PCI for Lesion with In-stent Restenosis

The history of angioplasty is …

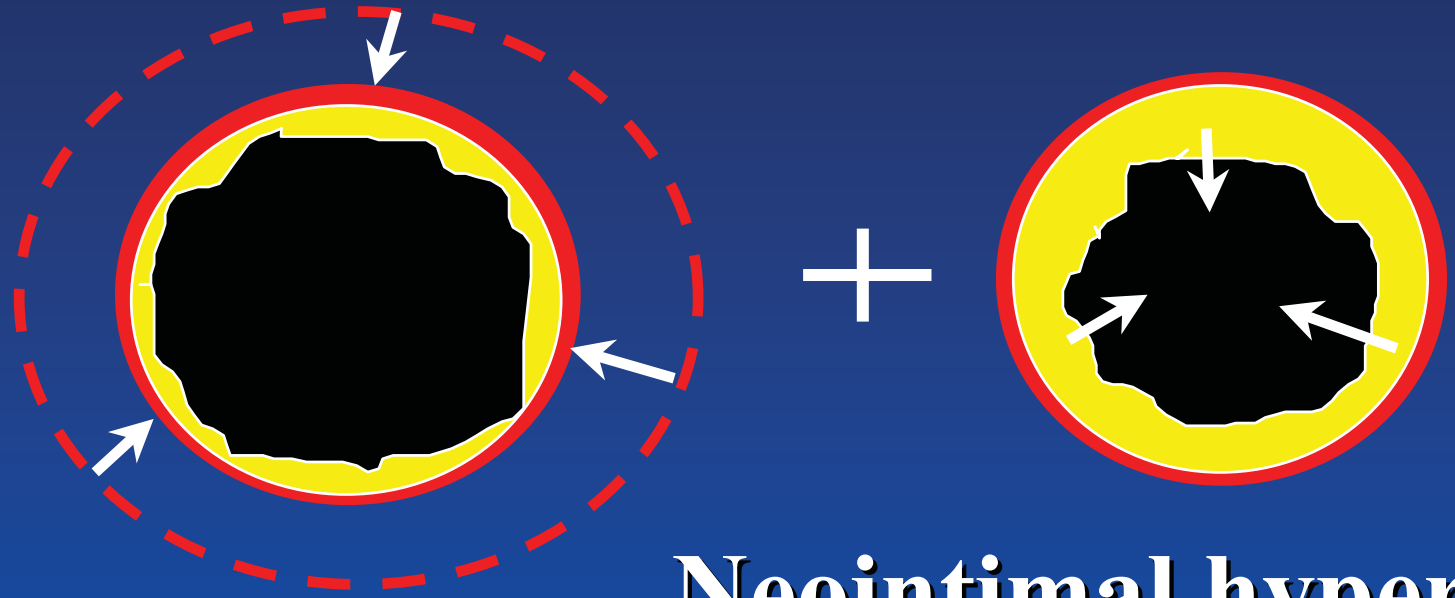
… The history of response to Restenosis

An Evolutionary Process of PCI

1977 – 1988	Balloon Angioplasty
1988 – 1993	New Device Angioplasty
1993 –	Stent Era
1997 –	Vascular brachytherapy
2001 –	Drug-Eluting Stent

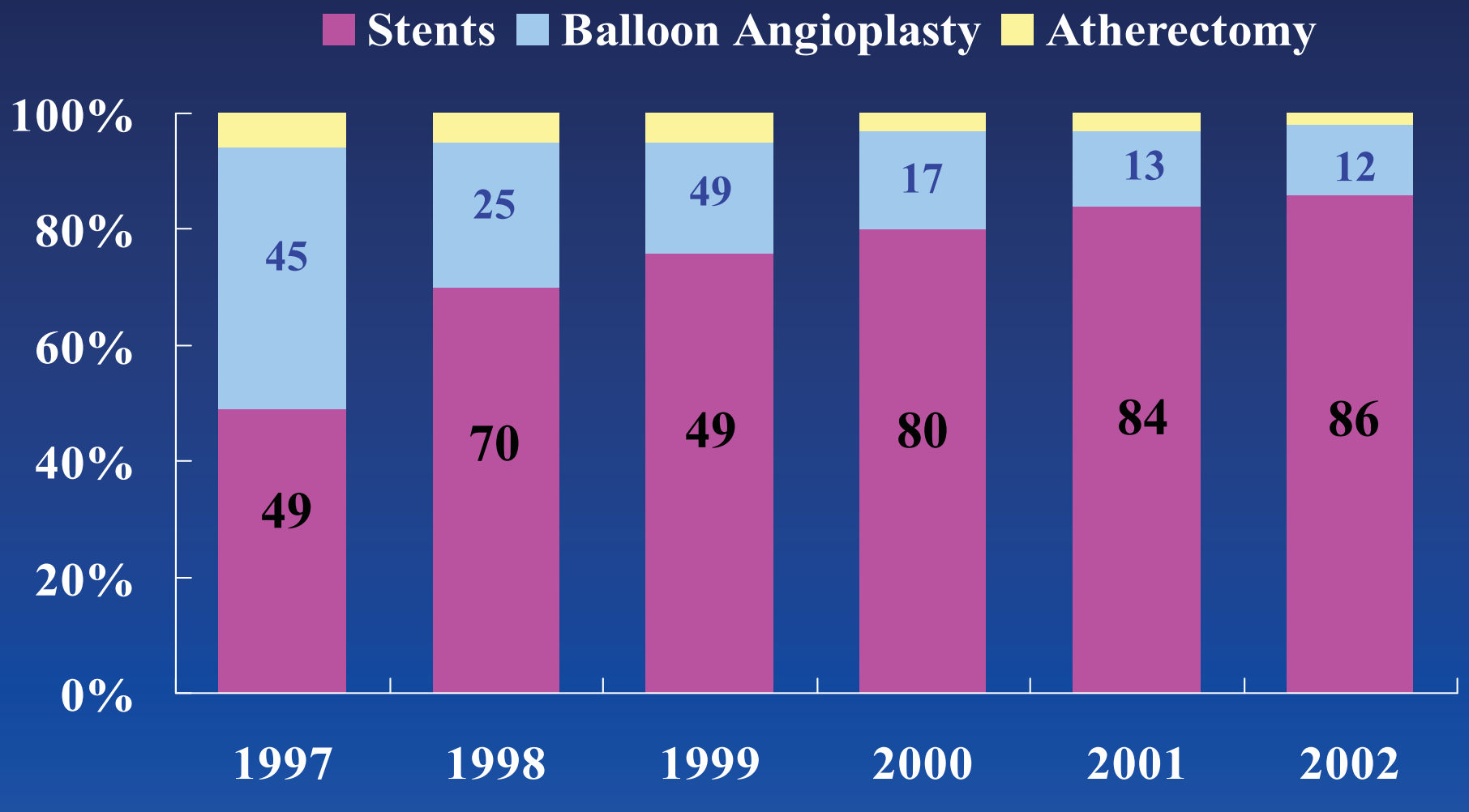
Balloon Angioplasty & Restenosis

Recoil and remodeling



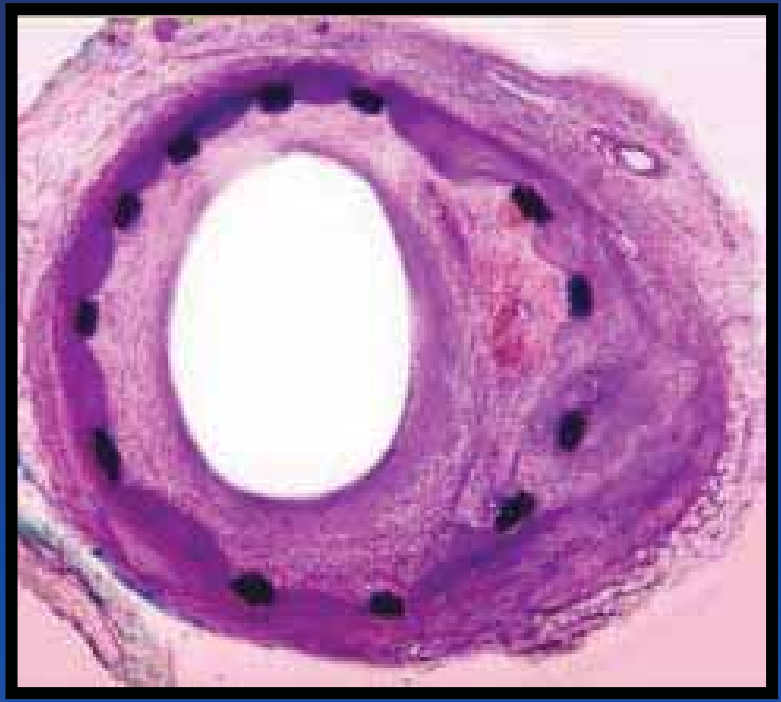
Neointimal hyperplasia

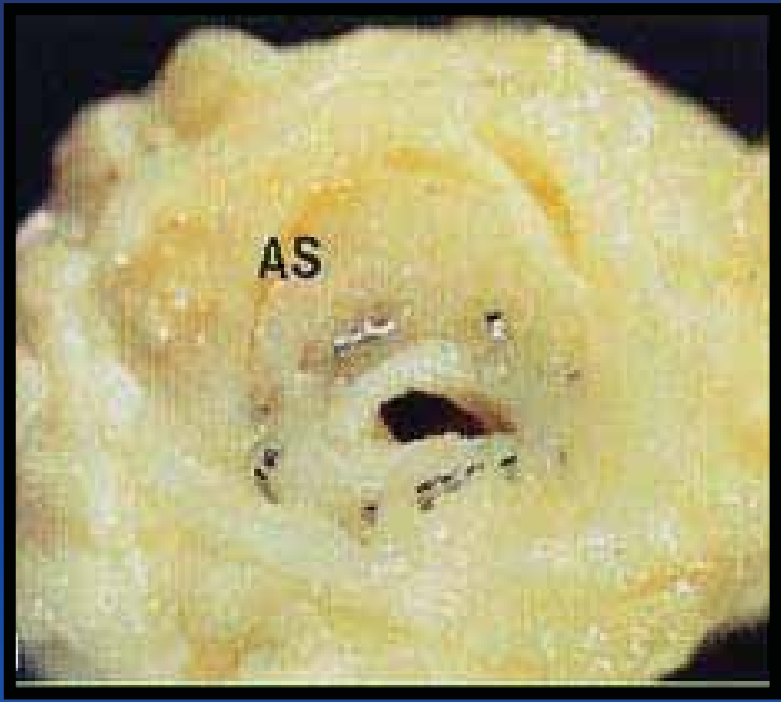
Intervention 2003



In-Stent Restenosis

is the most serious problem (20-25%)





“ The dream ”
of interventional cardiology will be …

No Restenosis !

Restenosis

Cause

Recoil and remodeling

Neointimal hyperplasia

Solution

- Stents will prevent vascular recoil and remodeling
- Active therapeutic agent is required to block neointimal hyperplasia

Treatment of Diffuse ISR

Effective Treatment Tools?

- Intracoronary Brachytherapy
- Drug-eluting stent

Intracoronary Brachytherapy

Mechanism of Radiation

Prevent Restenosis

- Target : Adventitial myofibroblast
- Inhibition of neointima
  and negative remodeling

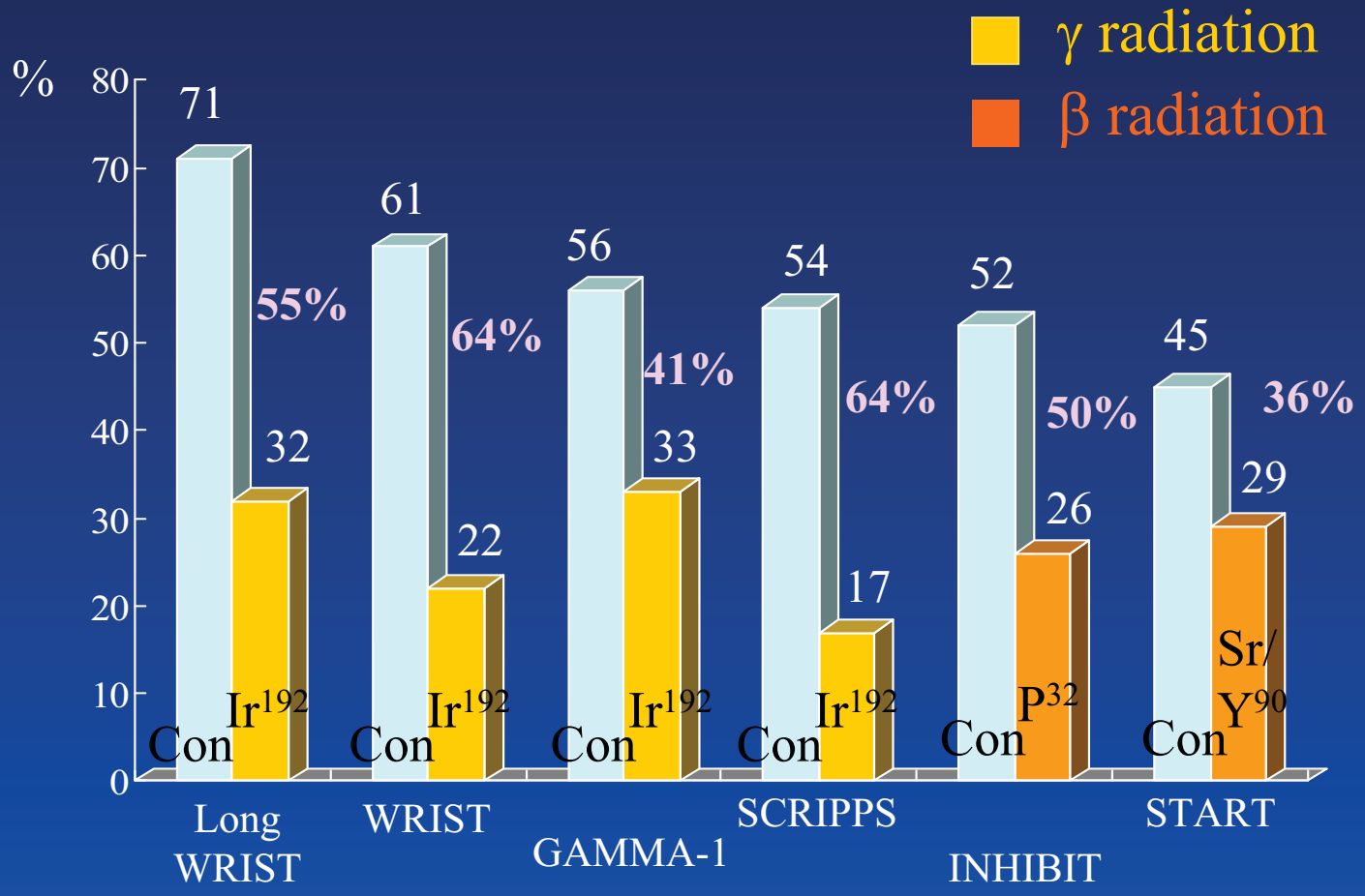
Brachytherapy

Reported Clinical Trials for ISR

TRIAL	Sourse	Length (mm)	Pts (n)	Restenosis % Placebo	Restenosis % 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

Brachytherapy to Treat ISR

Reduction of Re-ISR



Current Status
Vascular Brachytherapy

- Randomized trials showed a 35-70% reduction in the recurrence rate of instent restenosis
- The Late thrombosis phenomenon reported to resolved with prolonged antiplatelet therapy *(WRIST PLUS, SCRIPPS III, START, INHIBIT)*

What We need As a Pretreatment Before Brachytherapy ?

Simple Balloon.

Rotablation.

Cutting Balloon.

^{188}Re-MAG_3 - Beta Radiation

- Rapid fall-off radiation dose within 2 mm
- The increased chance of inhomogeneous dose delivery to target tissue (esp. eccentric plaque)

Role of Rotablation

Rotational Atherectomy before Beta Radiation

Produce concentric and thinner neointima structure ; Radiation dose can be homogeneously delivered to target tissue

AMC Experience

R4 Trial

Radiation with ^{188}Re-MAG_3-filled balloon after Rotablation for diffuse in-stent Restenosis

SW Park, et al. JACC 2001:38:631-7

Inclusion Criteria

- Diffuse In-stent Restenosis (>10mm in length)
- Total occlusion

SW Park, et al. JACC 2001:38:631-7

Subject

From March 1999 to May 2001

103 patients (57 yrs, M/F: 80/20)

Diffuse ISR

(mean lesion length 24.1+21.9 mm)

SW Park, et al. JACC 2001:38:631-7

Design

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*

SW Park, et al. JACC 2001:38:631-7

Lesion Length

	Rota +RT (n=50)	Balloon +RT (n=53)
Mean Lesion Length	25.6±12.7	22.9±8.8 (mm)
>10,<20 (mm)	21(42)	20(38)
>20,<30	13(26)	23(43)
>30	16(32)	10(19)
*Total occlusion	10(20)	5(10)

SW Park, et al. JACC 2001:38:631-7

Minimal Lumen Diameter

	Rota+RT (n=50)	Balloon+RT (n=53)	p-value
Baseline (mm)	0.60 ± 0.44	0.70 ± 0.37	0.159
Final	2.68 ± 0.39	2.61 ± 0.44	0.355
Follow-up	2.31 ± 0.60	1.94 ± 1.00	0.004*
Acute gain	2.08 ± 0.46	1.91 ± 0.48	0.875
Late Loss	0.36 ± 0.64	0.66 ± 1.20	0.001*
Loss index	0.17 ± 3.10	0.45 ± 0.57	0.001*

SW Park, et al. JACC 2001:38:631-7

Immediate Results

	Rota +RT (n=50)	Balloon +RT (n=53)
Clinical Success(%)	100	100
Procedural Success(%)	100	86
New Stent due to;		
Edge dissection	0	6 (12%)
Intramural Hematoma	0	1 (2 %)
Major complication	0	0
Isotope leakage	0	0

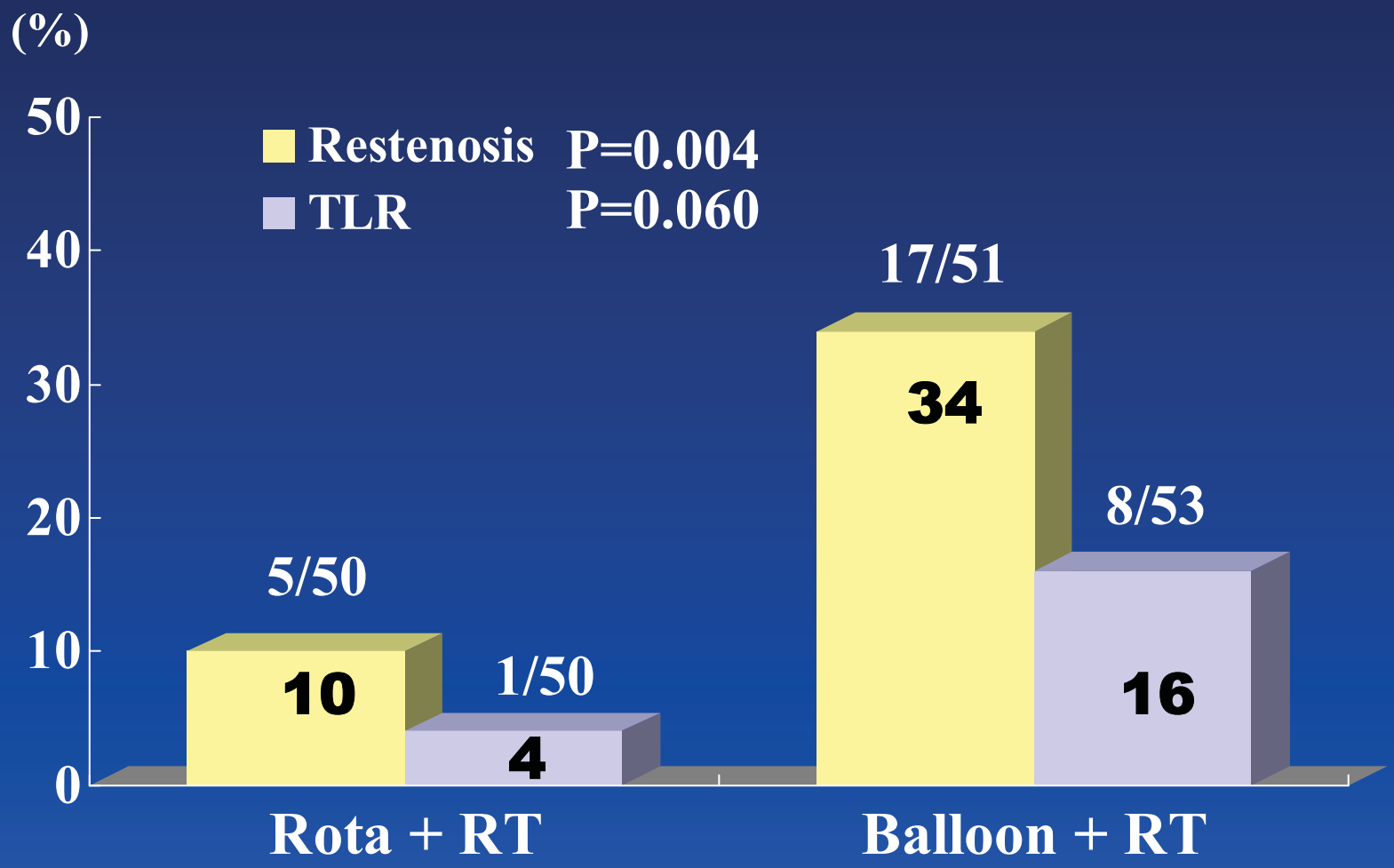
SW Park, et al. JACC 2001:38:631-7

6-month angiographic F/U

	Rota +RT (n=50)	Balloon +RT (n=53)
6 month angiographic F/U (%)	50/50 (100)	51/53 (98)
Restenosis Rate (%)	5/50 (10%)	17/51 (34%)
Instent	4	12
Edge	1	5

SW Park, et al. JACC 2001:38:631-7

6-month angiographic
Restenosis Rate & TLR

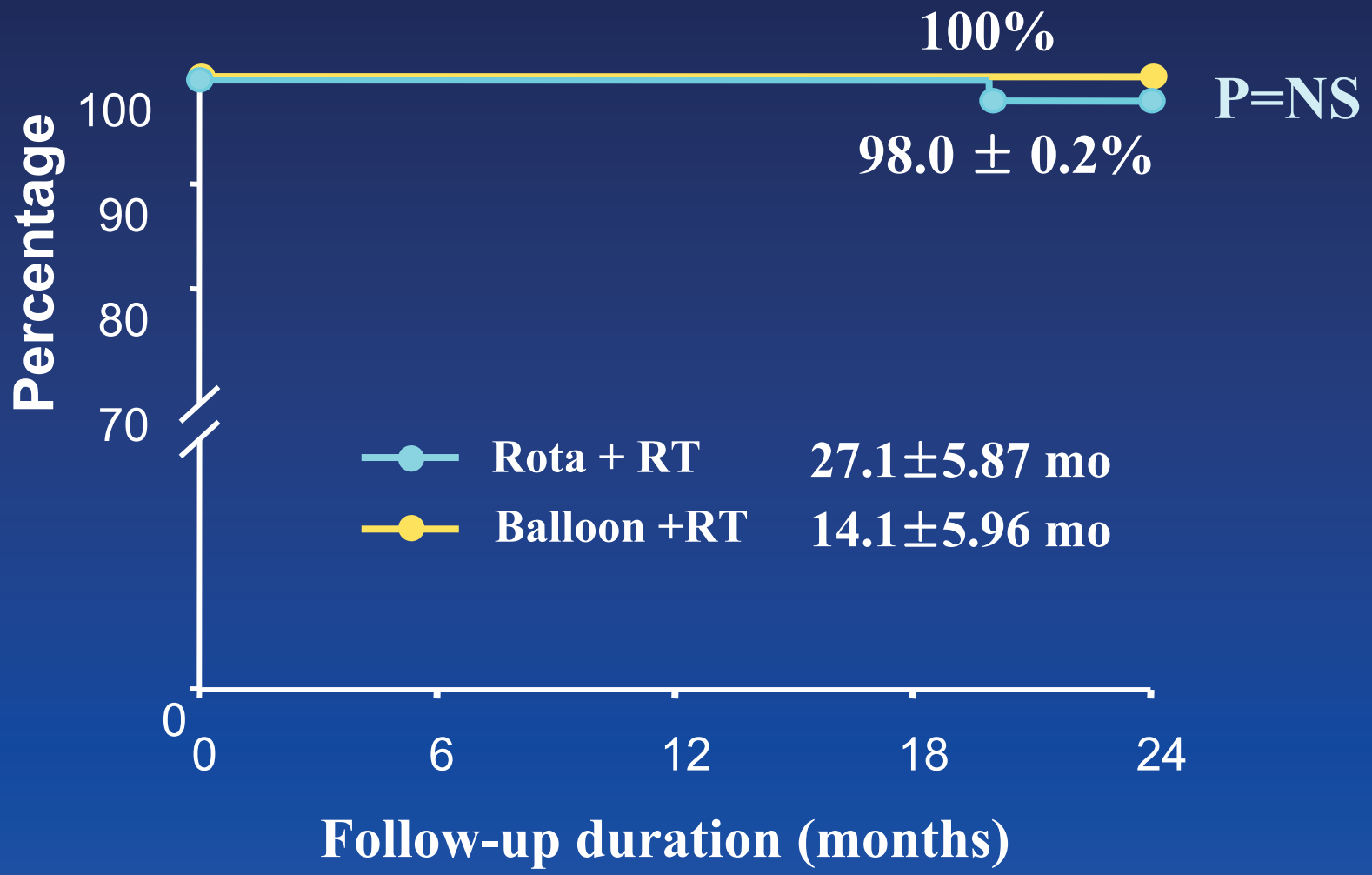


2 year Clinical Follow-Up

	Rota +RT (n=50)	Balloon +RT (n=50)
Restenosis Rate (%)	5/50 (10%)	17/50 (34%)
Symptom Recurrence	2 (4%)	5 (10%)
TLR (%)	2 (4%)	8/50 (16%)
PTCA	0	3
Stent	1	1
CABG	1	1
Rotablation	0	1
RT		1
Cutting balloon		1
Death	1 (2%), Non-cardiac	0

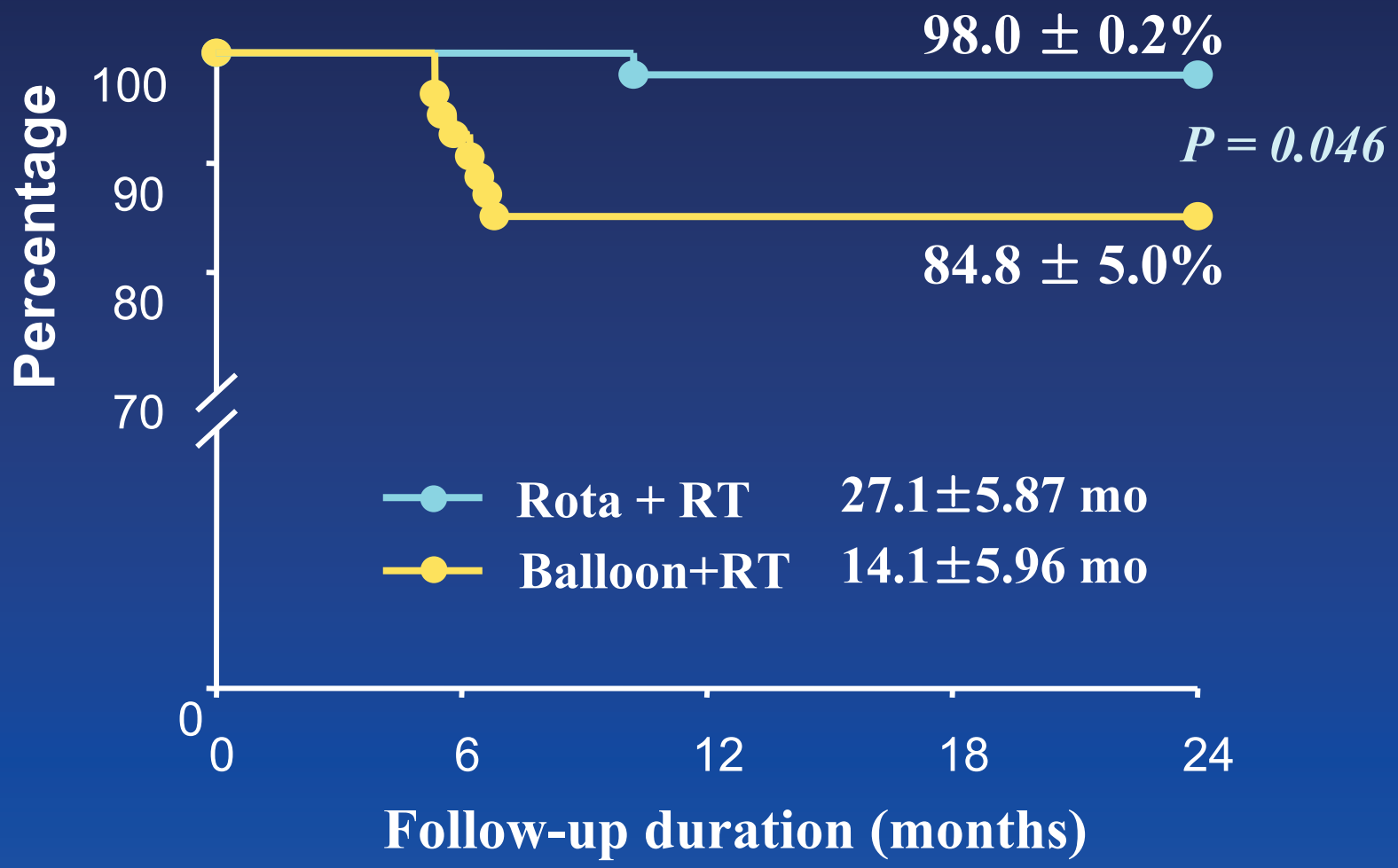
SW Park, et al. JACC 2001

Survival Curve



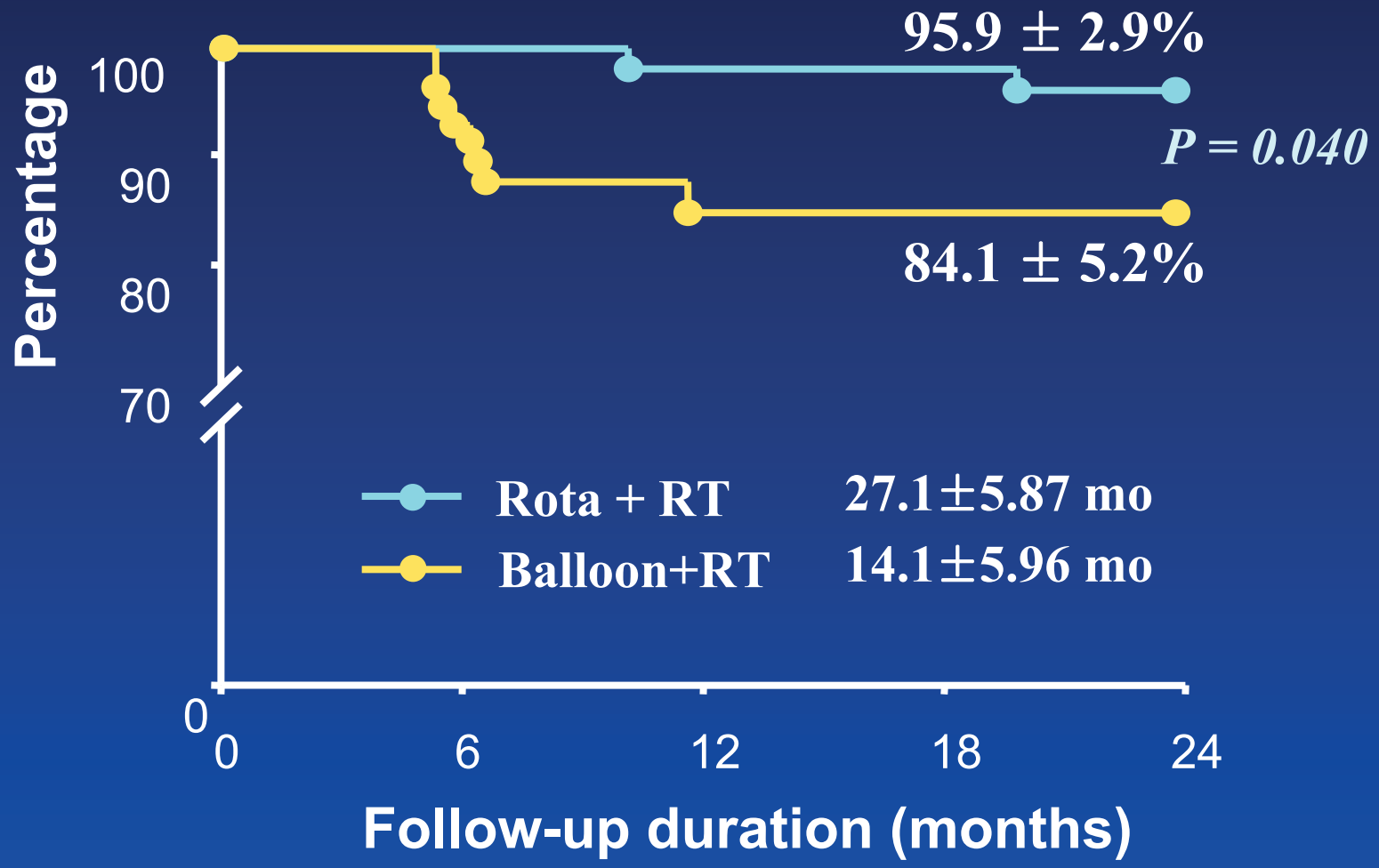
SW Park, et al. JACC 2001:38:631-7

TLR-free Survival Curve



SW Park, et al. JACC 2001:38:631-7

MACE-free Survival Curve



SW Park, et al. JACC 2001:38:631-7

Conclusion

- Intracoronary brachytherapy using ^{188}Re - MAG3 liquid filled balloon system for diffuse ISR is safe and feasible and, effective to prevent recurrent ISR
- Debulking using Rotablation prior to radiation seemed to be beneficial to the late clinical outcomes in restenosis rate and TLR.

SW Park, et al. JACC 2001:38:631-7

Role of Cutting Balloon

Role of Cutting Balloon Without Brachytherapy

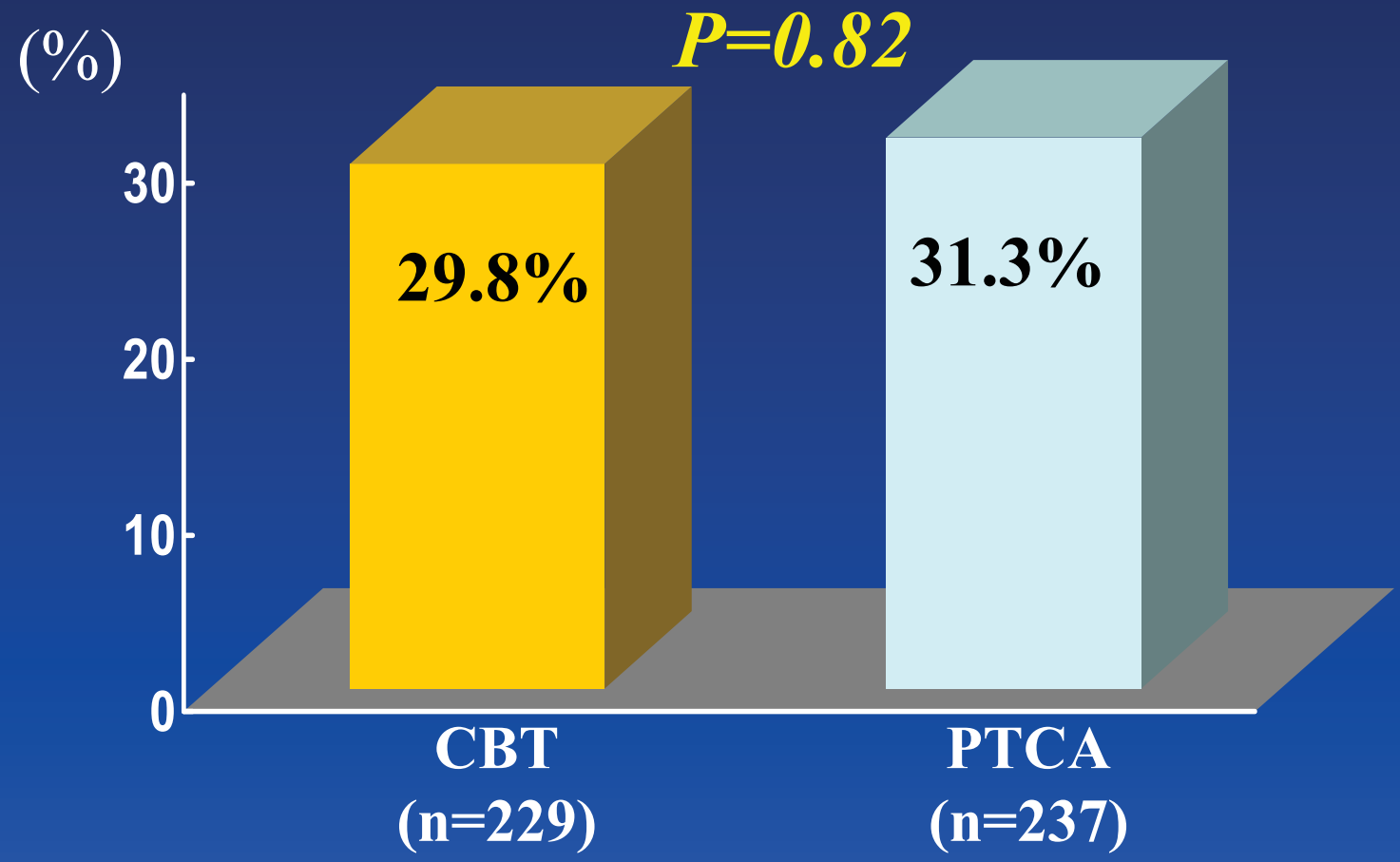
RESCUT

Lesion characteristics

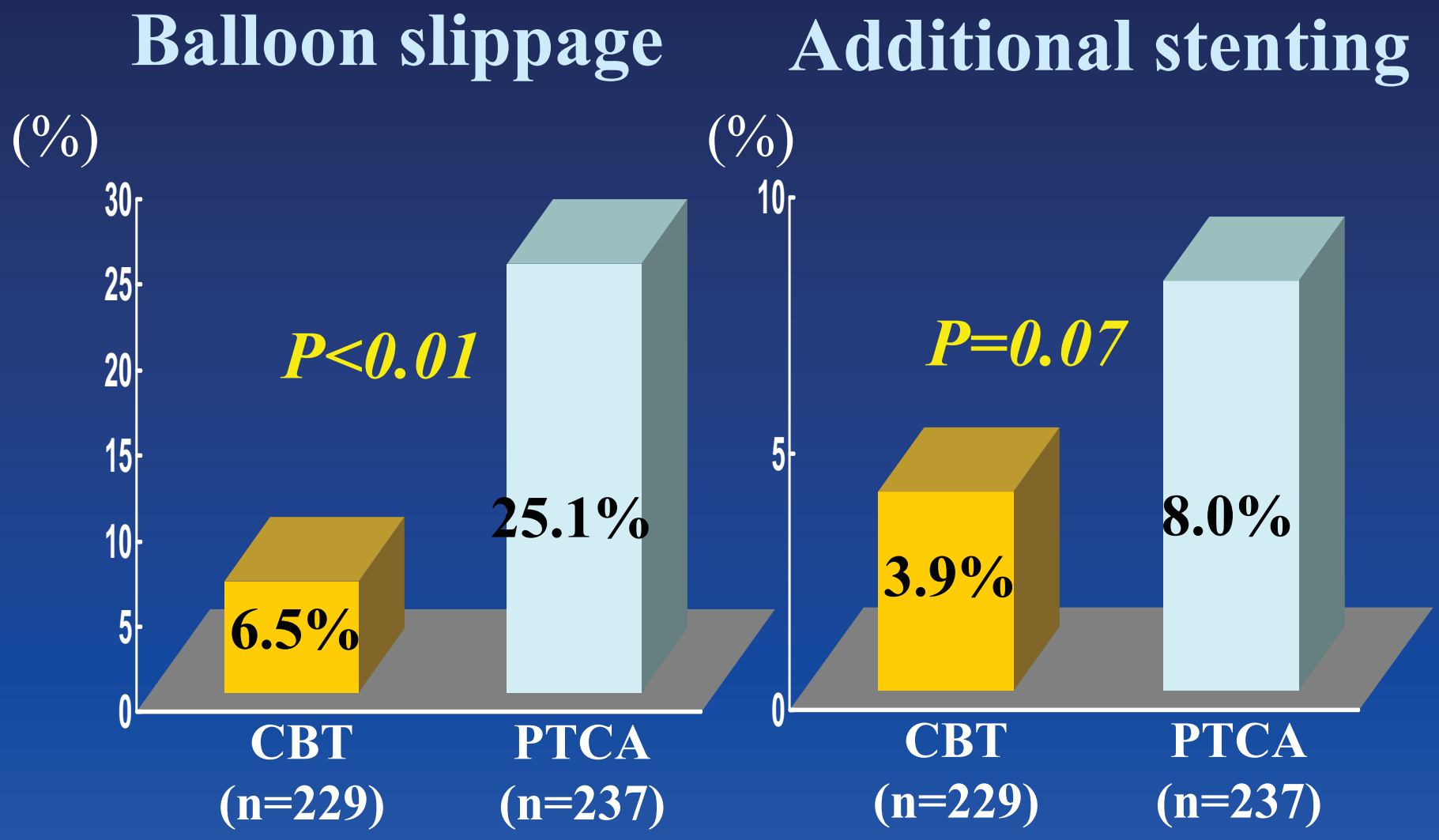
	CB (n=229)	PTCA (n=237)	P value
≤ 20 mm single stent	86.7 %	83.6%	0.44
Focal	55.3	42.3	
Multifocal	12.9	17.2	
Diffuse/Proliferative	31.8	40.5	
> 20 mm single/multiple	13.3 %	16.4%	
Focal	23.1	18.8	
Multifocal	46.1	18.8	
Diffuse/Proliferative	30.8	62.4	

Role of Cutting Balloon Without Brachytherapy RESCUT

Binary Restenosis



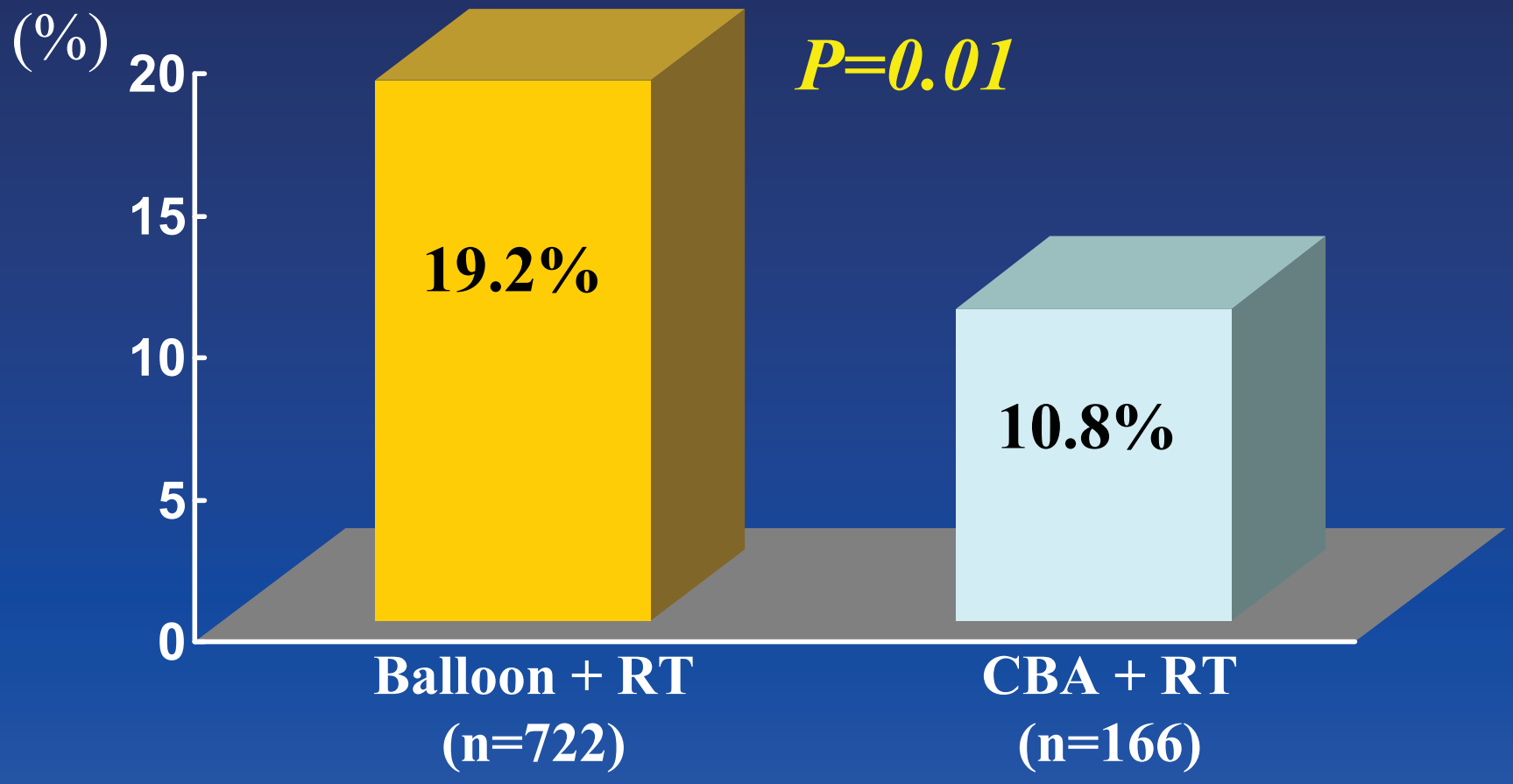
Role of Cutting Balloon Without Brachytherapy RESCUT



Cutting Balloon before Brachyehrapy

RENO Registry (n=1111)

6 Month MACE



Cutting Balloon Angioplasty Vs. Rotational Atherectomy Performed Before Beta Radiation Therapy for In-Stent Restenosis:

AMC Experience

Cutting Balloon or Rotablation before RTx

	Rota + RT (n=70)	Cutting + RT (n=69)	*p*-value
Lesion length, mm	21.0 ± 10.2	21.6 ± 10.3	0.72
Ref artery size,mm	2.92 ± 0.40	2.88 ± 0.48	0.60
Balloon/Artery ratio	1.10 ± 0.16	1.17 ± 0.19	0.03
Rotablation			
Burr size(mm)	2.02 ±0.21		
Burr/Artery ratio	0.70 ± 0.12		
Frequency	4.8 ±2.5		

Subject

139 patients (M/F: 89/50, 59 yrs)

Diffuse ISR

(mean lesion length 20.3±8.9 mm)

Design

In-Stent Restenosis (N=139)

Rota + RT
N=70

Cutting + RT
N=69

Procedure-related Data

	Rota + RT (n=70)	Cutting + RT (n=69)	*p*-value
Lesion length, mm	21.0 ± 10.2	21.6 ± 10.3	0.72
Ref artery size,mm	2.92 ± 0.40	2.88 ± 0.48	0.60
Balloon/Artery ratio	1.10 ± 0.16	1.17 ± 0.19	0.03
Rotablation			
Burr size(mm)	2.02 ±0.21		
Burr/Artery ratio	0.70 ± 0.12		
Frequency	4.8 ±2.5		

Procedure-related Data

	Rota + RT (n=70)	Cutting + RT (n=69)	*p*-value
MLD, mm			
Baseline	0.76 ± 0.40	0.83 ± 0.40	0.35
Final	2.63 ± 0.40	2.68 ± 0.50	0.50
Diameter stenosis			
Baseline	74.0 ± 13.2	71.4 ± 13.8	0.27
Final	9.2 ± 12.9	6.0 ± 17.3	0.22
Pressure (atm)	6.1 ± 2.2	5.7 ± 1.8	0.21

Radiation Coverage

	Rota + RT (n=70)	Cutting + RT (n=69)	*p*-value
Radiation Balloon Length (mm)	40.3±11.0	38.7±12.0	0.41
≤ 30 mm	17 (24%)	27 (39%)	
30< ≤40 mm	42 (60%)	32 (46%)	
60 mm (overlap)	10 (14%)	8 (12%)	
80 mm (overlap)	1 (1%)	2 (3%)	
RT Time (sec)	191±86	185±87	0.69

Immediate Results

	Rota + RT (n=70)	Cutting + RT (n=69)
Success rate (%)	100	100
New Stent due to Edge dissection	7 (10%)	3 (4%)
Major complication	0	0
Isotope leakage	0	0

6-Month Angiographic F/U

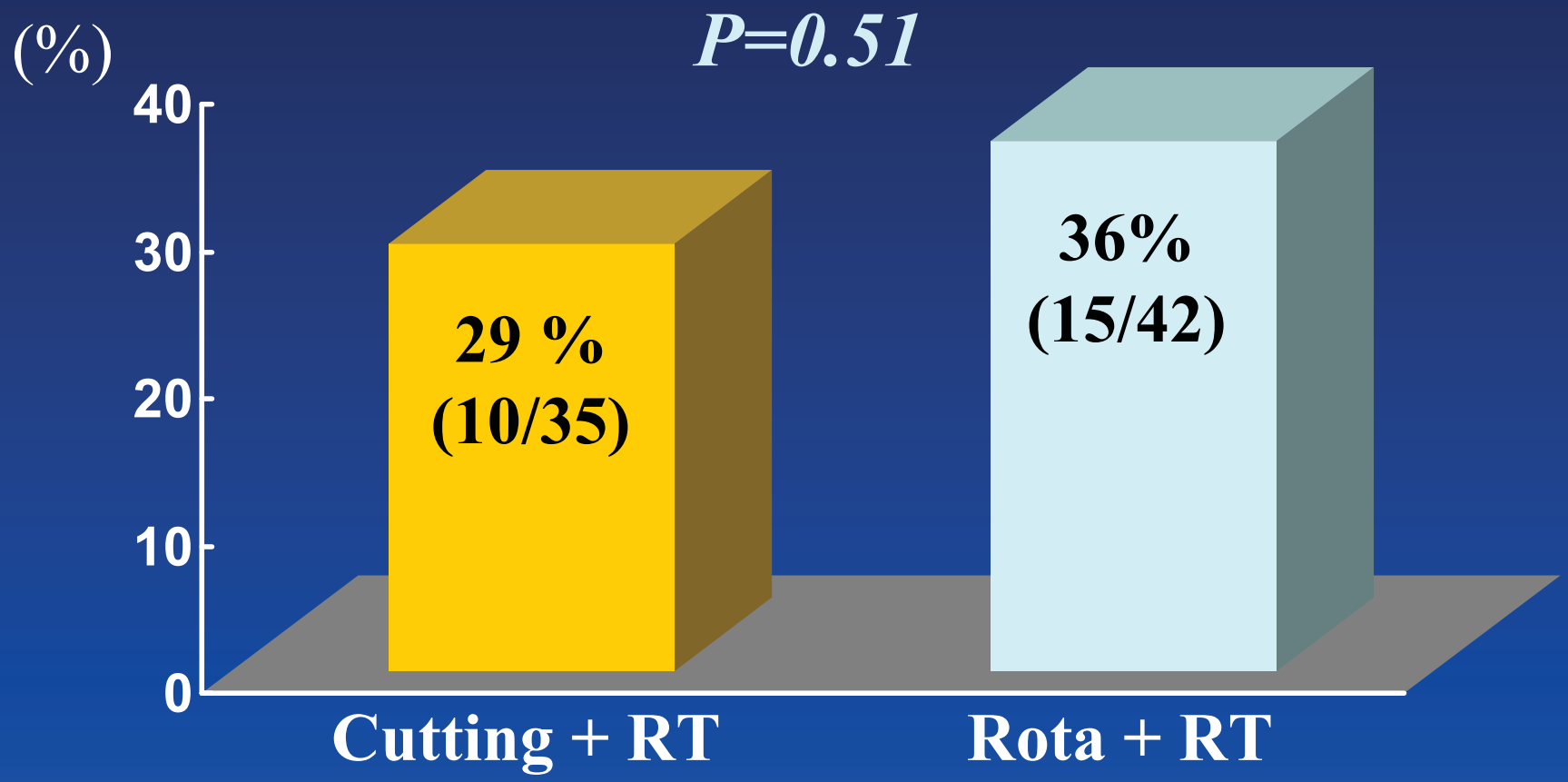
- **Eligible 101 patients**
- **Angiographic follow-up rate = 76% (77/101)**

  - Rota + RT (69%, 35/51)
  - Cutting + RT (84%, 42/50)

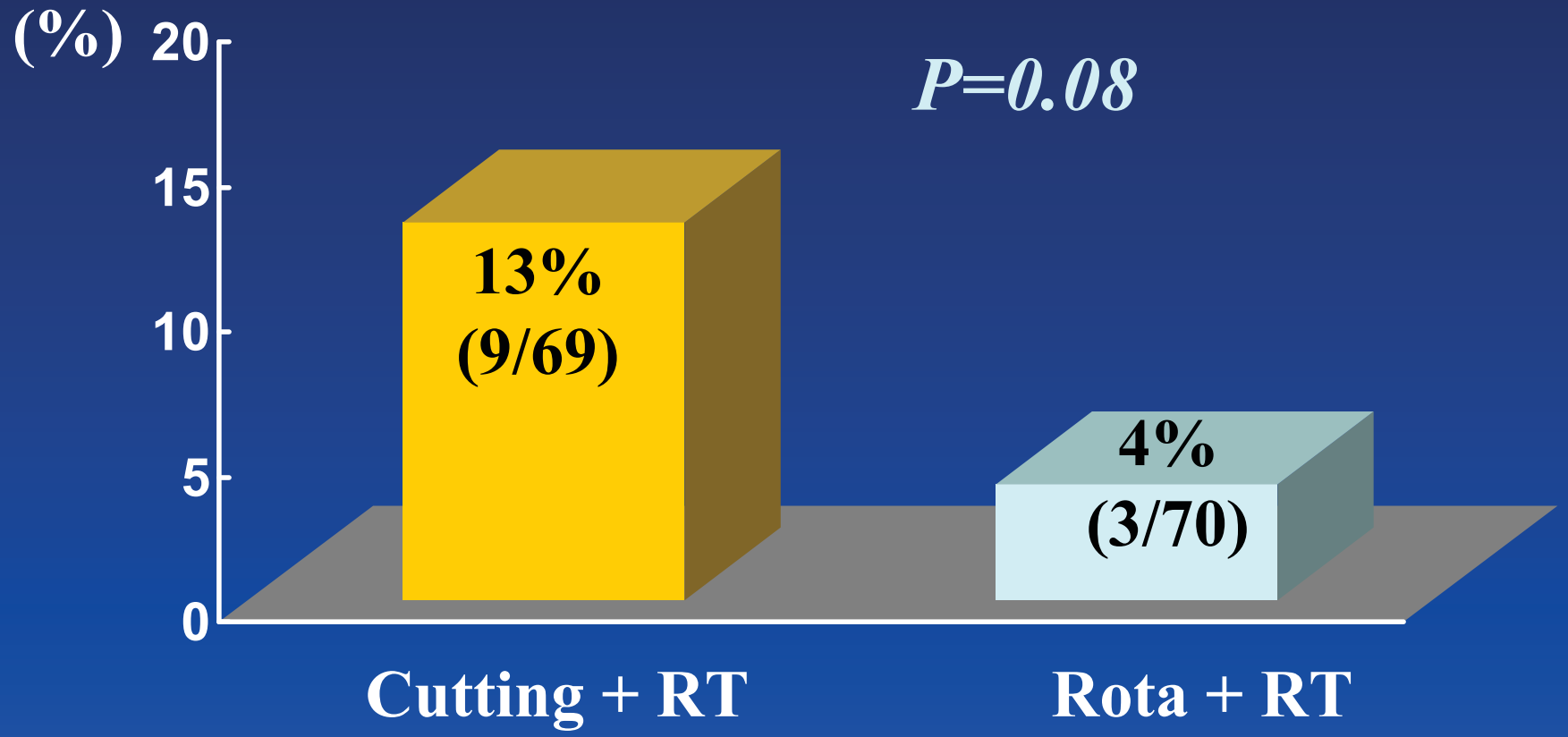
6-Month Angiographic F/U

	Rota + RT (n=35)	Cutting + RT (n=42)	*p*-value
Pre MLD (mm)	0.77±0.41	0.86±0.37	0.33
Post MLD (mm)	2.57±0.43	2.73±0.40	0.10
F/U MLD (mm)	1.74±0.71	1.82±0.85	0.66
Acute gain (mm)	1.74±0.49	1.87±0.42	0.21
Late loss (mm)	0.84±0.83	0.91±0.79	0.68
Loss index	0.44±0.48	0.53±0.47	0.45

Restenosis Rate



8-months TLR Rate



Conclusion

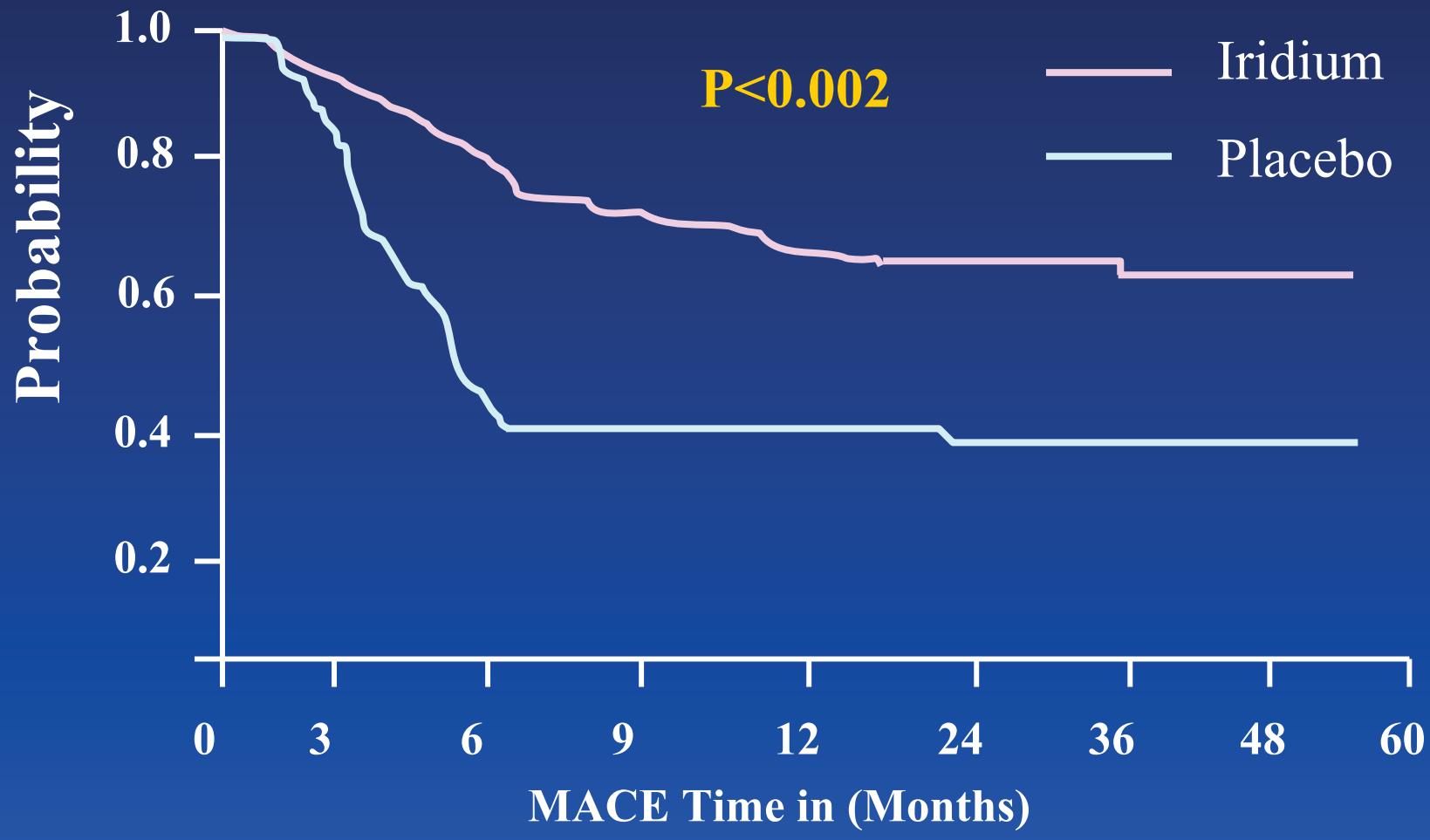
The cutting balloon angioplasty and rotational atherectomy before brachytherapy using ^{188}Re-MAG$_3$ filled balloon showed similar favorable acute and long-term outcomes.

Brachytherapy

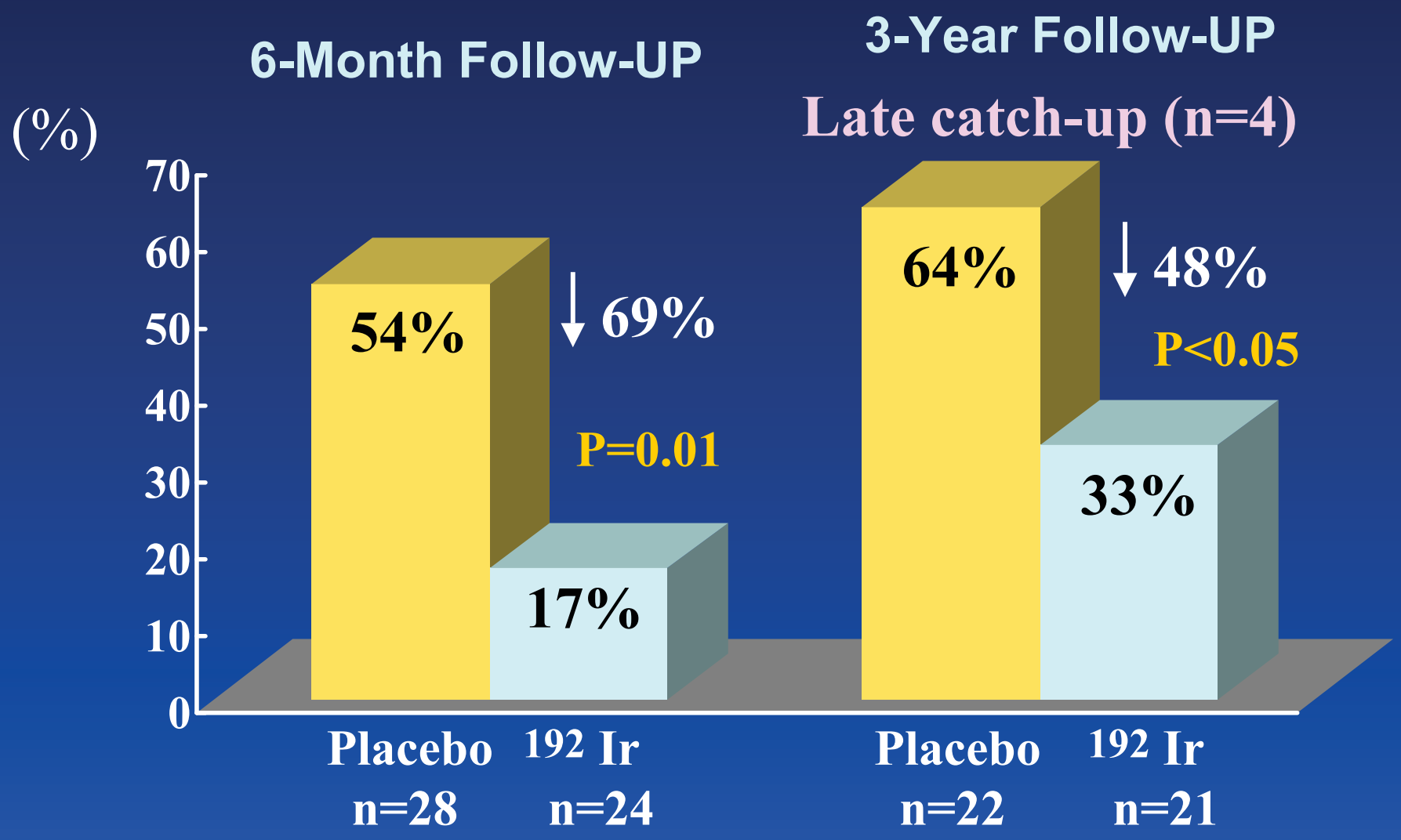
Durable effect ?

WRIST-Five year F/U (MACE)

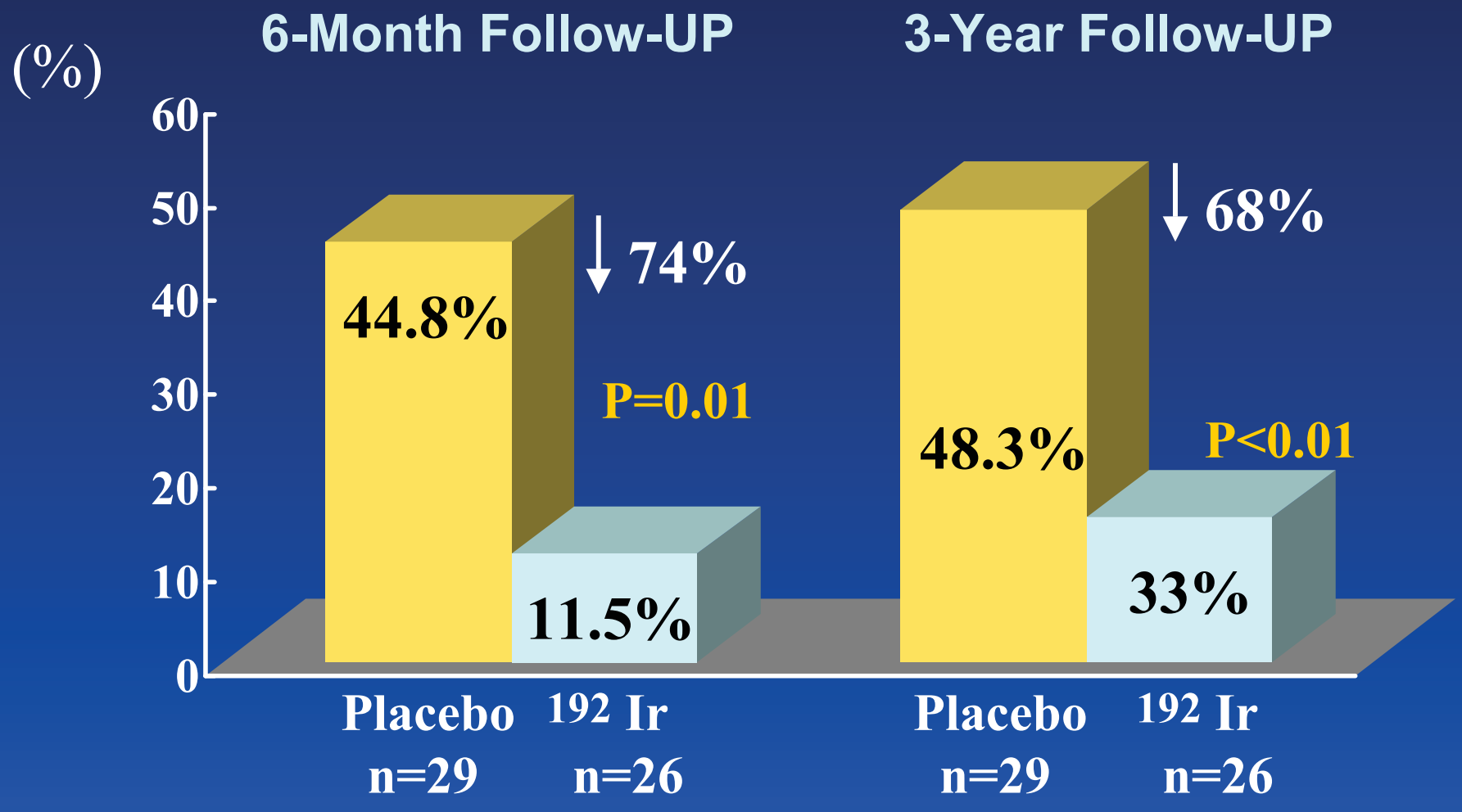
Freedom from death, MI , TLR



SCRIPPS-Late Catch-Up

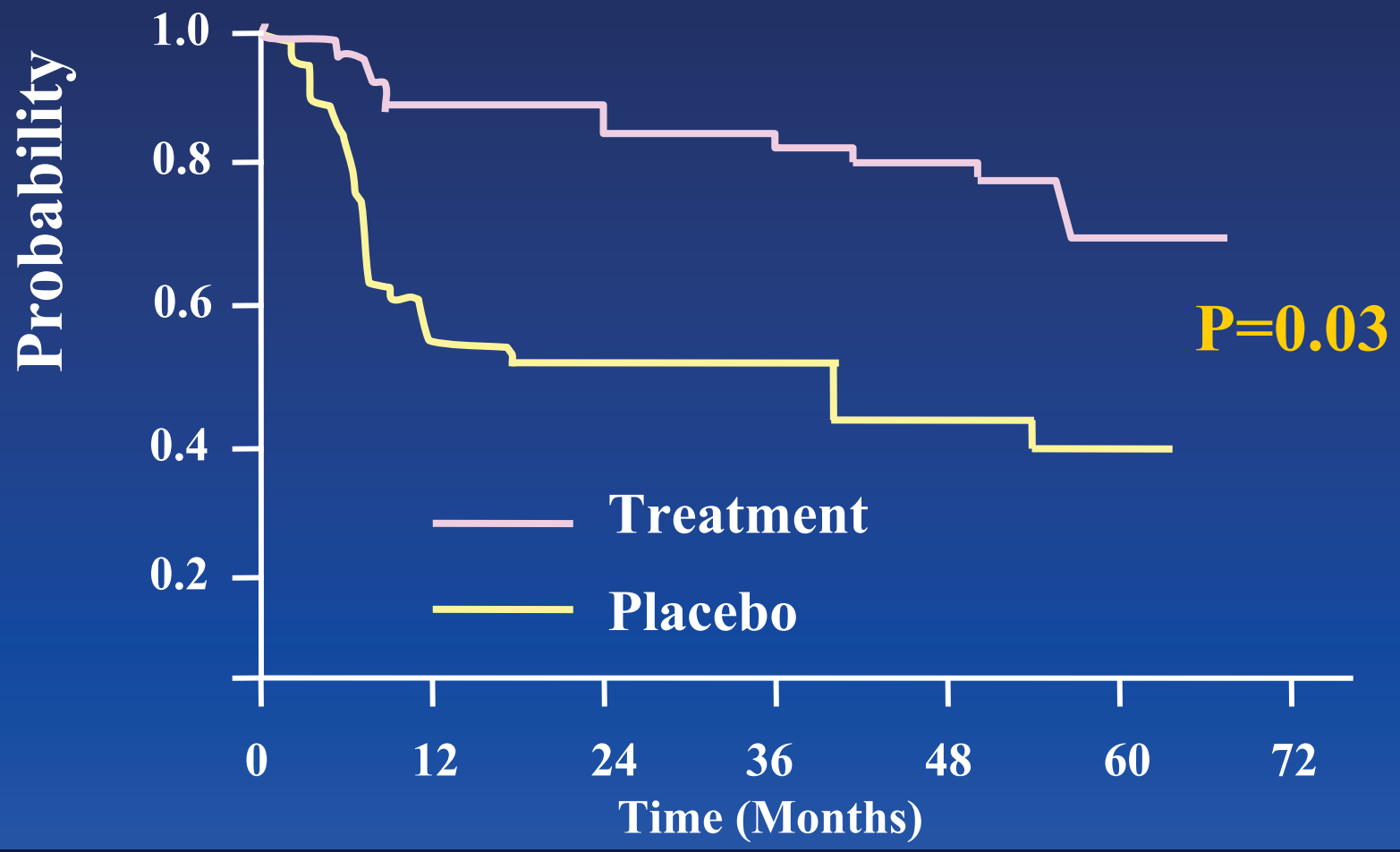


SCRIPPS-3 Years TLR



SCRIPPS-Five year F/U (MACE)

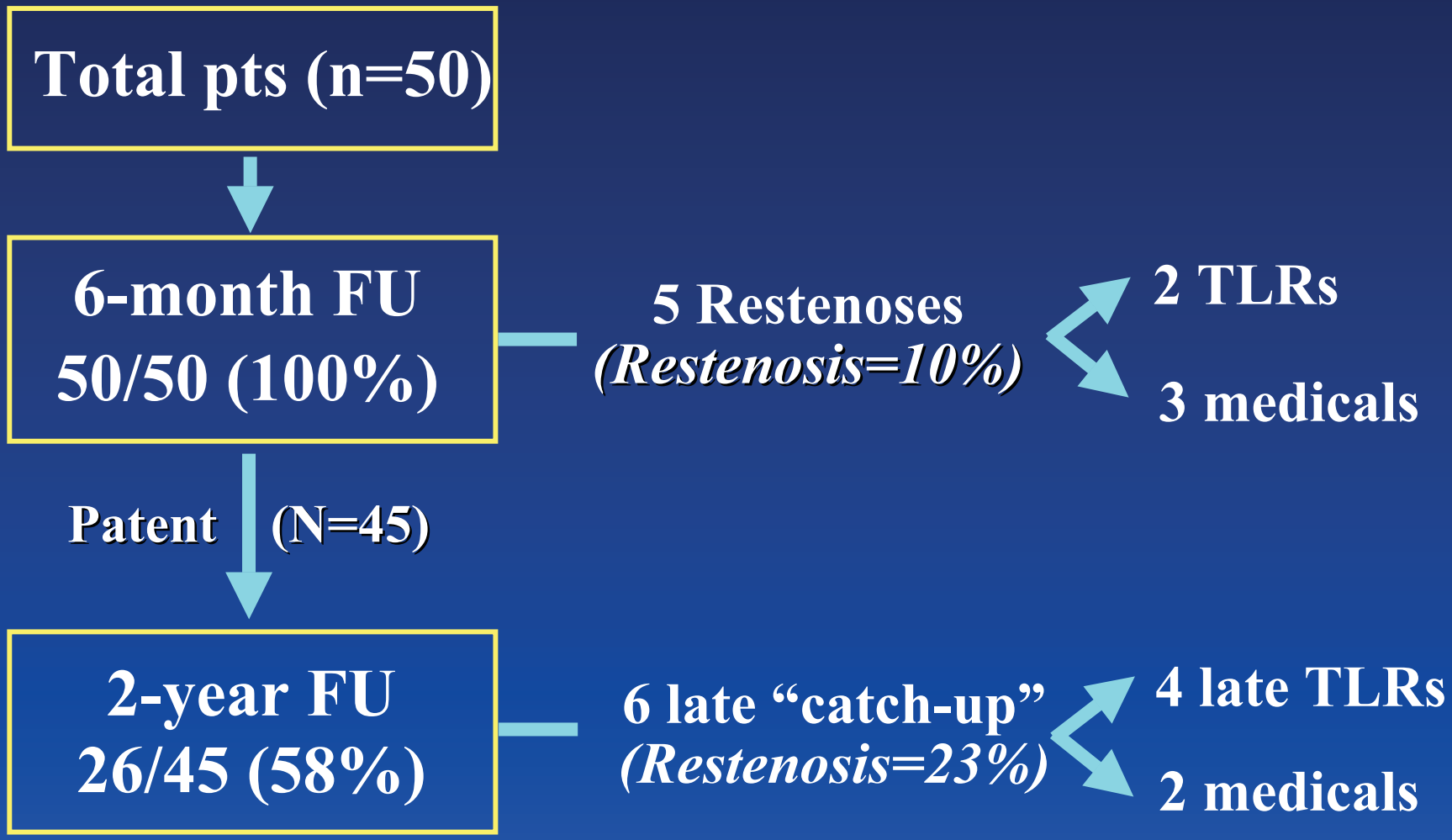
Freedom from death, MI , TLR



Two-Year Angiographic Follow-Up In Rota + RT Group

AMC Experience

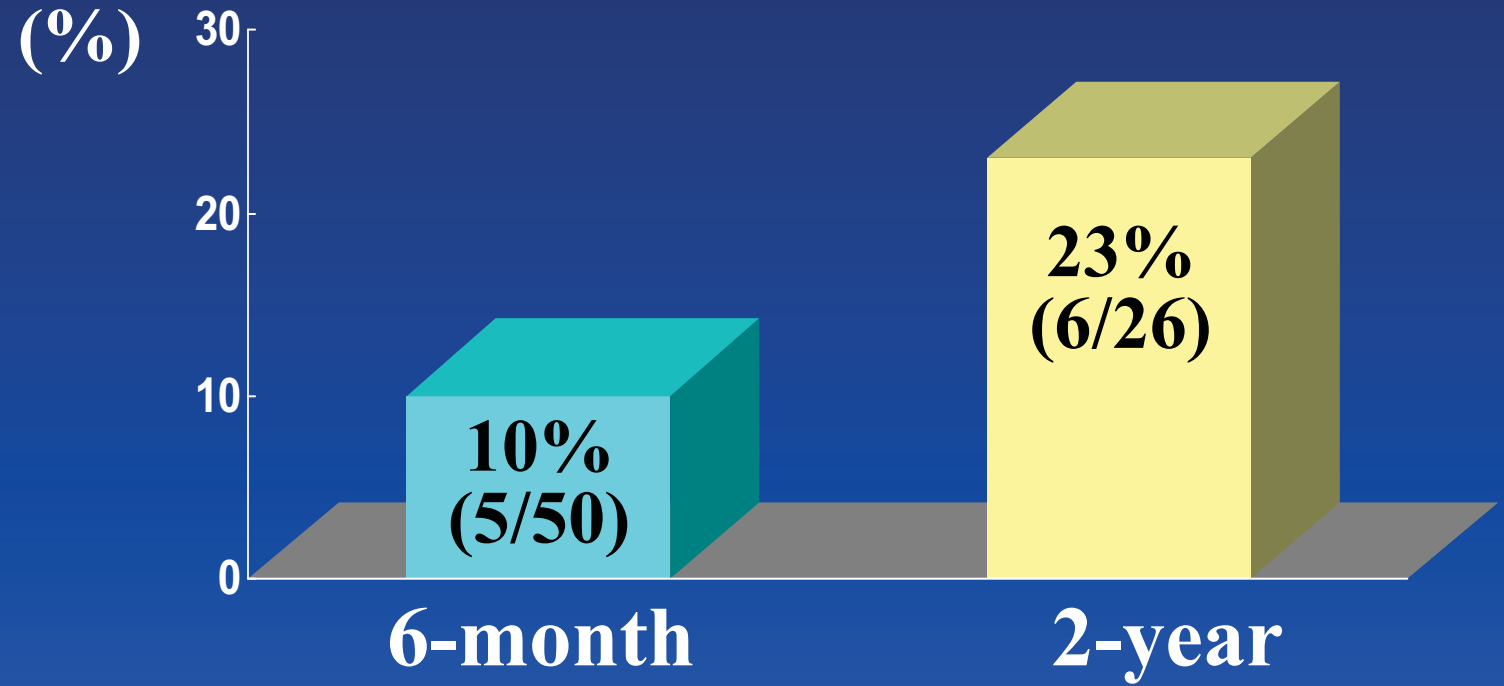
6-month & 2-yr angiographic FU



6-month & 2-year angiographic
Restenosis Rate

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

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



2-year angiographic
Restenosis & TLR Pattern

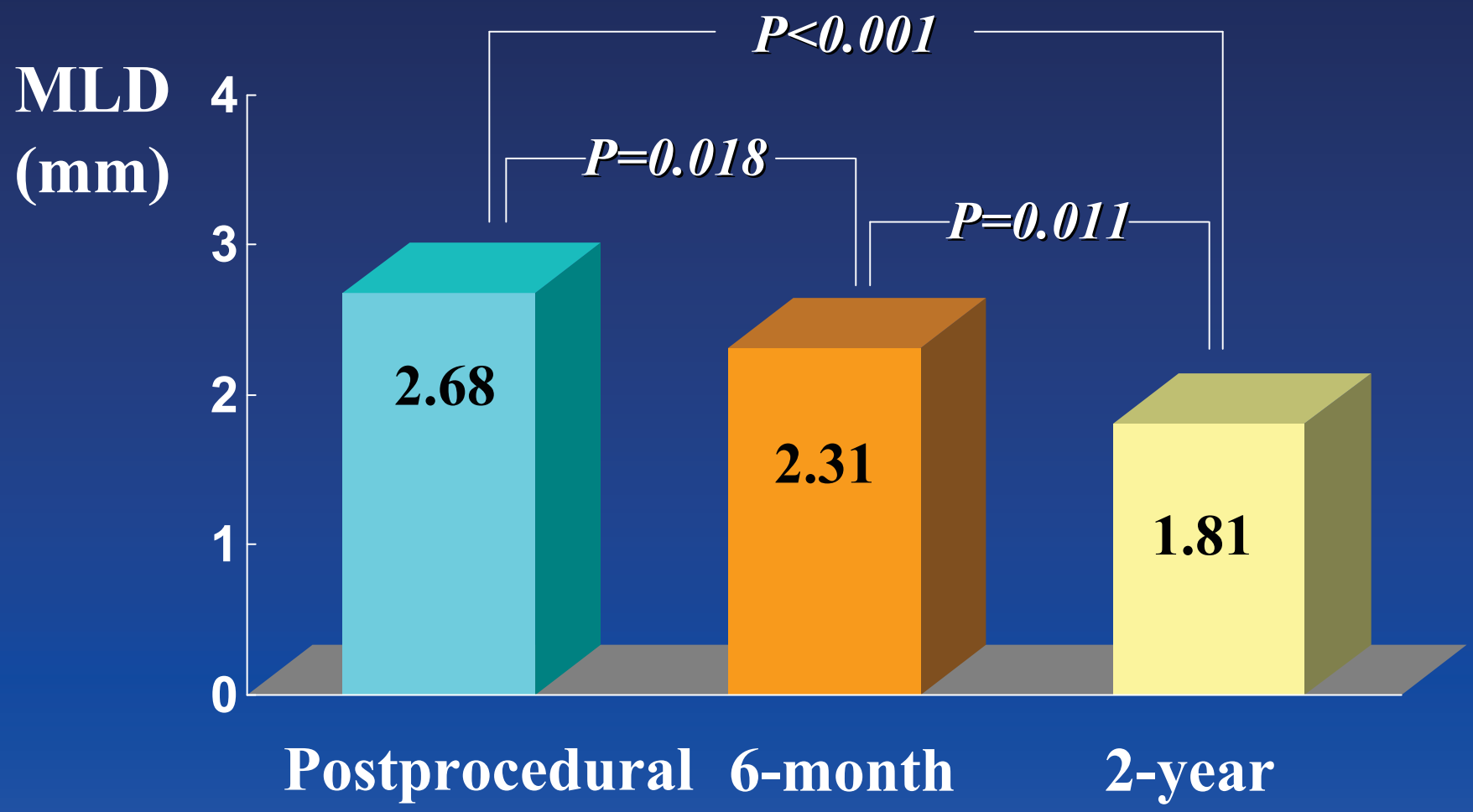
- *Focal* 2

Intrastent	1	→	1 Cutting balloon
Edge	1	→	1 Medical

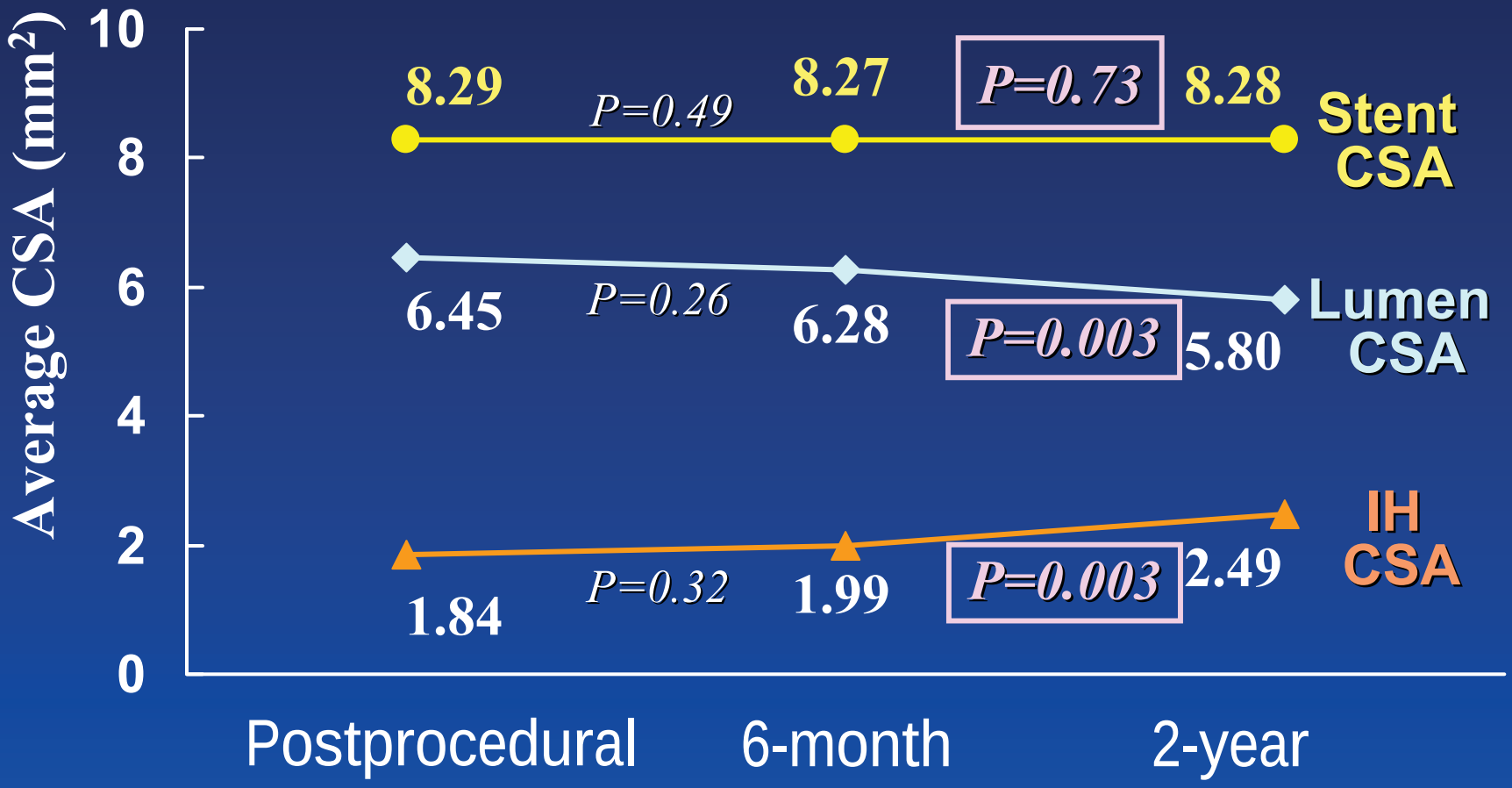
- *Diffuse* 4

Intra-stent	1	→	1 Medical
Total occlusion	3	→	2 Cutting balloons
		→	1 CABG

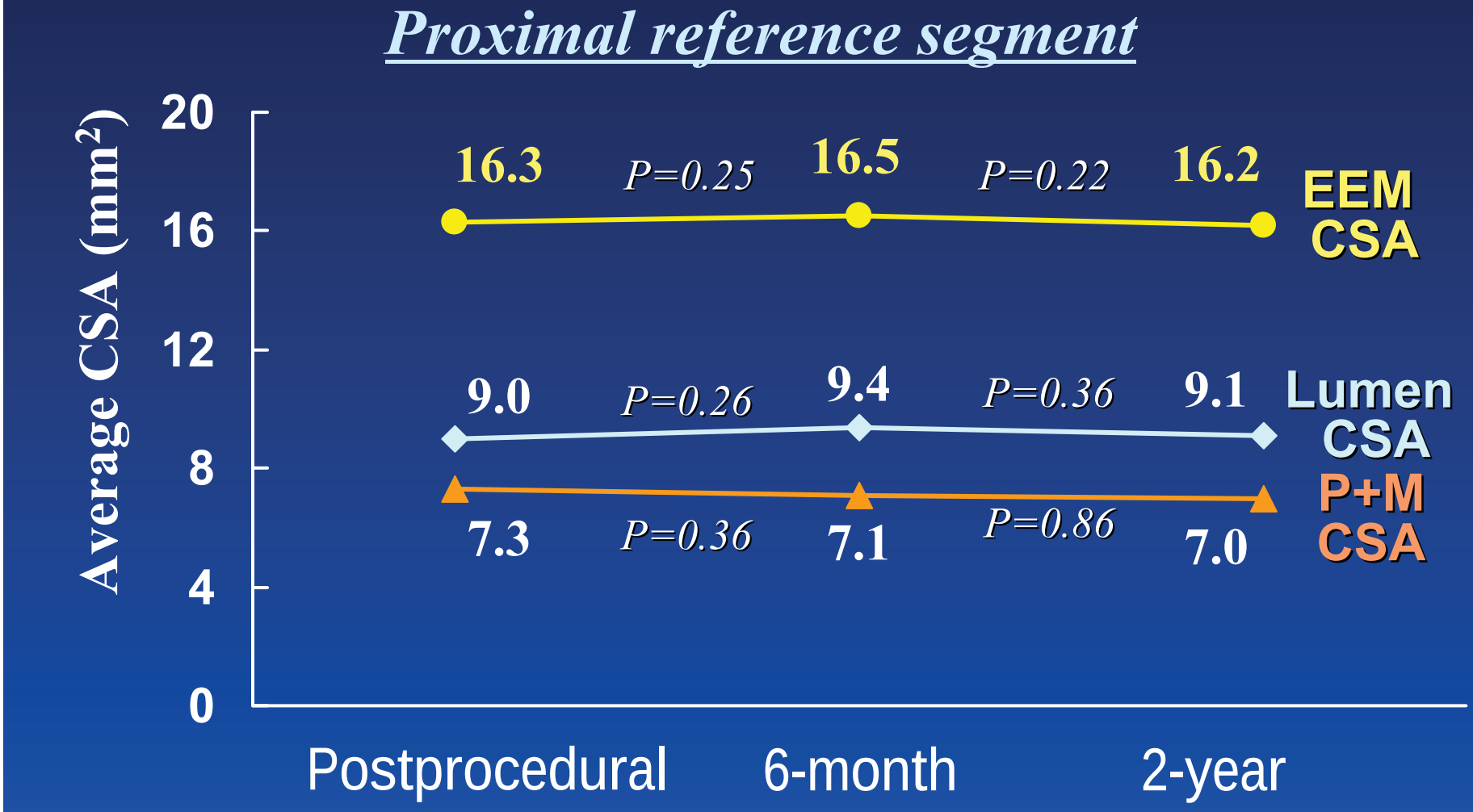
6-month & 2-yr angiographic MLD



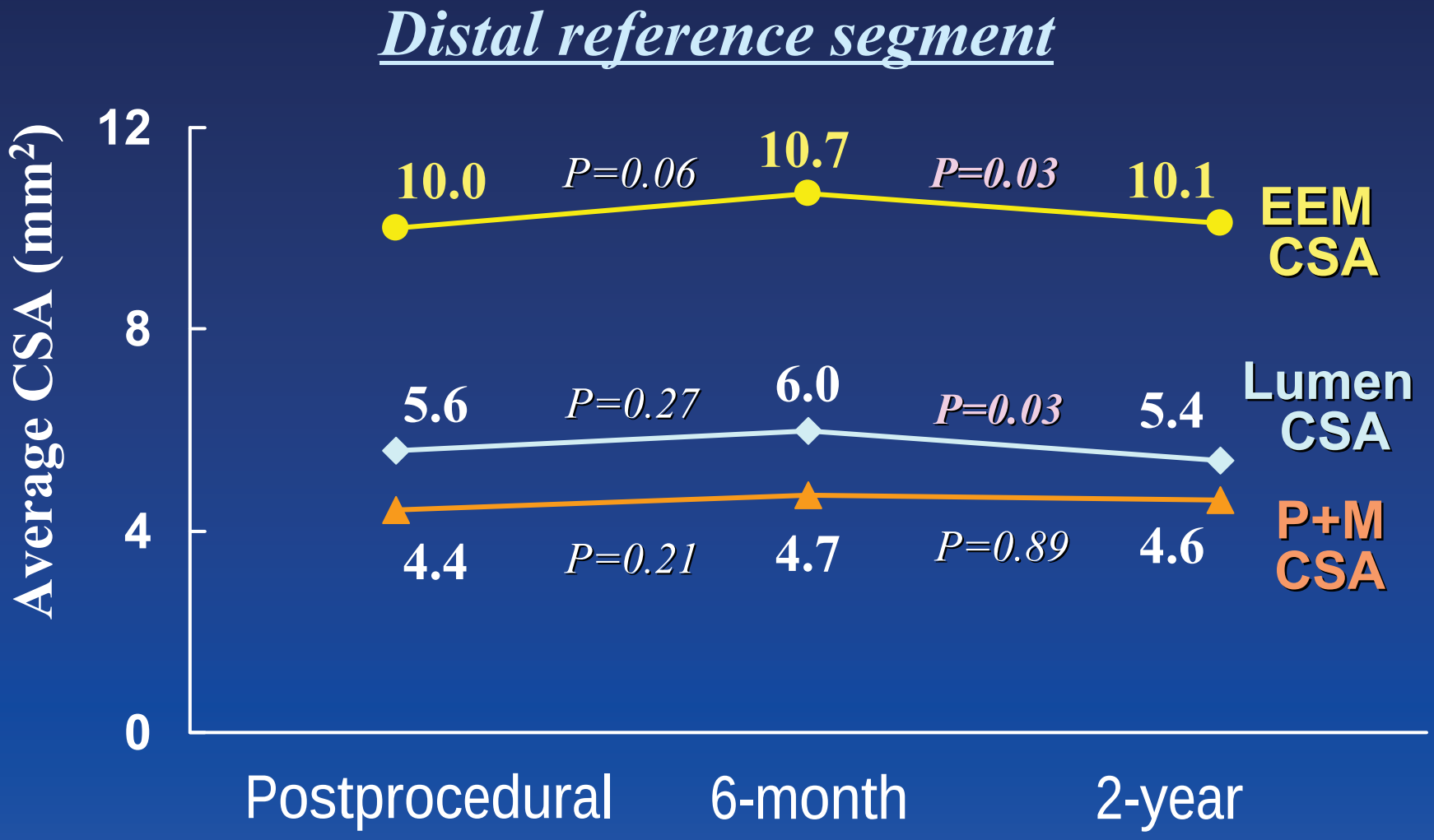
6-month & 2-year IVUS Data



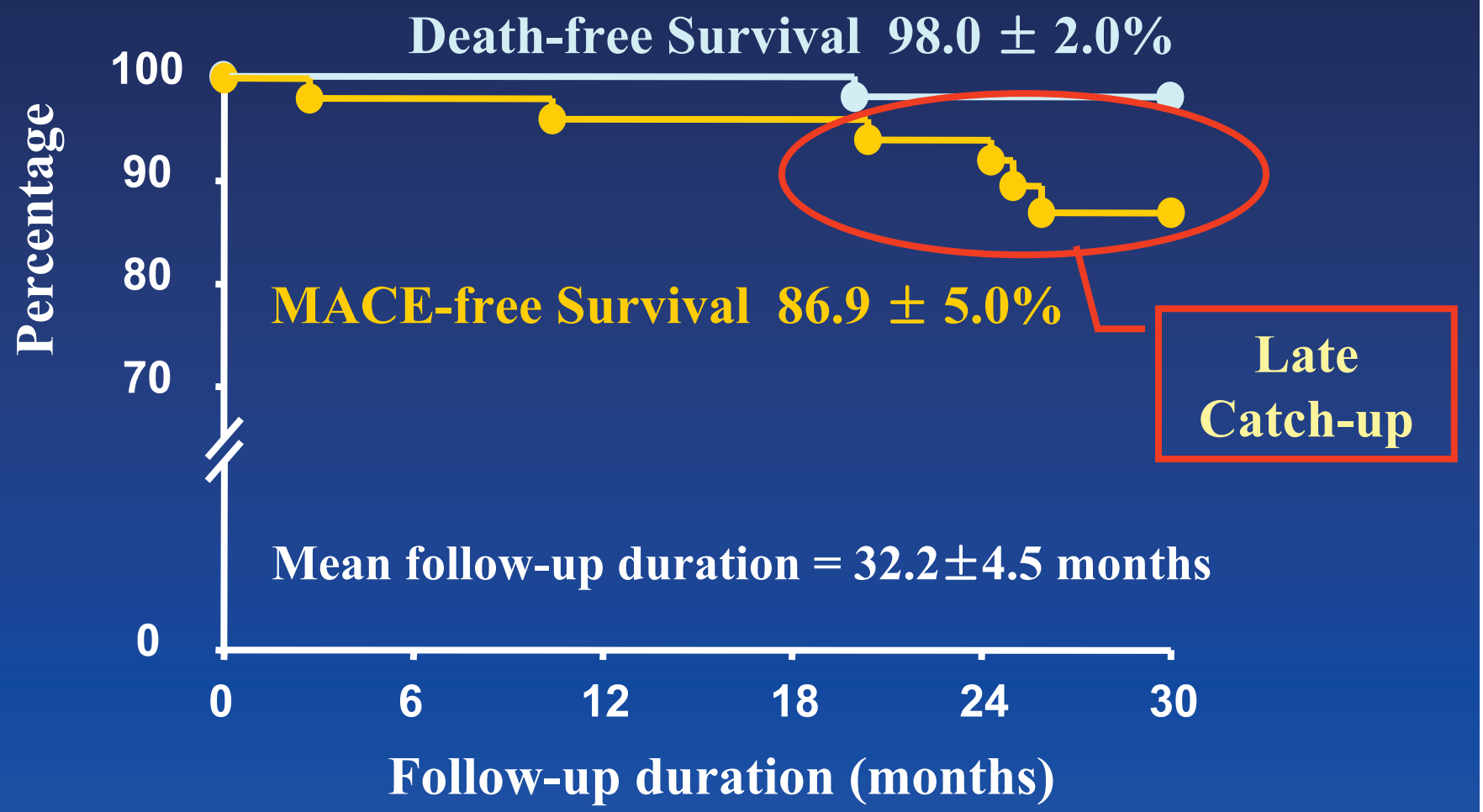
6-month & 2-year IVUS Data



6-month & 2-year IVUS Data



Event-free Survival



Conclusion

- Beta-irradiation using a ^{188}Re-MAG$_3$-filled balloon after rotational atherectomy is safe and feasible in patients with diffuse ISR.
- Long-term angiographic and clinical outcome appears favorable for this highly restenosis prone group.
- *However,* late "catch-up" phenomena were observed in some patients after brachytherapy.

Drug-Eluting Stent for In-Stent Restenosis

Safe and efficacious ?

Paclitaxel Stent for ISR

Pilot Study (n=21 pts)

Re-Restenosis

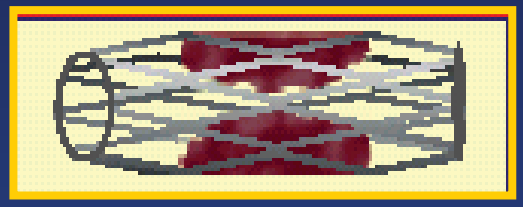
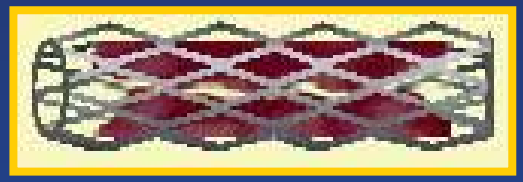
9 pts with optimal coverage → **0 / 9 pts**

12 pts with a mismatch between the injured zone and the paclitaxel stent → **3 / 12 pts**

Overall : 14%

De Scheerder IK, TCT

TAXUS III for ISR

		(N=27)
Focal		10 (35.8%)
Diffuse		13 (46.4%)
Proliferative		4 (14.3%)
Total occlusion		1 (3.6%)

TAXUS III -MACE

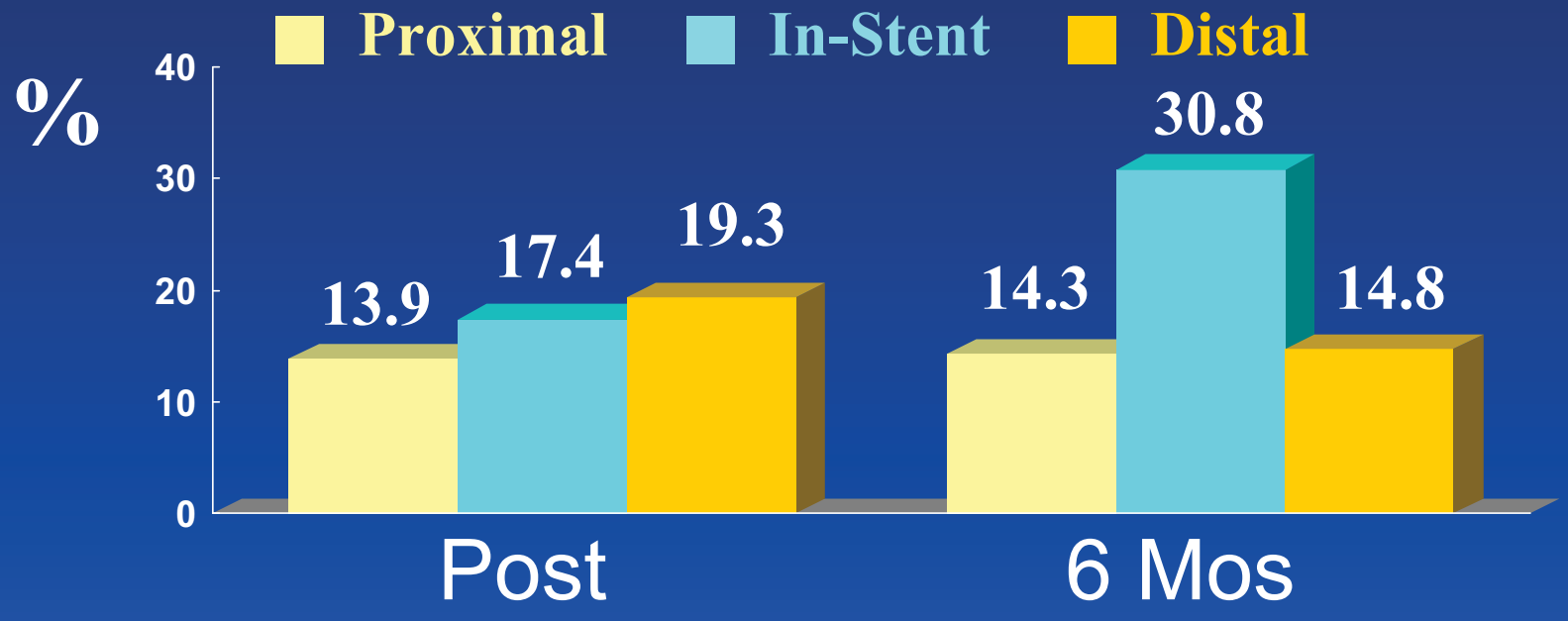
	30 day	6 month
Death	0	0
Q-Wave MI	0	0
Non Q-Wave MI	1 (3.6%)	1 (3.6%)
TLR	0	6 (21.4%)
CABG	0	1 (3.6%)
6-Month MACE	0	8 (29%)

TAXUS III for ISR

2 Clinical Centers (n=28 pts)

Re-Restenosis = 4 / 25 (16%)

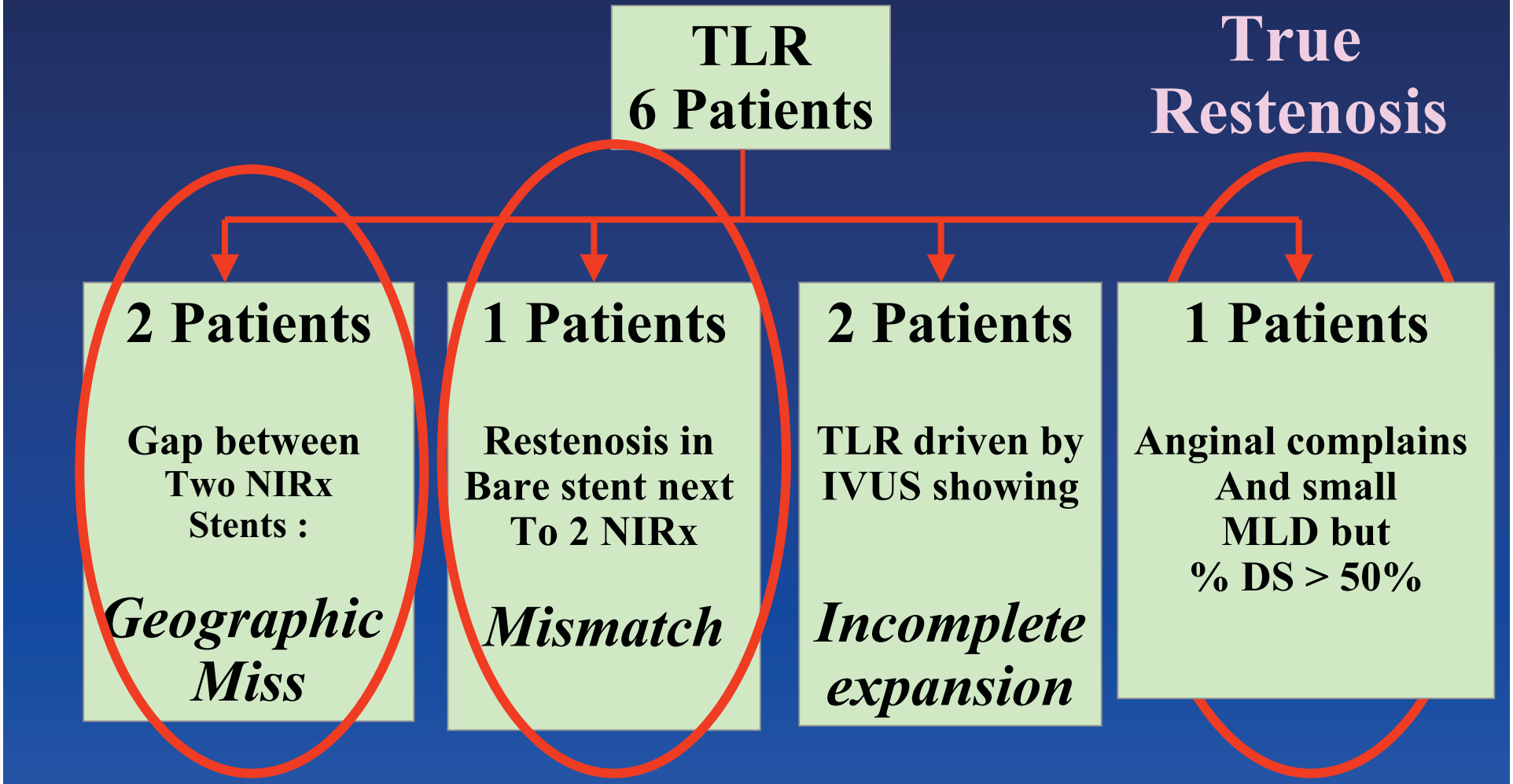
Percent diameter stenosis



K Tanabe, Circulation 2003;107

TAXUS III for ISR

Characteristics of TLR Patients

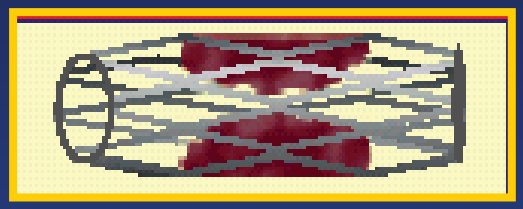
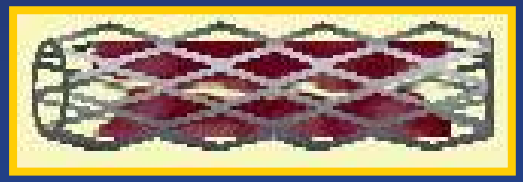


TAXUS III for ISR

Restenosis Pattern

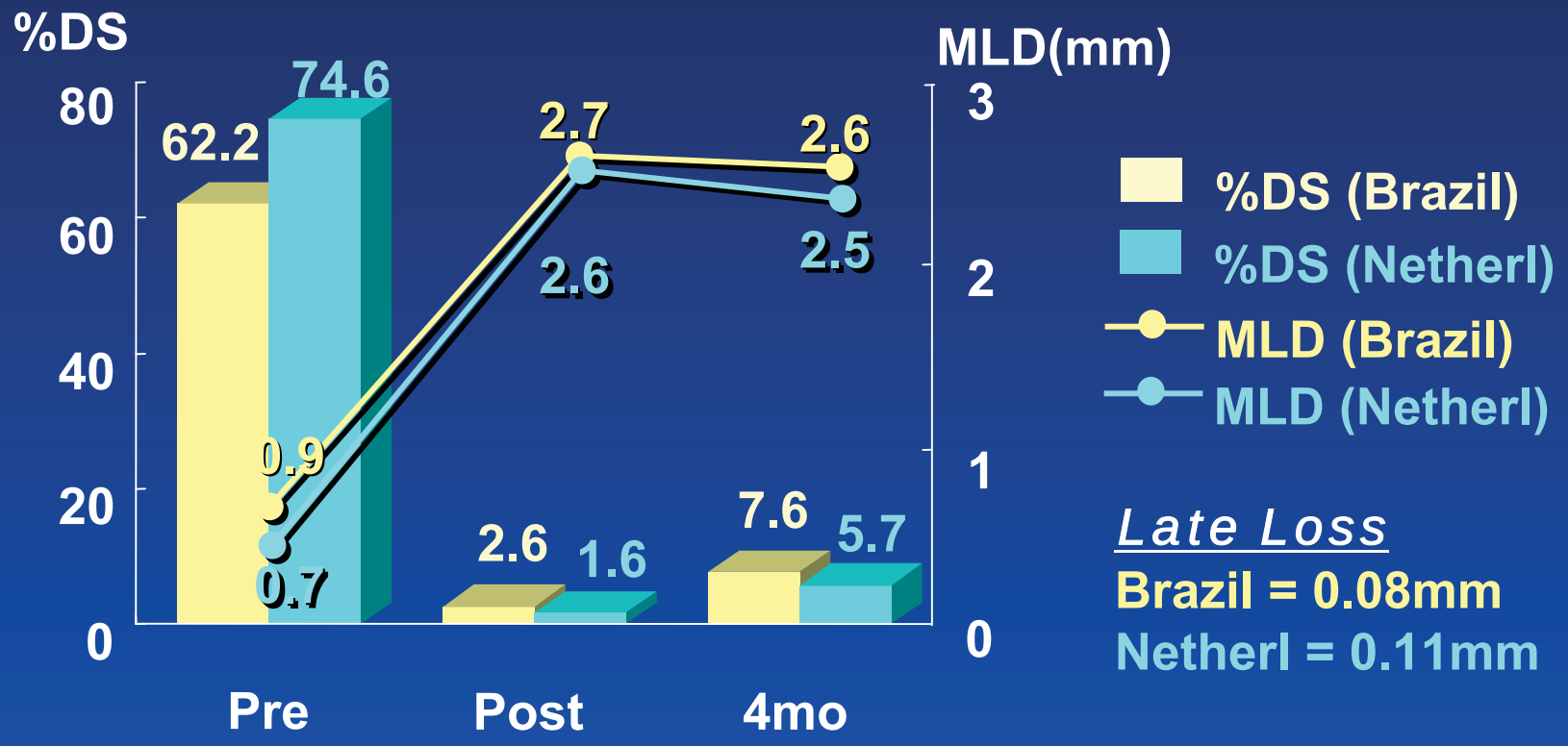
Restenosis rate	**16 % (4/25)**
Single stent	**0% (0/13)**
Multiple stents	**33% (4/12)**
Subanalysis excluding mismatch and GM	**4.5 % (1/22)**

Sirolimus-coated Stent for ISR

		Brazil (n=25)	Netherlands (n=16)
Focal		10 (40%)	3 (19%)
Diffuse		8 (32%)	4 (31%)
Proliferative		7 (28%)	5 (31%)
Total occlusion		0 (0%)	3 (19%)

Sirolimus-coated Stent for ISR

First-In-Man Experience (n=38/41)



Late Loss

Brazil = 0.08mm

Netherl = 0.11mm

AHA 2002

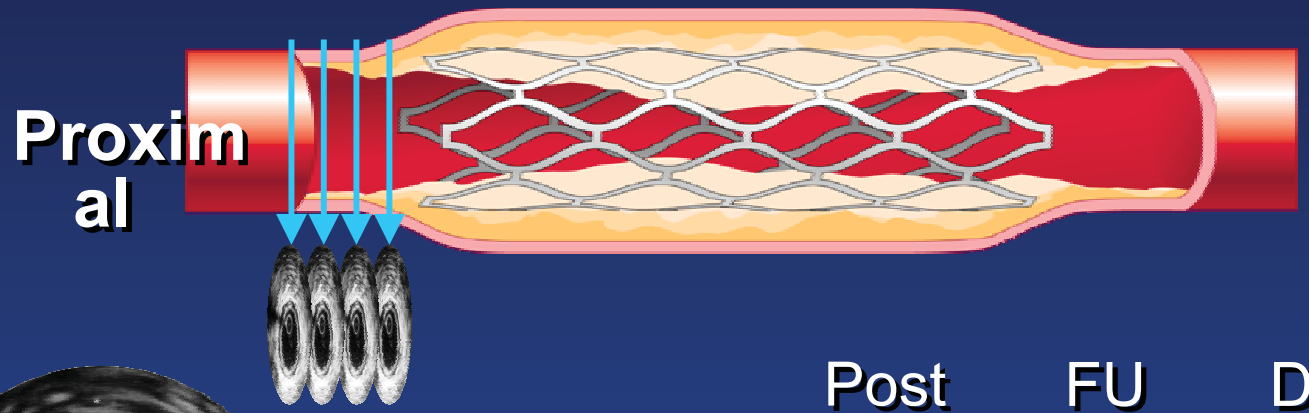
Sirolimus-coated Stent for ISR

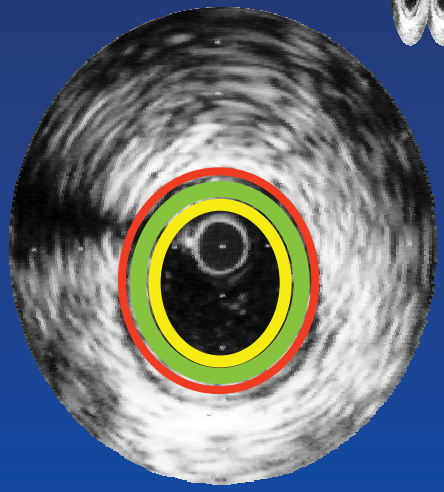
1-Year Clinical Events

	Brazil N=25	Rotterdam N=16	Pooled N=41
Death	0 (0%)	2 (12.5%)	2 (4.9%)
MI	0 (0%)	1 (6.3%)	1 (2.4%)
TLR	0 (0%)	2 (12.5%)	2 (4.9%)
Restenosis	1 (4%)	2 (12.5%)	3 (7.3%)

AHA 2002

IVUS Volumetric Analysis at Proximal Reference



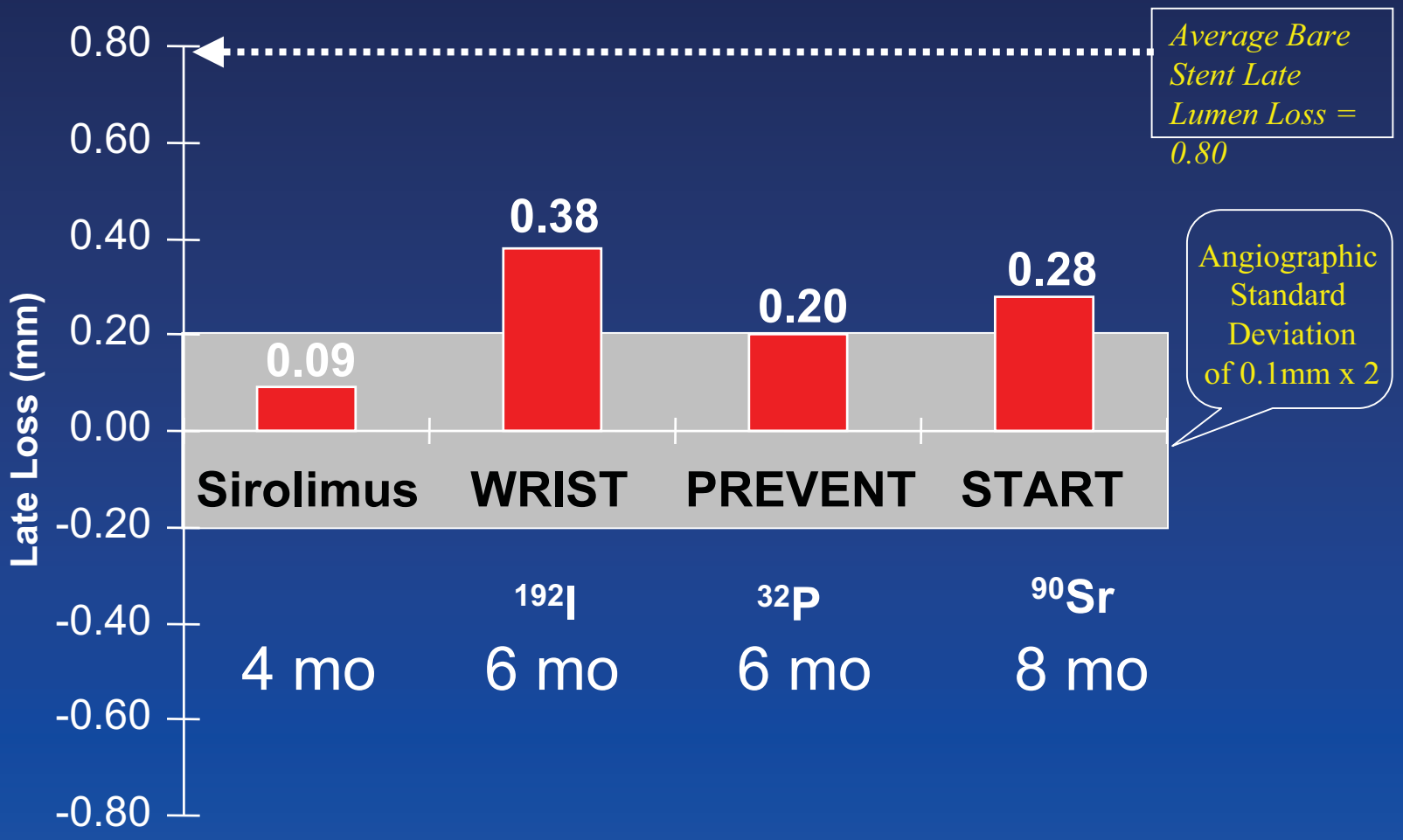


	Post	FU	Delta
Vessel volume	72±44	72±46	-0.84
Lumen volume	50±5	52±60	-1.81
Plaque volume	34±23	34±22	0.08

All values in mm^2 *p=NS*

Edge effect was not seen in Cypher stent !

Late Lumen Loss in Drug-Eluting Stent vs. Radiation in ISR Trials



Drug-Eluting Stent for In-Stent Restenosis

We need more data.
However, we suppose that it may be an alternative standard therapy to intracoronary brachytherapy.