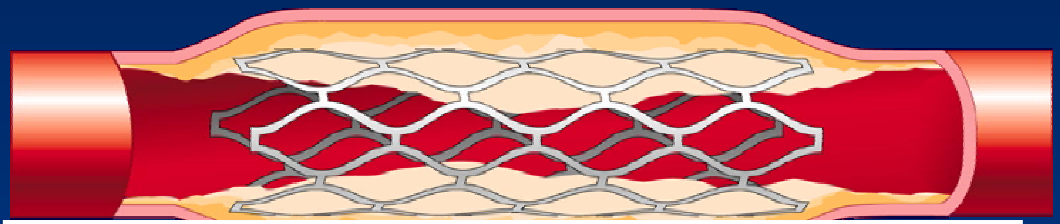


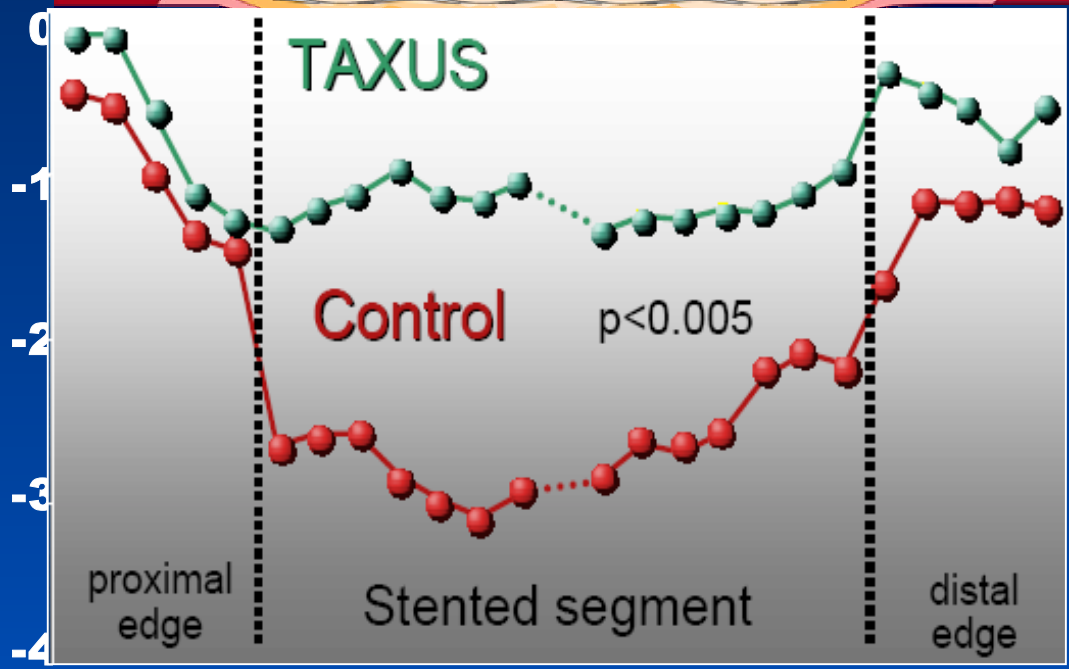
SIRIUS – IVUS Subset Analysis

Plaque Area at Both Margins

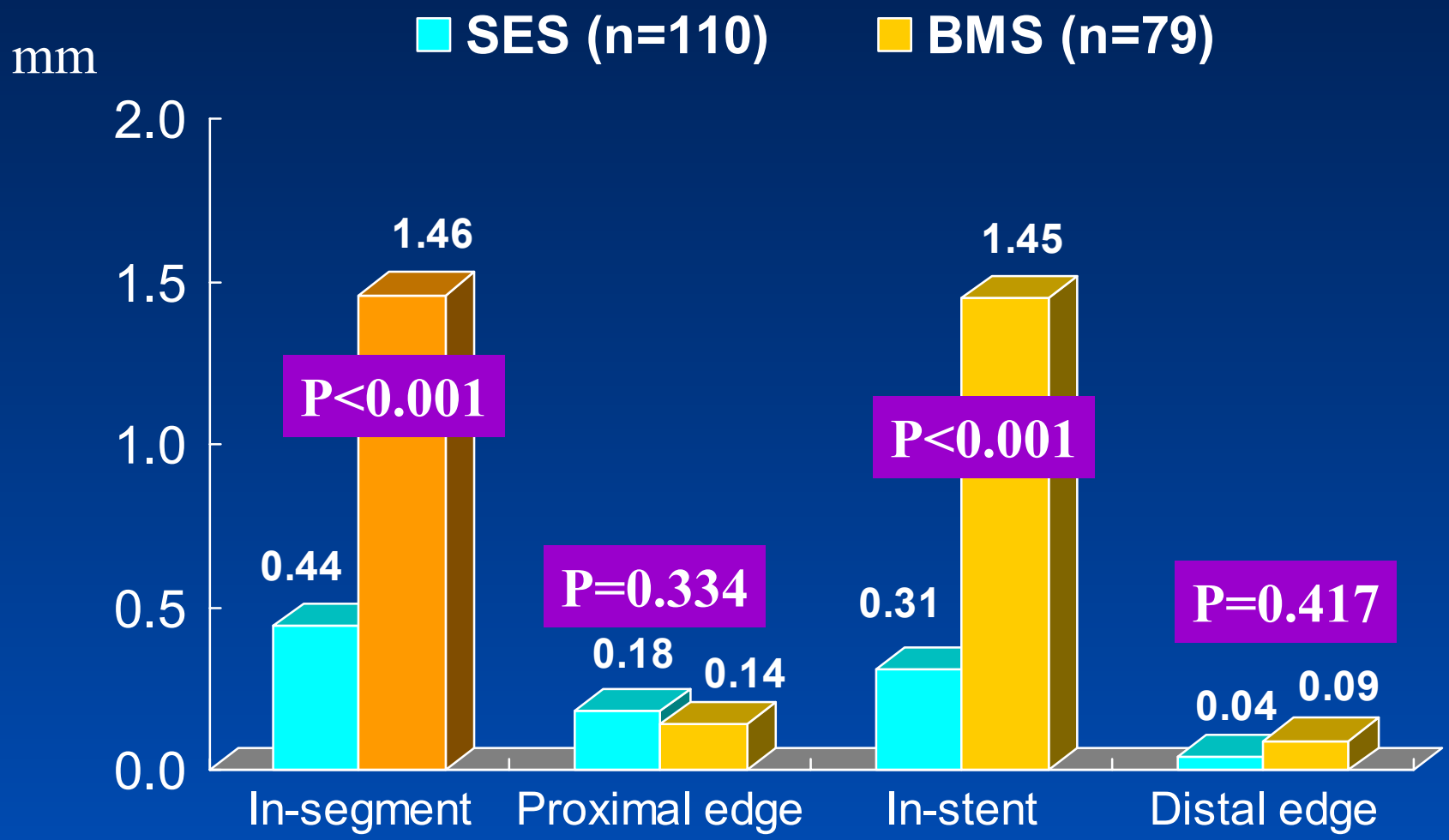


Even Suppression of Neoinitma Without Edge Effect





Late Loss


SES (n=110)
BMS (n=79)
mm
2.0
1.5
1.0
0.5
0.0
1.46
0.44
P<0.001
0.18
0.14
P=0.334
1.45
0.31
P<0.001
0.04
0.09
P=0.417
In-segment
Proximal edge
In-stent
Distal edge

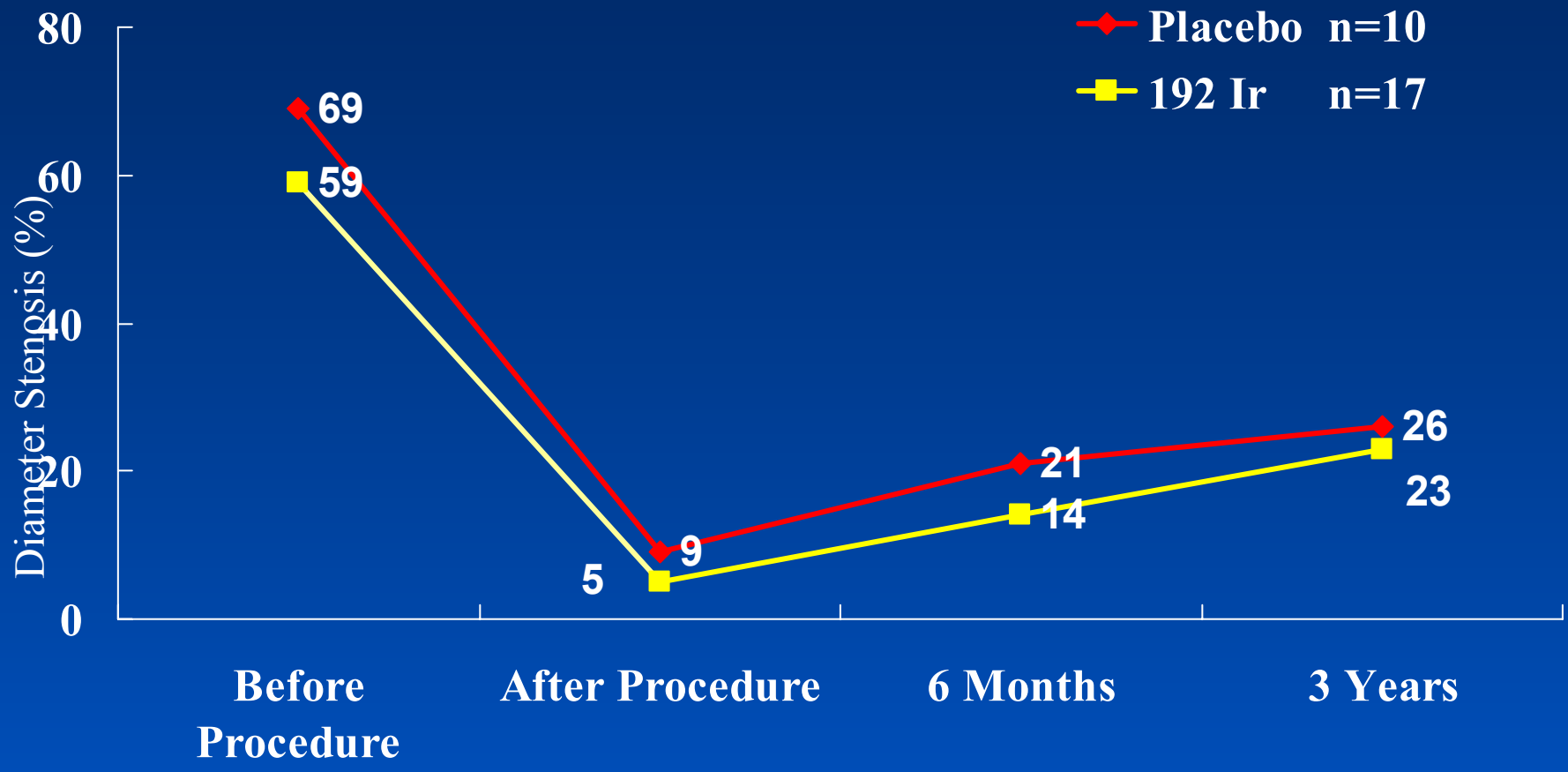
RT vs. DES

Theoretical Issues

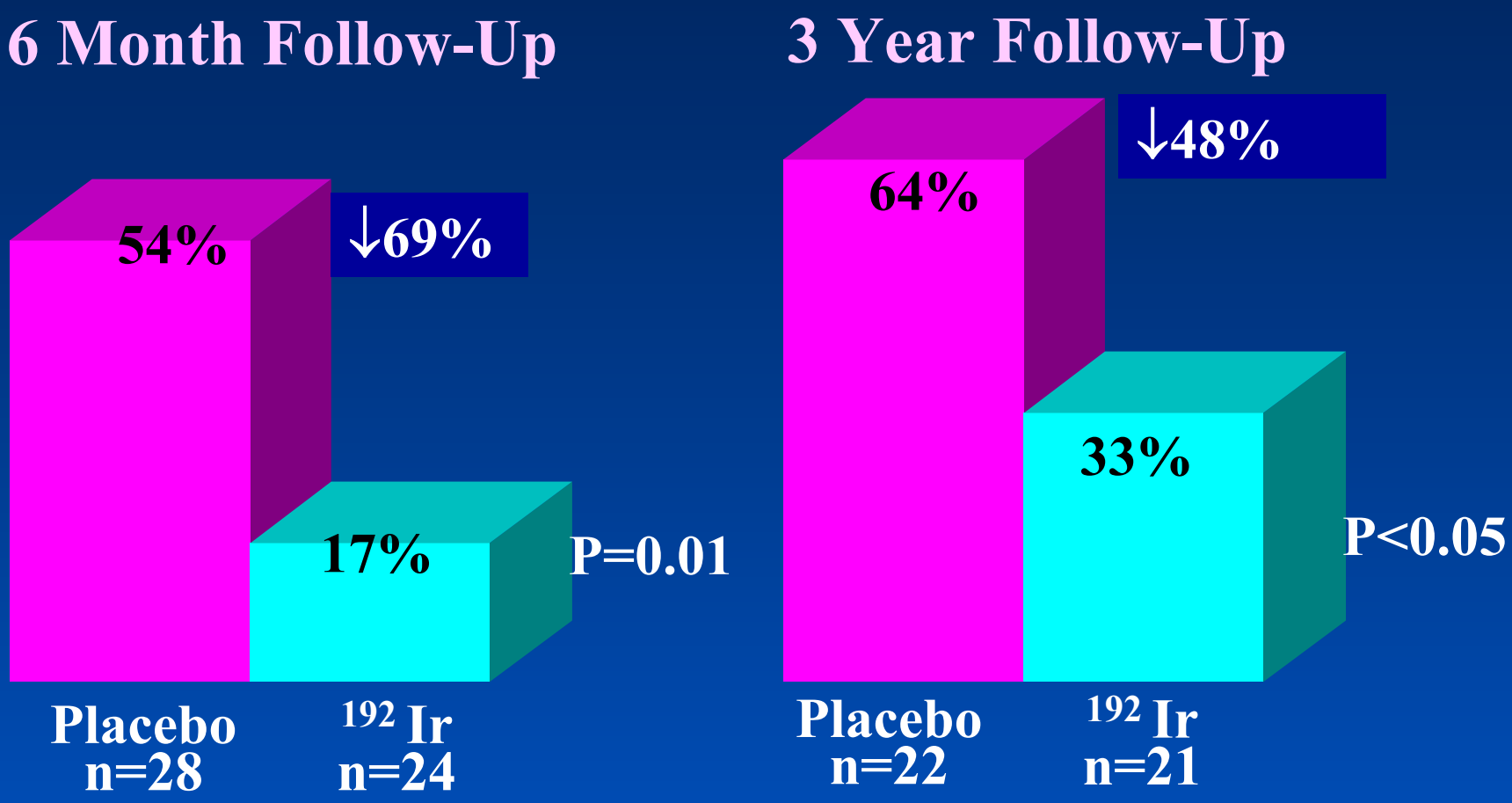
- Technical consideration
- Late thrombosis
- Edge effect
- Late catch-up

SCRIPPS Trial : 3 Year Follow-Up

Diameter Stenosis in Subgroup of Patients without TLR by 6 month angiogram



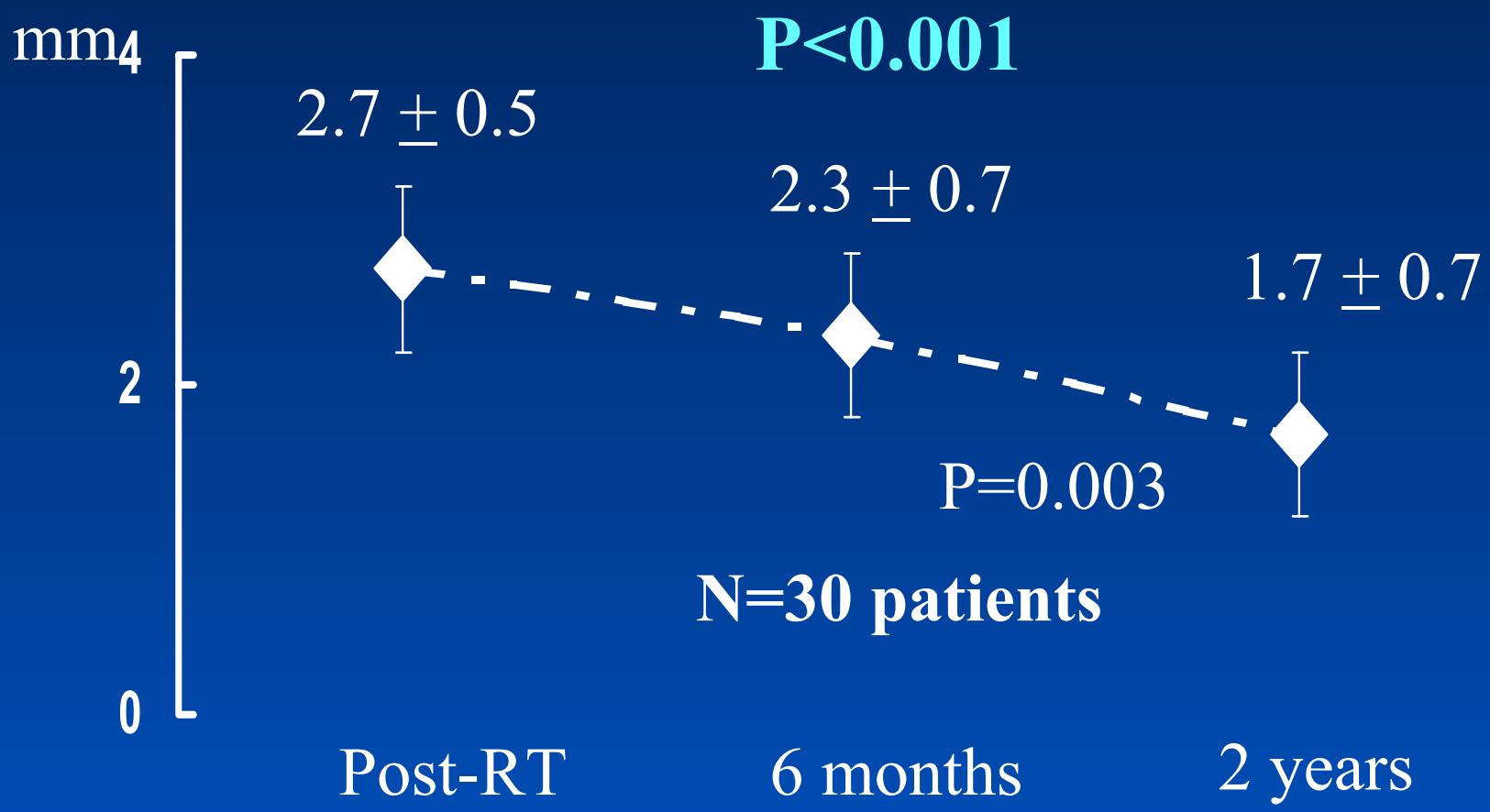
SCRIPPS Trial : 3 Year Follow-Up
Restenosis Rate



Teirstein et al, Circulation 2000;101:360

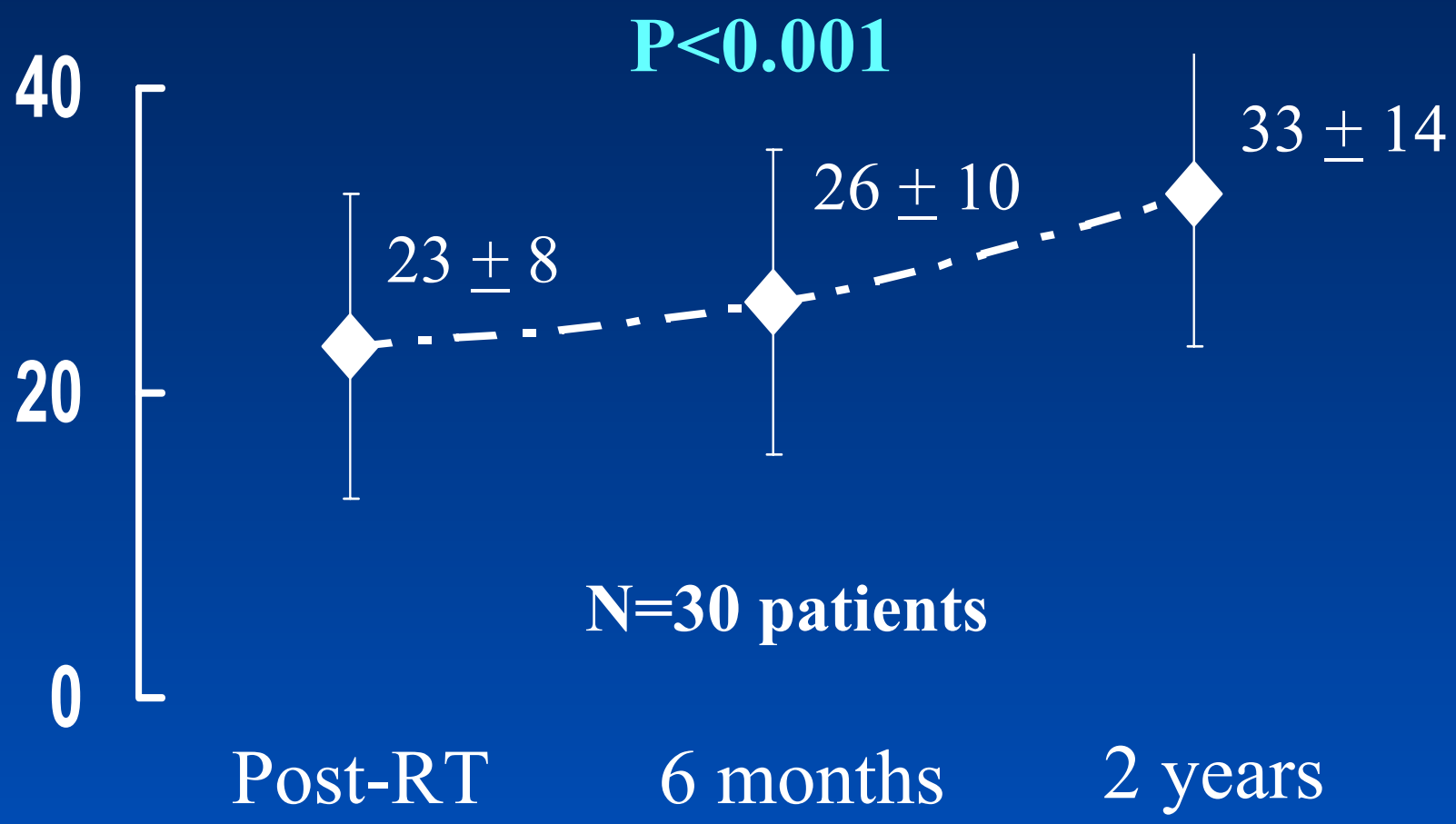
Beta-Radiation for Diffuse ISR

Minimal Lumen Diameter



Beta-Radiation for Diffuse ISR

Intimal Hyperplasia Volume

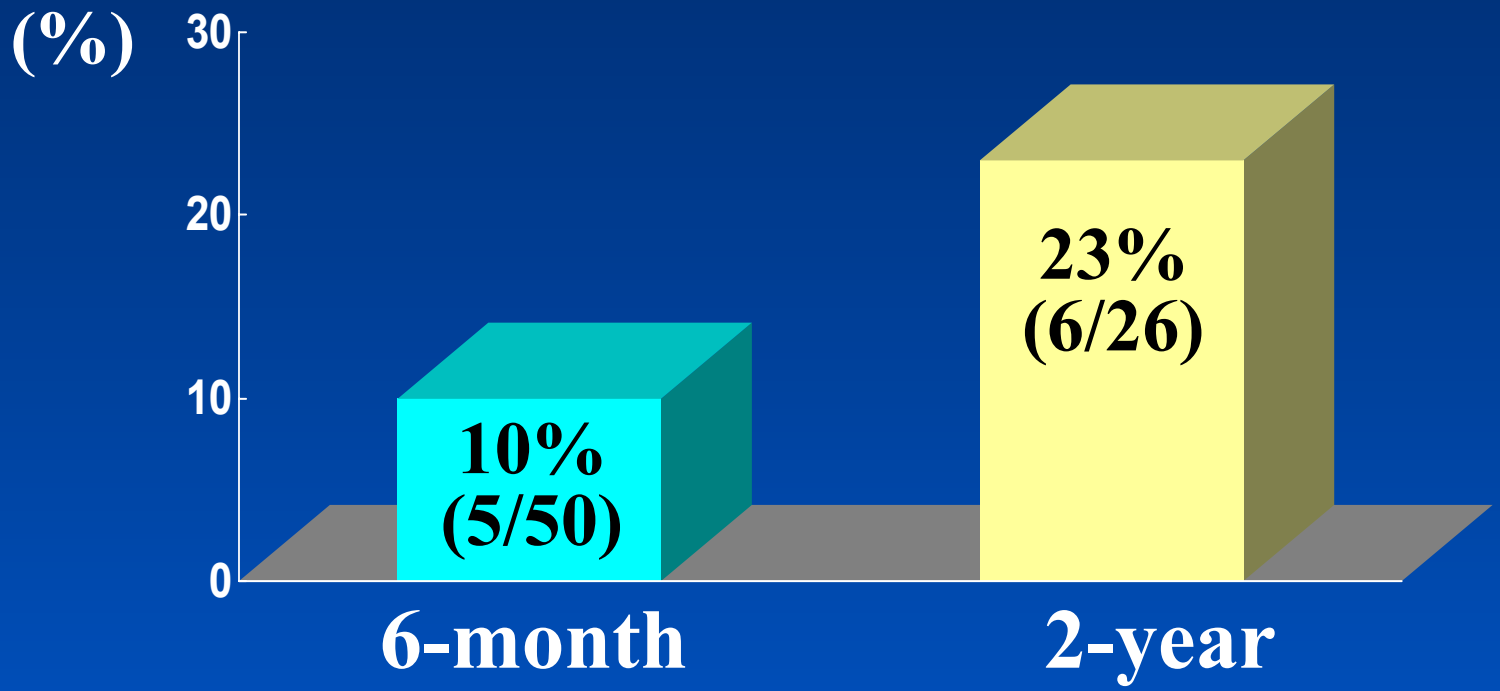


Rotablation and RT for Diffuse ISR

Restenosis Rate

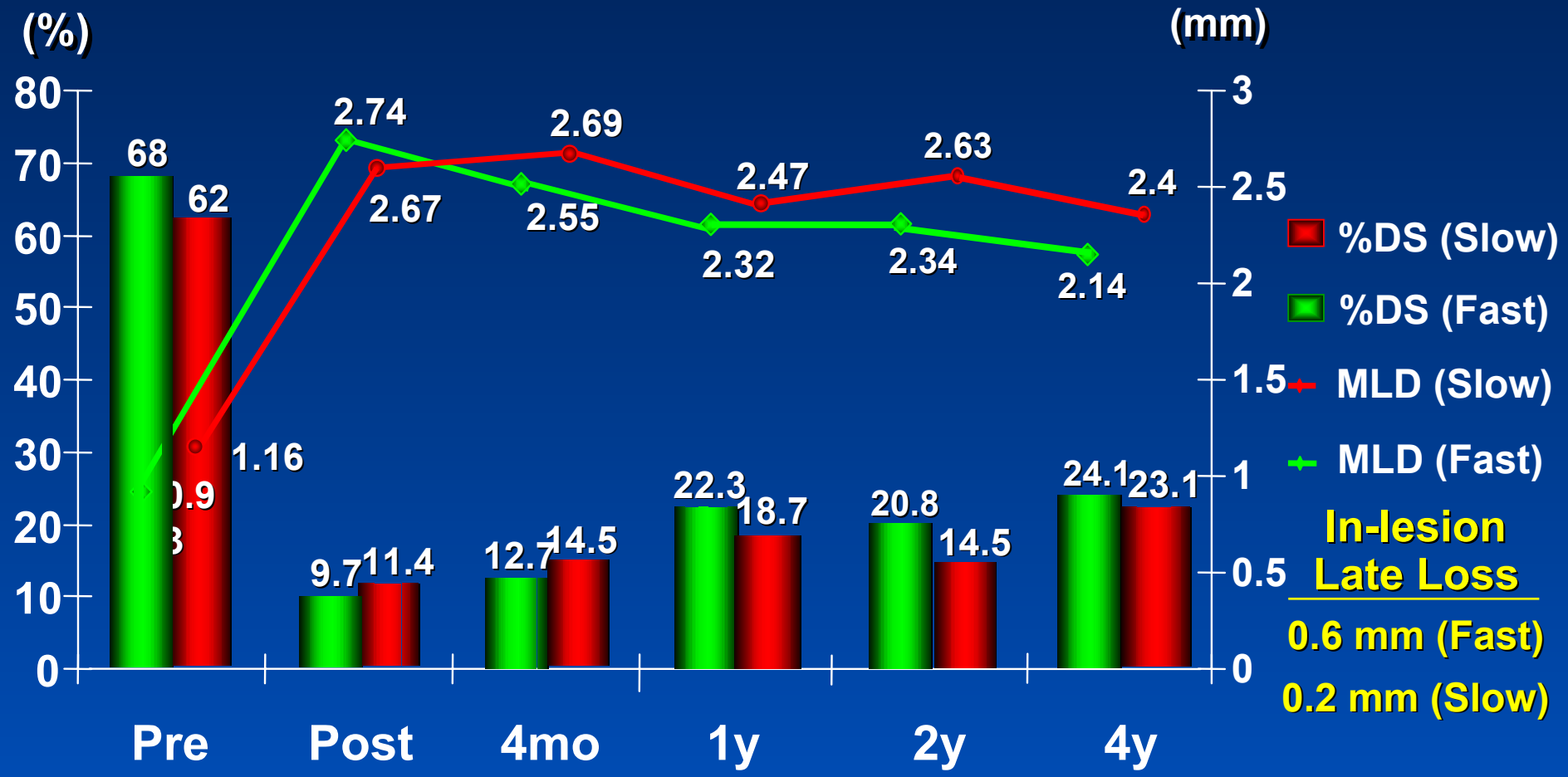
N = 50 patients
FU = 50/50 (100%)

N = 45 patients
FU = 26/45 (58%)



FIM (Siirolimus-Eluting Stent)

% DS and MLD of In-lesion



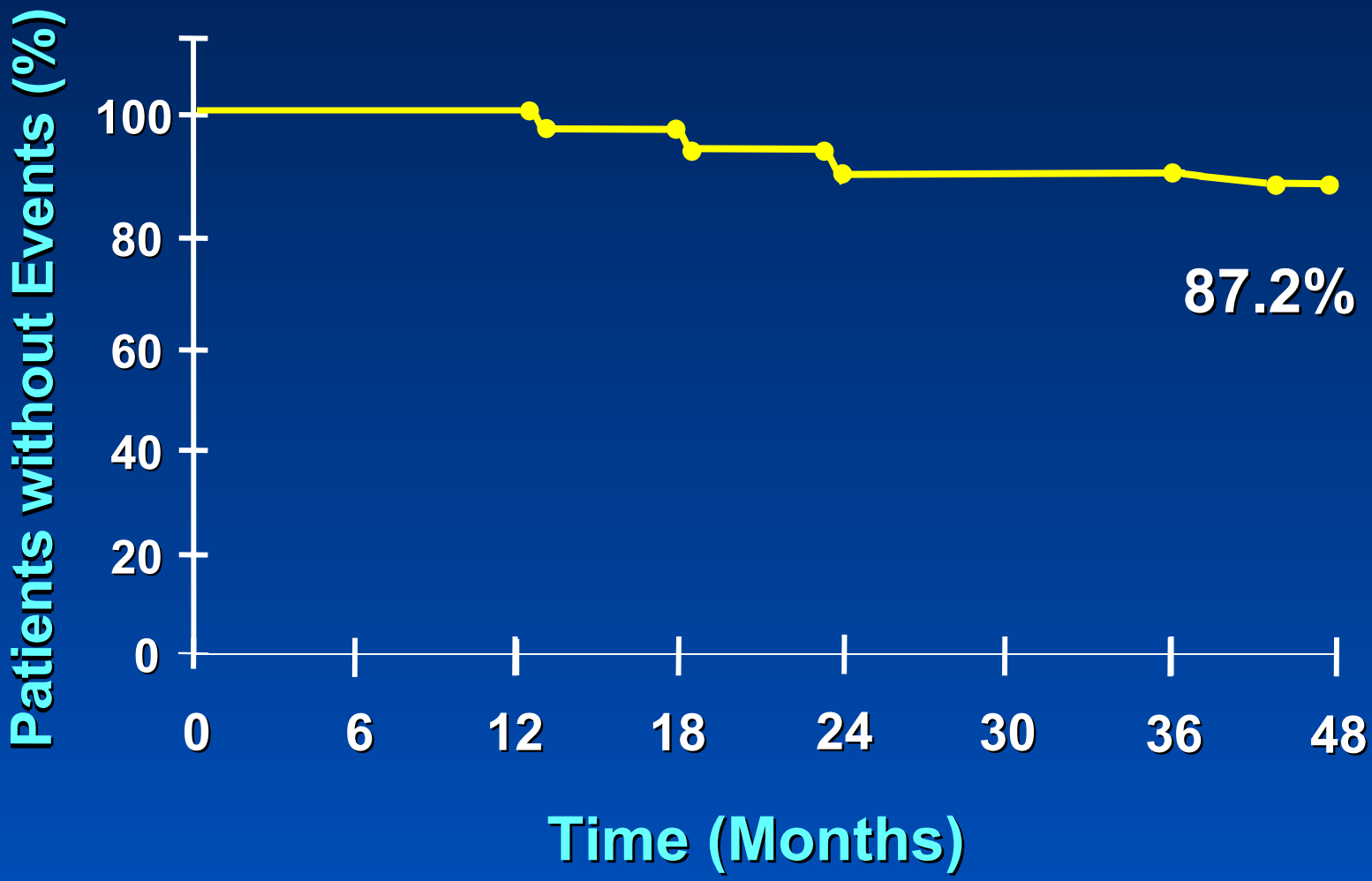
FIM (Siirolimus-Eluting Stent)
Volumetric Analysis in In-Stent

	Fast Release (n = 14)			Slow Release (n = 14)		
	1y	2y	4y	1y	2y	4y
Stent volume (mm^3)	147.5	160.5	140.4	136.2	124.9	145.9
Lumen volume (mm^3)	145.2	145.8	130.1	132.8	120.9	137.3
NIH volume (mm^3)	2.4	14.5*	12.5*	3.4	4.0	8.7
Obstruction (%)	2.3	9.2	9.1	2.2	3.3	5.7

* p = 0.001

FIM Trial

4-Year Event Free Survival (Death, MI, CABG, Re-PCI)



RT vs. DES

Theoretical Issues

- Technical consideration
- Late thrombosis
- Edge effect
- Late catch-up

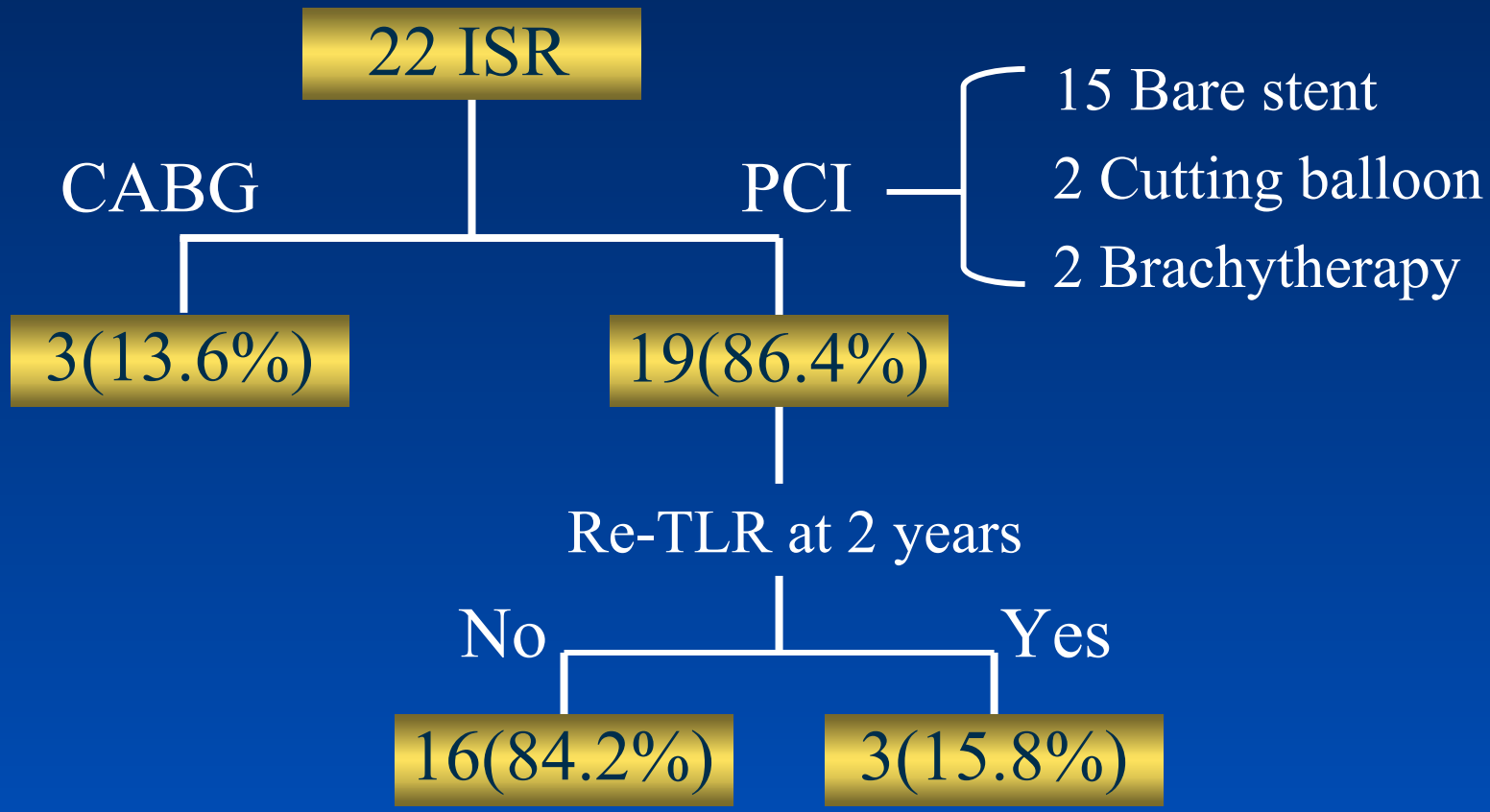
DES is more user-friendly and better outcomes (?) than RT

RT vs. DES

Data at the present time

Fate of ISR in DES

22 ISRs of 528 patients in SIRIUS



RT vs. Cypher

RESEARCH

Non-randomized comparison

Brachytherapy

Catheter-delivered ß-radiation
-Betacath (Novoste, Norcross, GA)
-Galileo (Guidant corporation, Santa Clara CA, USA)

Irradiated length
48 ± 12 mm

Radiation dose
23 ± 2 Gy

SES

Stent implanted
2.0 ± 1.4 stents/patient

Stented length
28 ± 20 mm/lesion

Stent implantation: 27% of patients

Saia F et al. Catheter Cardiovasc Interv, in press

RT vs. Cypher

RESEARCH

	VBT (n=43 pts)	SES (n=44 pts)	p
Age, y ± SD	61±10	63±13	0.5
Males, n (%)	31(73)	32(73)	0.9
Diabetes mellitus, n (%)	11(26)	11(25)	0.1
Hypertension, n (%)	13(30)	21(48)	0.09
Previous MI, n (%)	20(47)	23(52)	0.6
Previous CABG, n (%)	9(21)	10(23)	0.8
Multivessel disease, n (%)	20(47)	22(50)	0.7
Stable angina, n (%)	34(79)	32(73)	0.6
ACS	9(21)	12(27)	-

Saia F et al. Catheter Cardiovasc Interv, in press

RT vs. Cypher

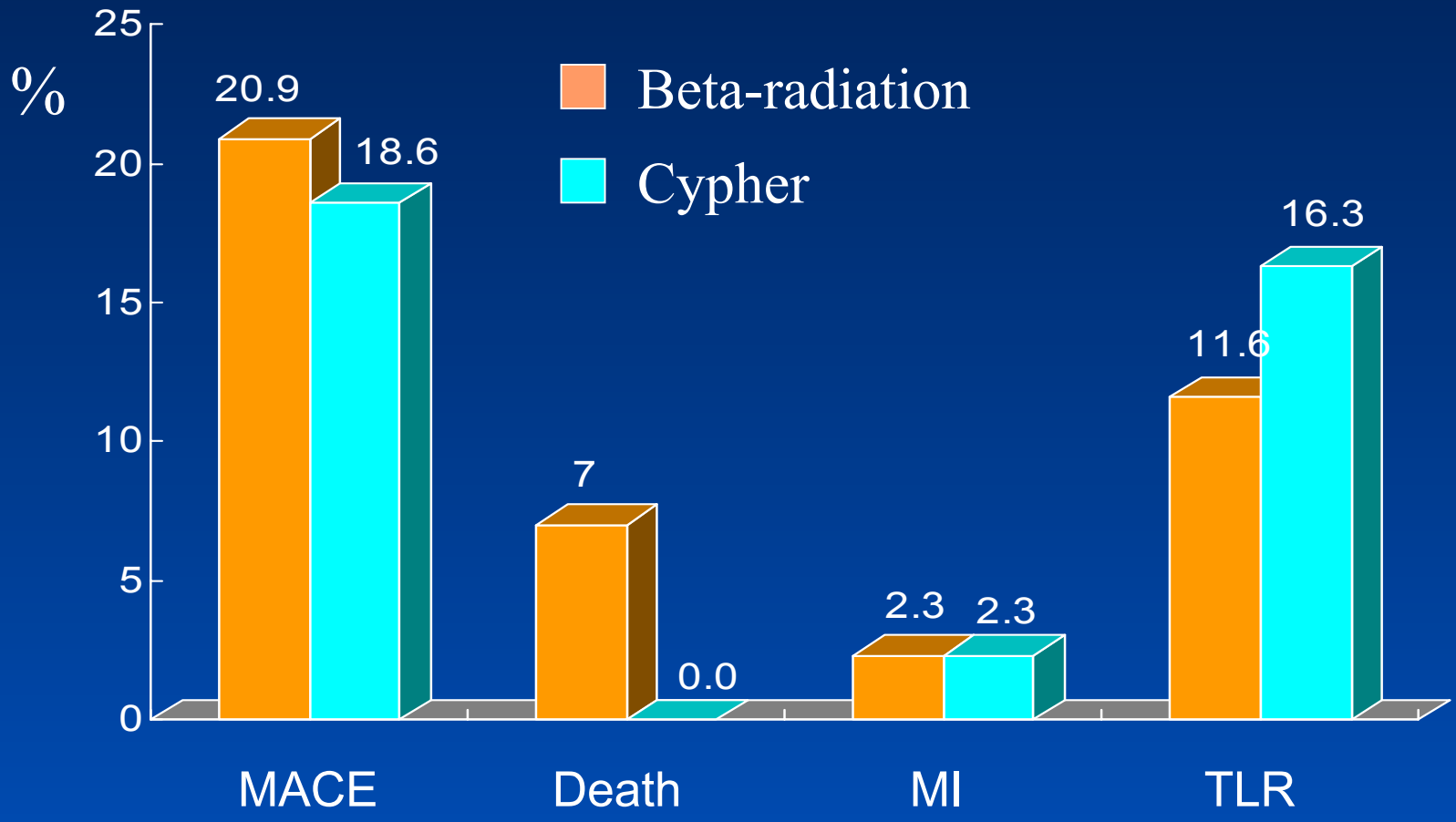
RESEARCH

	VBT (n=43 pts)	SES (n=44 pts)	p
Number lesions treated	44	53	-
Lesions per patients	1.0±0.2	1.2±0.5	0.02
Mehran class I-II, %	66	63	0.7
Mehran class III-IV, %	34	37	0.7
Procedural success, %	98	98	0.1
IIb/IIIa inhibitors, %	33	9	0.007
Clopidogrel, mo ± SD	7.5±5.5	5.9±2.6	0.005

Saia F et al. Catheter Cardiovasc Interv, in press

RT vs. Cypher

9-Month Outcomes in RESEARCH Registry



Saia F et al. Catheter Cardiovasc Interven (In press)

Randomized Comparison in AMC

Diffuse (≥ 10mm) In-Stent Restenosis

Randomization (1:1)

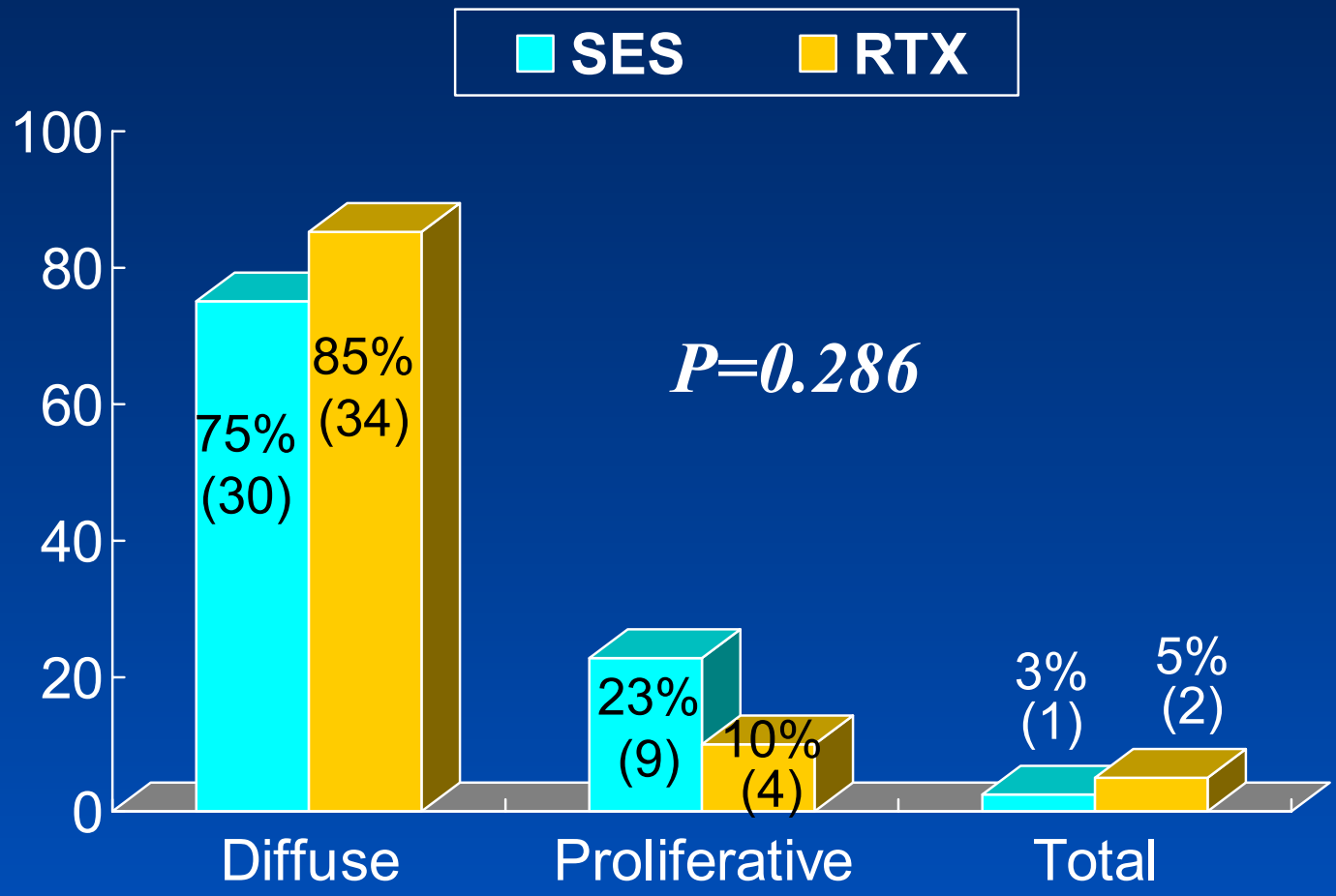
Sirolimis-Eluting Stent Implantation

Complete lesion coverage with Cypher stents

Brachytherapy with ^{188}Re after cutting balloon angioplasty

Radiation dose of ***20 Gy at a depth of 1.0 mm*** into the vessel wall

Restenosis Pattern



QCA Analysis

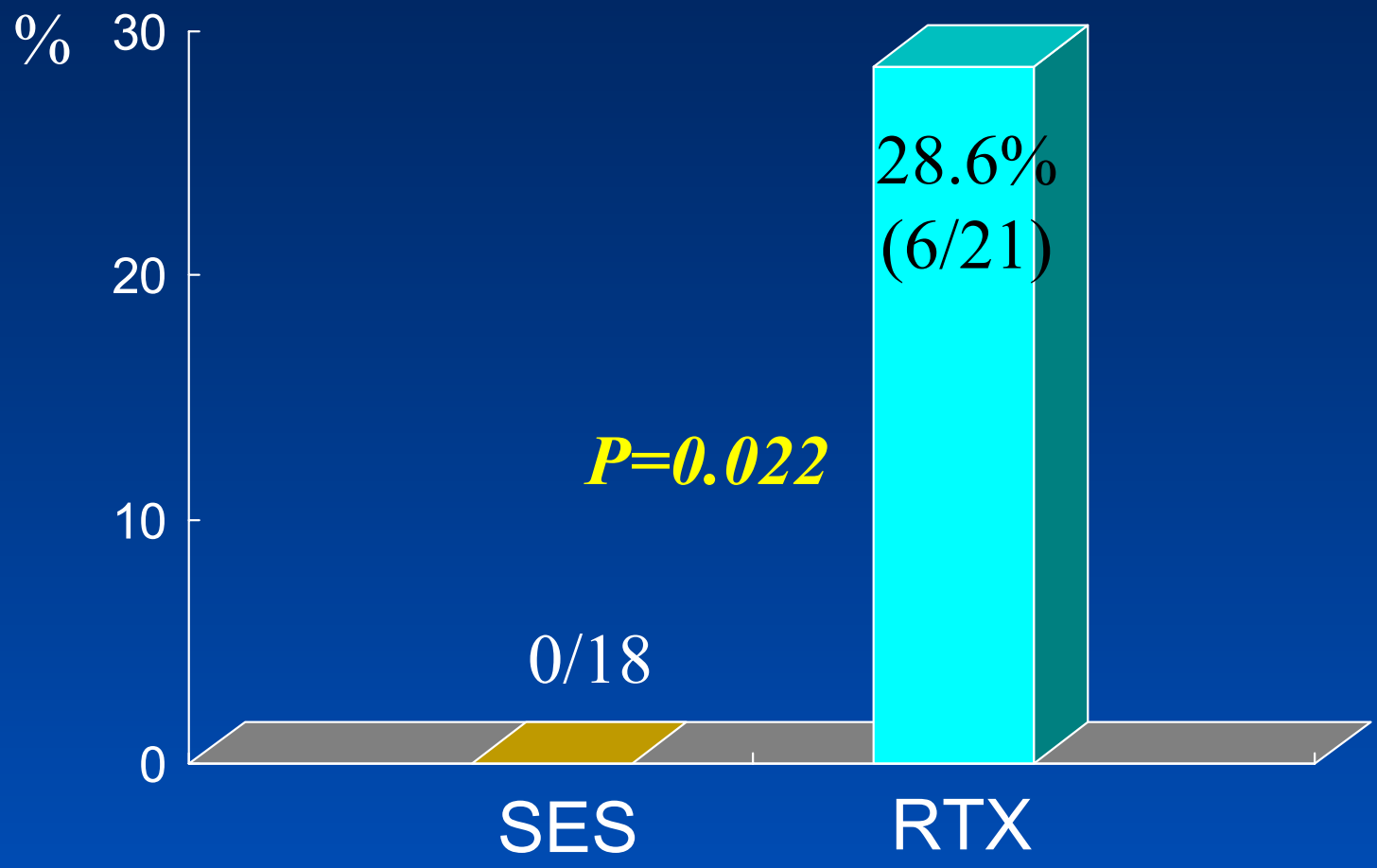
	Cypher	RT	P value
Pre-procedure			
Reference vessel (mm)	2.96±0.55	2.86±0.56	0.446
MLD (mm)	0.89±0.43	0.83±0.35	0.473
Diameter stenosis (%)	69.9±13.8	70.6±12.6	0.831
Lesion length (mm)	31.7±12.4	32.8±16.6	0.744
Post-procedure			
MLD (mm)	2.92±0.45	2.42±0.44	<0.001
Diameter stenosis (%)	0.19±13.6	14.2±14.1	<0.001
Acute gain (mm)	2.02±0.51	1.59±0.52	<0.001

QCA Analysis

Follow-UP Results

	Cypher	RT	p
Follow-up	18	21	
Reference (mm)	2.83±0.44	2.74±0.36	0.606
MLD (mm)	2.38±0.66	1.67±0.73	0.017
DS (%)	15.4±19.9	39.6±24.0	0.012
Late loss (mm)	0.75±0.39	0.94±0.66	0.388

Restenosis Rate



6-Month Clinical Results

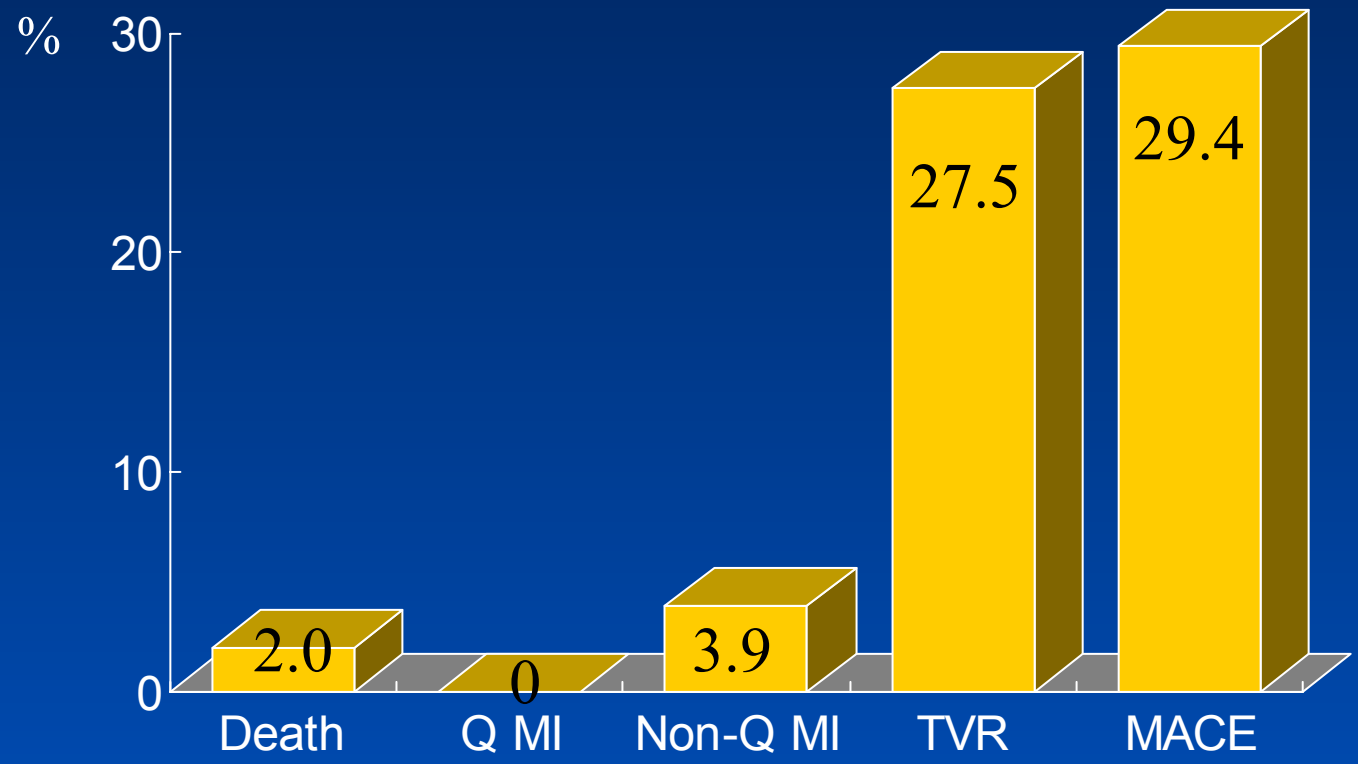
	Cypher	RT	P value
Eligible	24	27	
Death	0	0	
MI	0	0	
Q-wave			
Non-Q-wave			
Thrombosis	1 (4%)	0	1.000
TLR	1 (4%)	3 (11%)	0.612
MACE	1 (4%)	3 (11%)	0.612

How to treat RT failure lesion ?

Very little data

Repeat RT for RT Failure

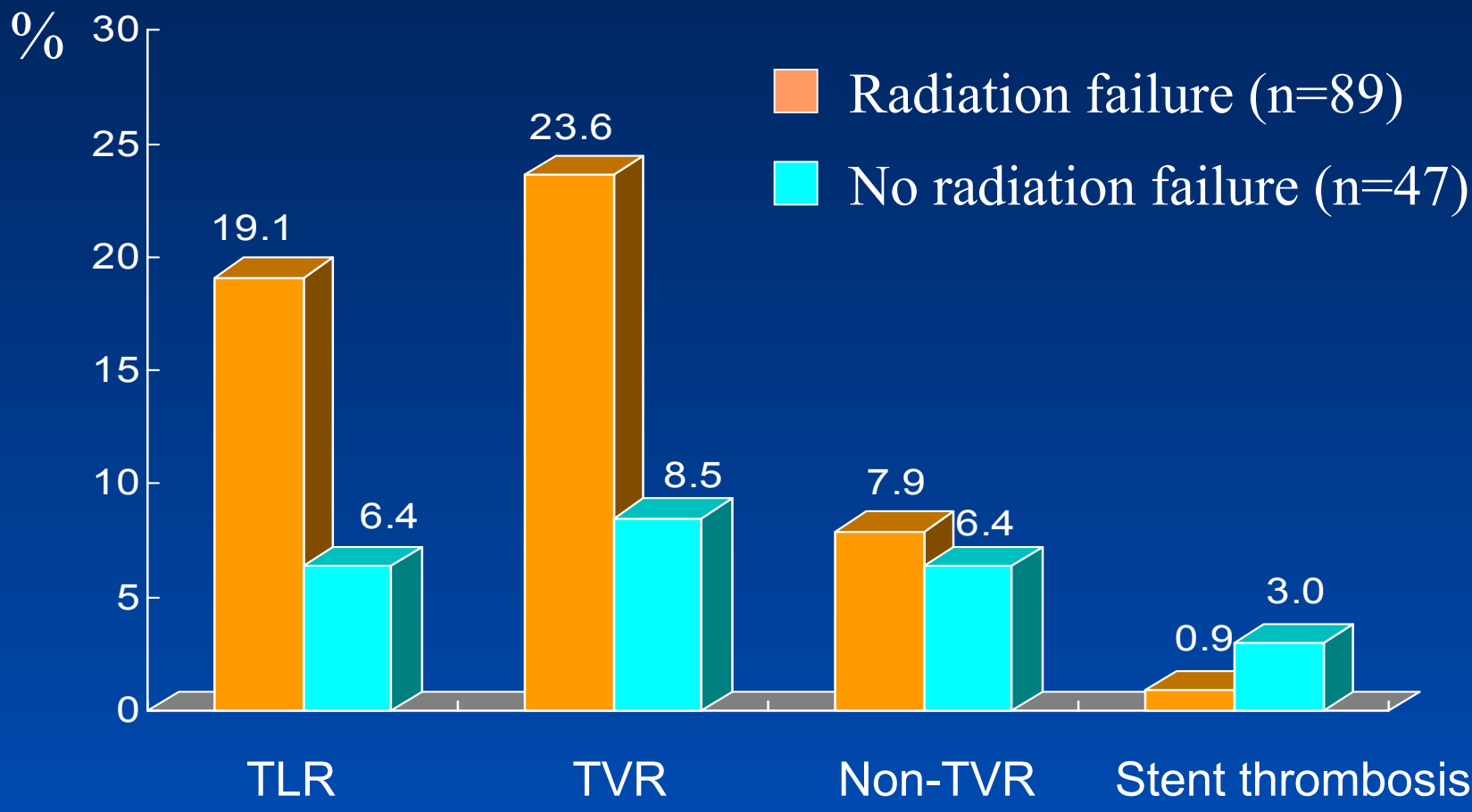
9-Month Events of 51 patients



Waksman R et al. ***Circulation*. 2003;108:654**

Cypher for Radiation Failure

6-Month Outcomes in SECURE registry



Teirstein PS et al. AHA 2003

Conclusions

- Intracoronary radiation therapy has been a viable therapeutic option for ISR lesions.
- However, recent studies have shown encouraging results for drug-eluting stent implantation for ISR lesions.
- Large randomized study comparing the efficacy of DES with brachytherapy for diffuse ISR is warranted.