Safety and Efficacy of Cypher on Complex Lesions

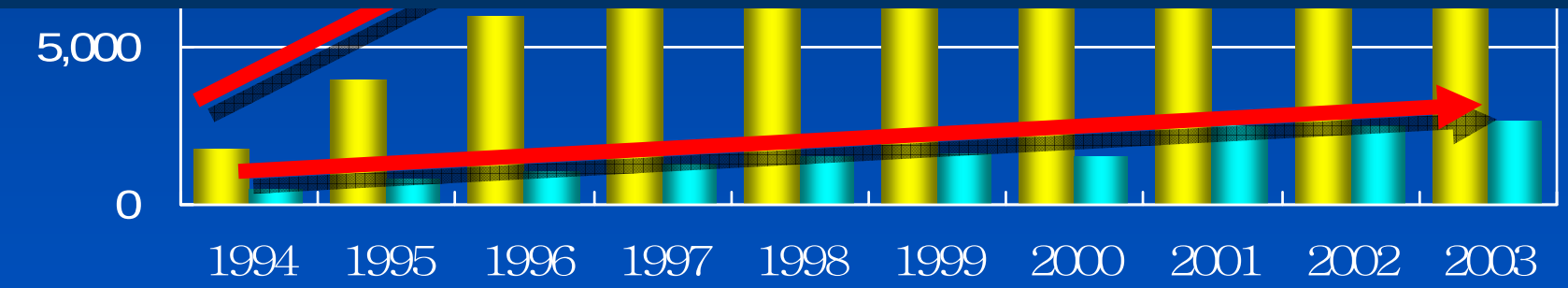
Seung-Jung Park, MD, PhD, FACC

Professor of Internal Medicine
Asan Medical Center, *Seoul, Korea*

What is changing now in real world practice with DES ?

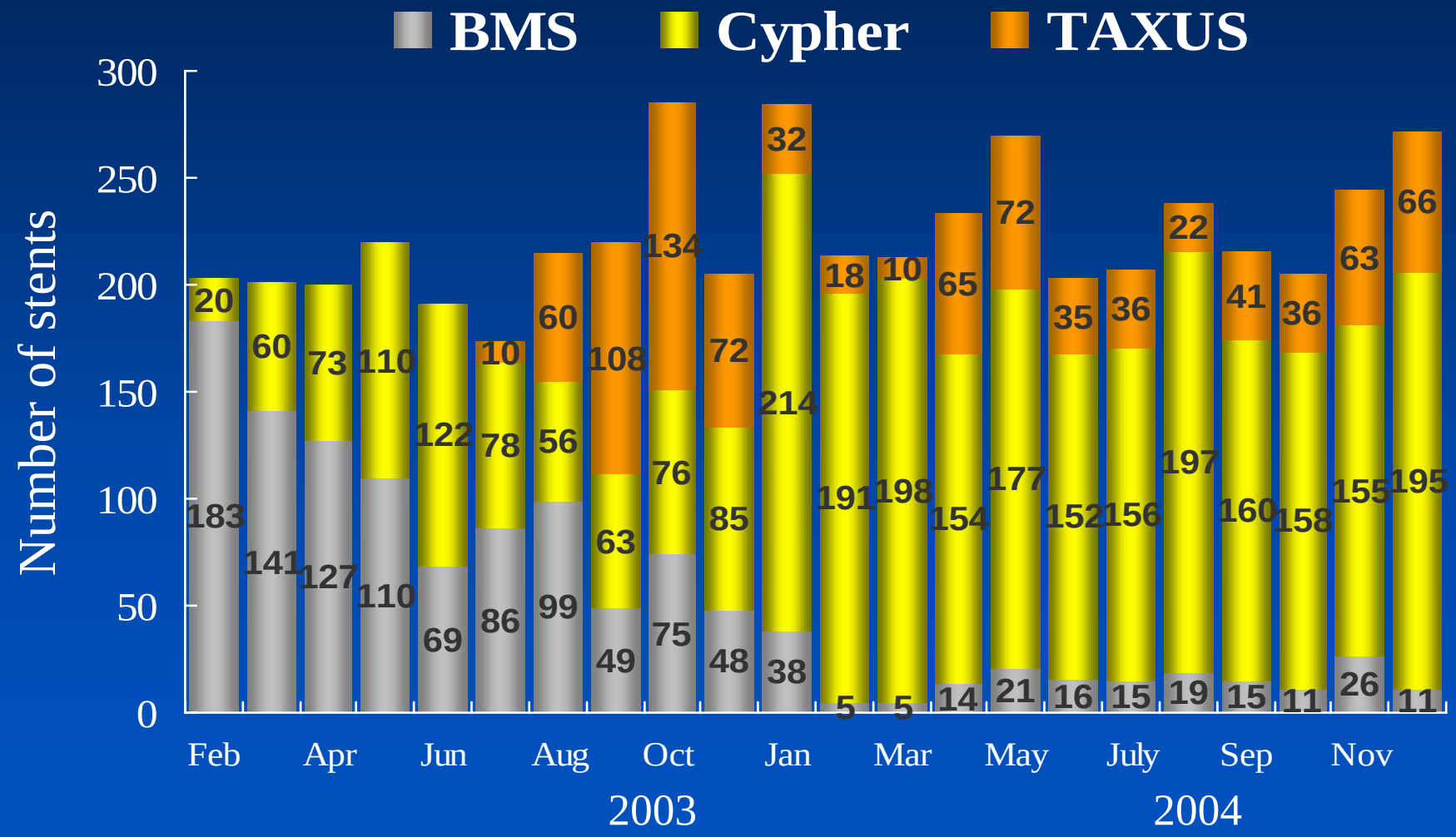
PCI vs CABG

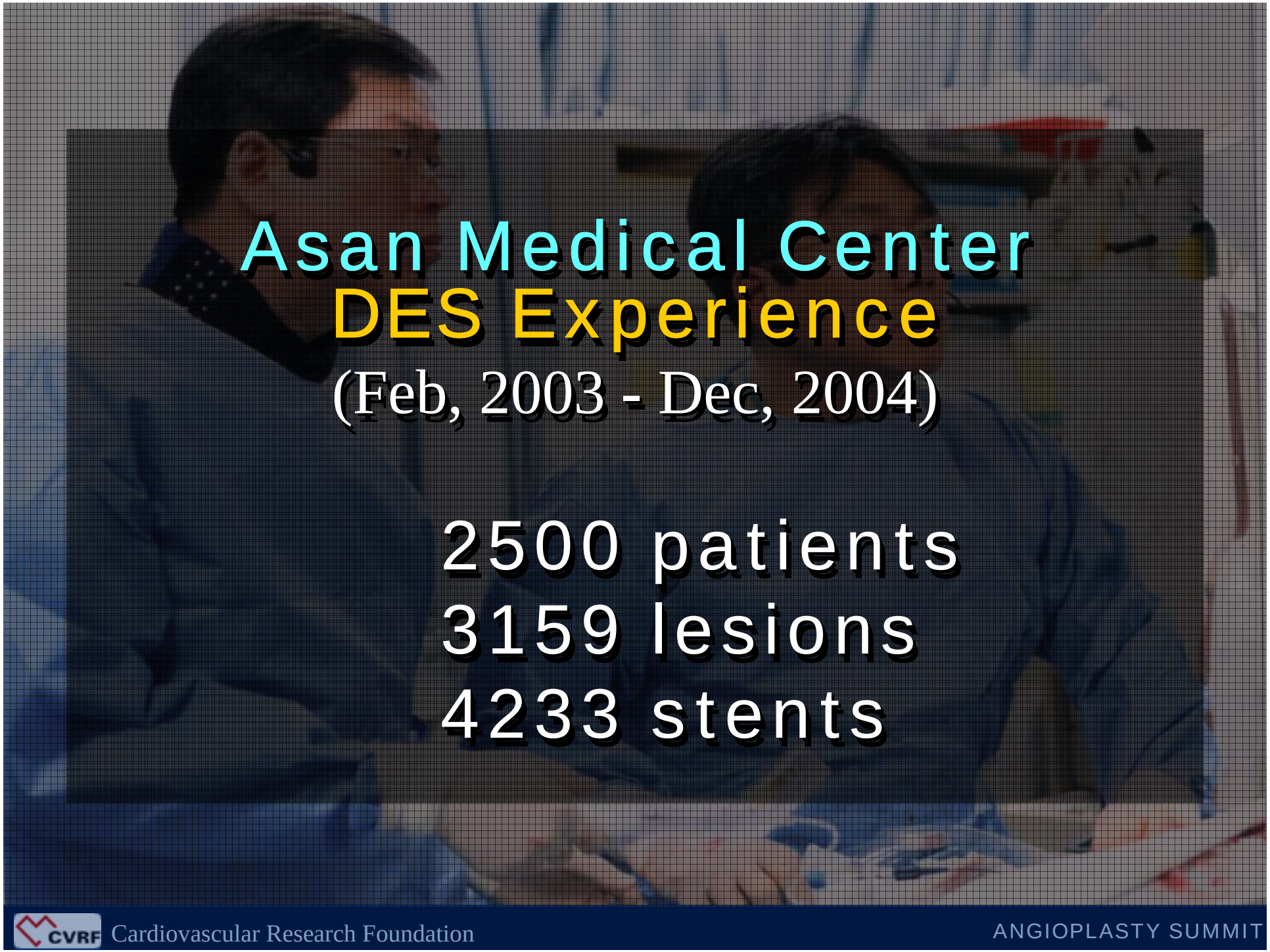
Rapid Increase No. of PCI



DES Use in AMC

90% penetration



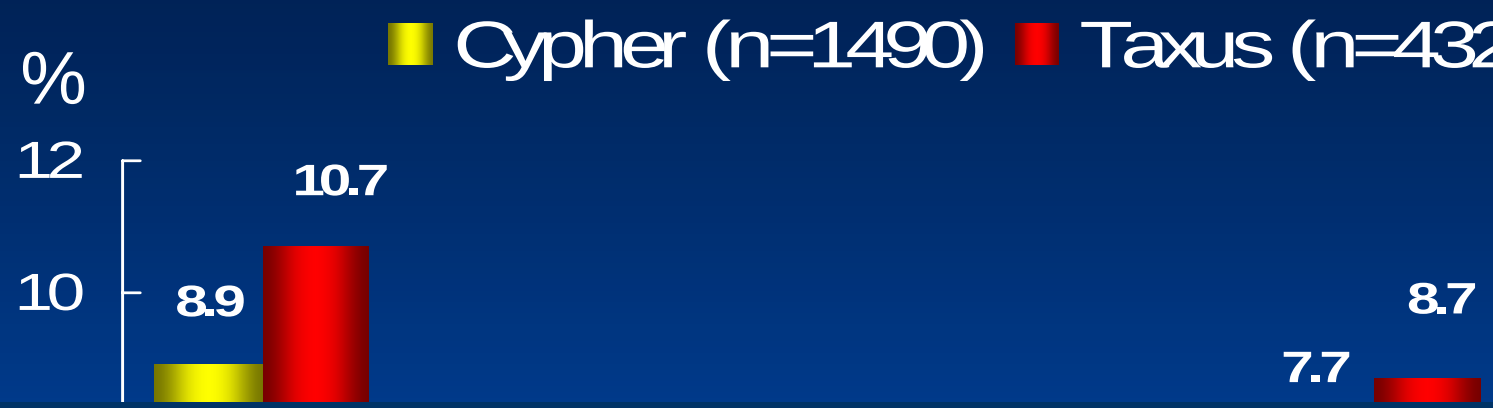

Asan Medical Center
DES Experience
(Feb, 2003 - Dec, 2004)
2500 patients
3159 lesions
4233 stents

Very Complex Patients and Lesions…

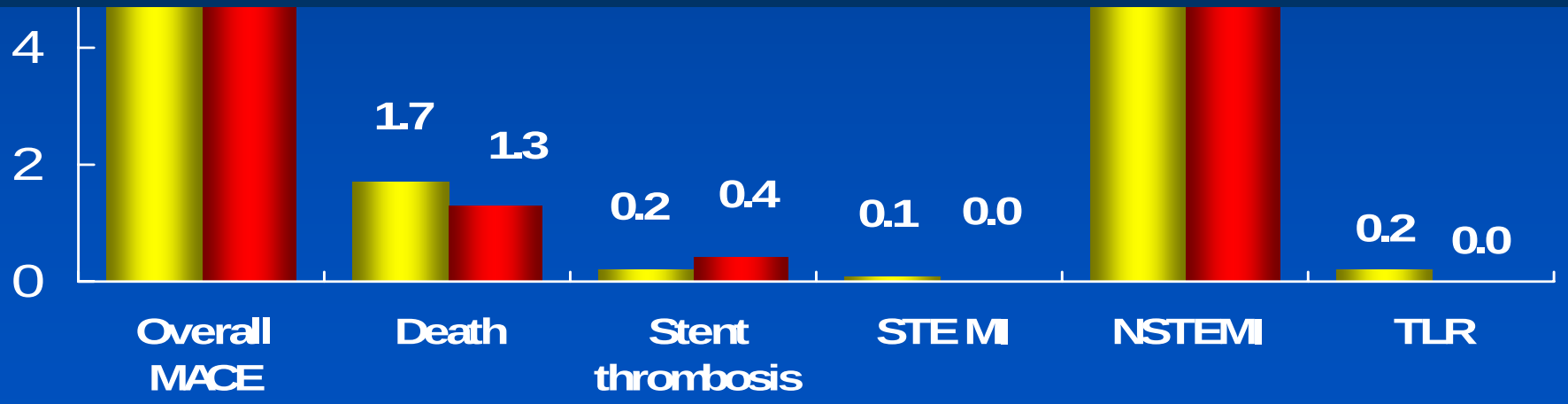
	Cypher	Taxus
Patients	**1753**	**538**
Multivessel PCI	**563 (32%)**	**275 (32%)**
Diabetes	**458 (24%)**	**370 (40%)**
Bifurcation lesion (≥2.0mm)	**398 (18%)**	**80 (12%)**
Chronic total occlusion	**131 (6%)**	**26 (4%)**
Left main coronary artery	**195 (9%)**	**11 (2%)**
In-stent restenosis	**234 (10%)**	**23 (4%)**
Infarct-related artery	**175 (8%)**	**26 (4%)**

We treated
more complex patients and
more complex lesion subsets…

In-Hospital Events

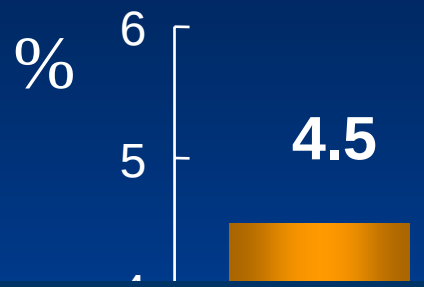


Acceptable SAT rate < 0.5%

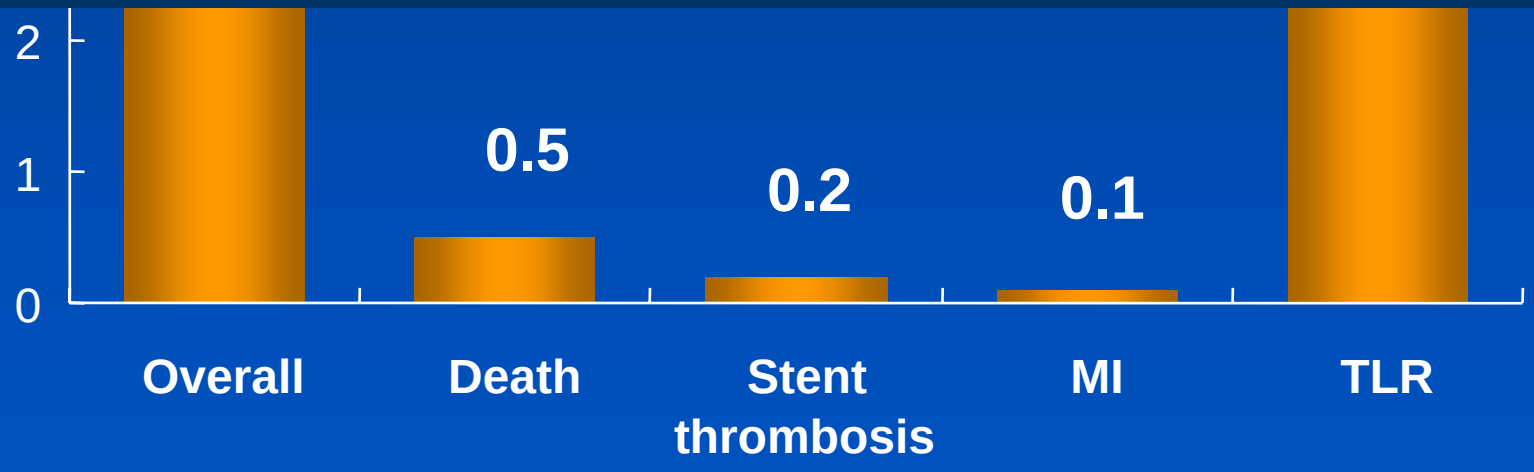


6-Month TLR

1958 patients with Cypher or Taxus implantation & 6-month F/U



Very Low TLR rate : 2.7%



We need more data about DES for complex lesions…

- Left Main disease
- Bifurcation disease
- ISR, diffuse
- Long Lesions
- Acute Myocardial Infarction
- Small vessels. CTO lesions
- SVG disease
- Multivessel disease
- Diabetics patients
- Peripheral disease

Efficacy Concerns

Left Main Disease

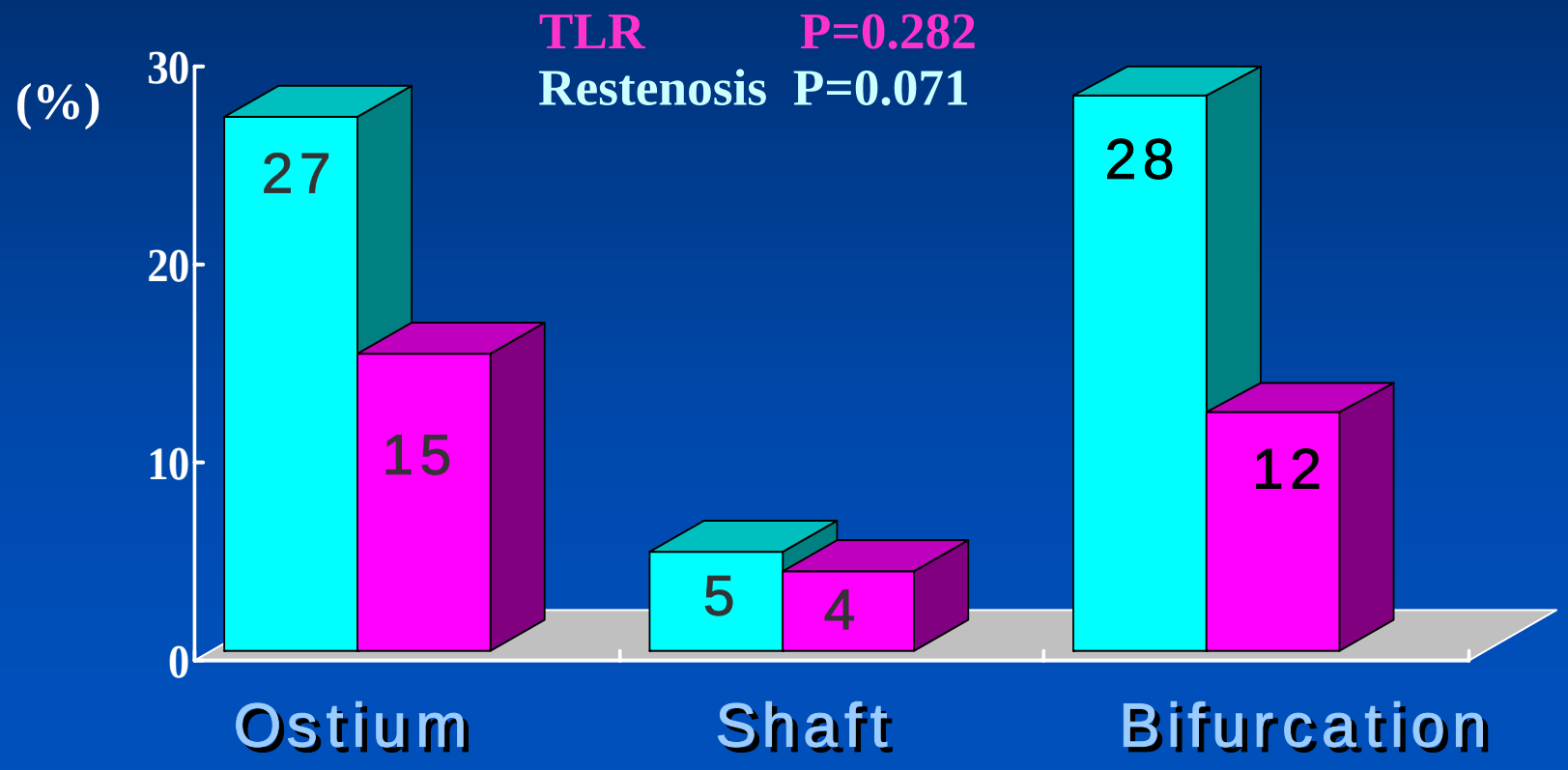
Left main stenting with BMS

Since 1995…

Issues in BMS era...

AMC

Restenosis and TLR



Left main stenting with DES

Not enough data,
But promising…

Published Data using DES

- Arampatzis CA, et al. Catheter Cardiovasc Interv. 2004;62:292-6

  Elective sirolimus-eluting stent implantation for left main coronary artery disease: six-month angiographic F/U and 1-year clinical outcome.

- Arampatzis CA, et al. Am J Cardiol. 2003;92:327-9.

  Effectiveness of sirolimus-eluting stent for treatment of left main coronary artery disease.

- Chieffo A, et al. Circulation 2005;111:791-5

  Early and mid-term results of drug-eluting stent implantation in unprotected left main.

- Park SJ, et al. J Am Coll Cardiol. 2005;45:351-6.

  Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation.

SES Implantation from RESEARCH

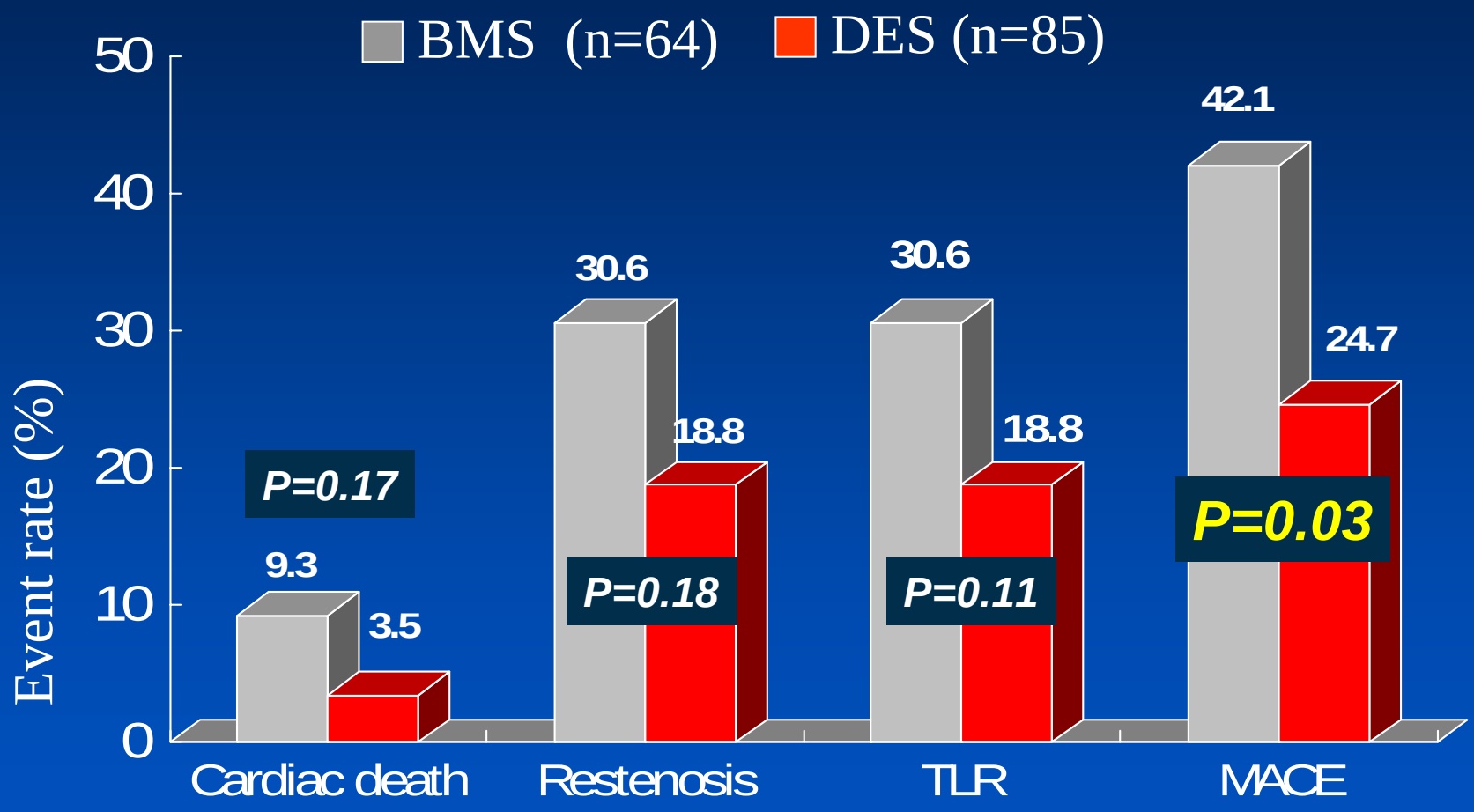
16 Elective (9 unprotected) LMCA Intervention

In-hospital outcome	
Deaths	0
MI	1 (6%)
TLR	0
Overall MACE	1 (6%)
Late outcome at 1 year	
Deaths	0
MI	0
TLR	1 (6%)
Overall MACE	1 (6%)

Arampatzis CA et al. Catheter Cardiovasc Interv 2004;62:292

DES vs. BMS in Milan

Six-month clinical and angiographic follow-up

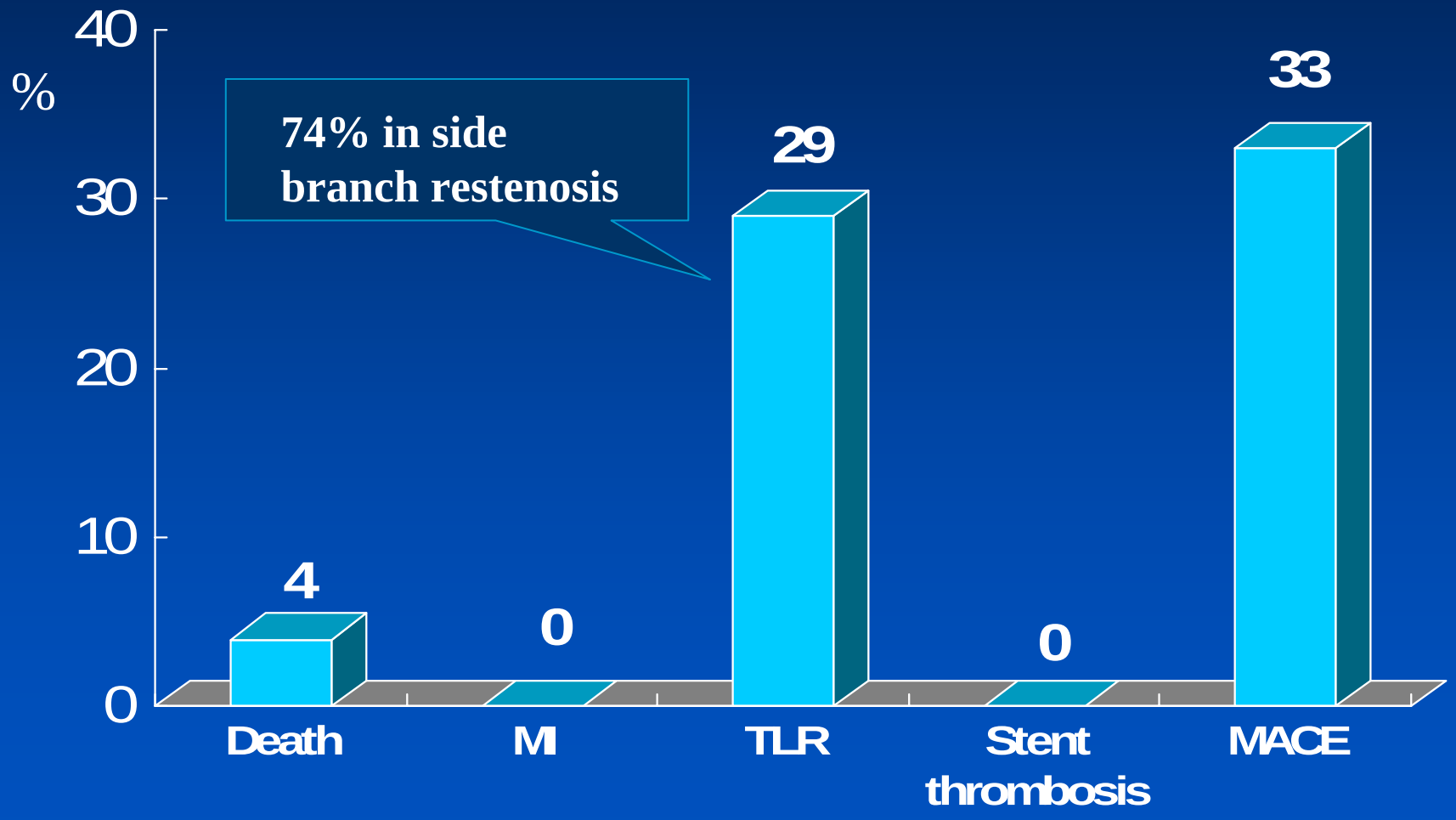


Chieffo A et al. Circulation 2005;111:791

Teirstein PS et al, TCT 2004

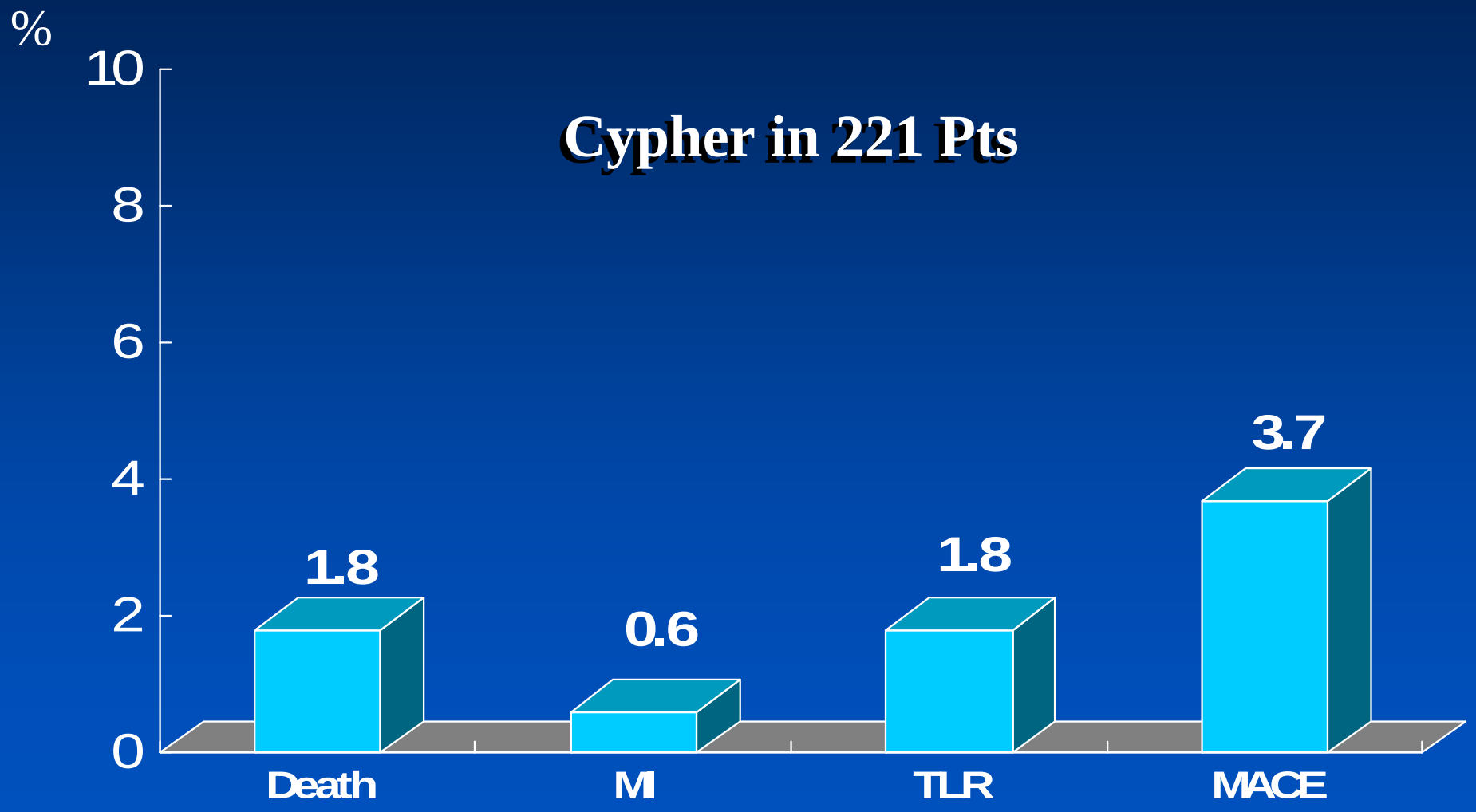
29% TLR at 3 Months

Cypher in 49 Pts



e - Cypher Registry, *Barragan P et al, AHA 2004*

Very low clinical event rates at 6 months



Summary…

DES for LMCA Stenosis

- Much improved early mortality : 0 – 4 % compared to that of BMS era
- Various TLR rates from 1.8 – 29%
- Stenting on the LM trunk would be good enough in real practice
- Left circumflex ostium is main TLR site
- LM bifurcation PCI should be needed appropriate treatment strategy

LM Cypher Study in AMC

- Comparison with BMS

Unprotected LMCA Cypher in AMC

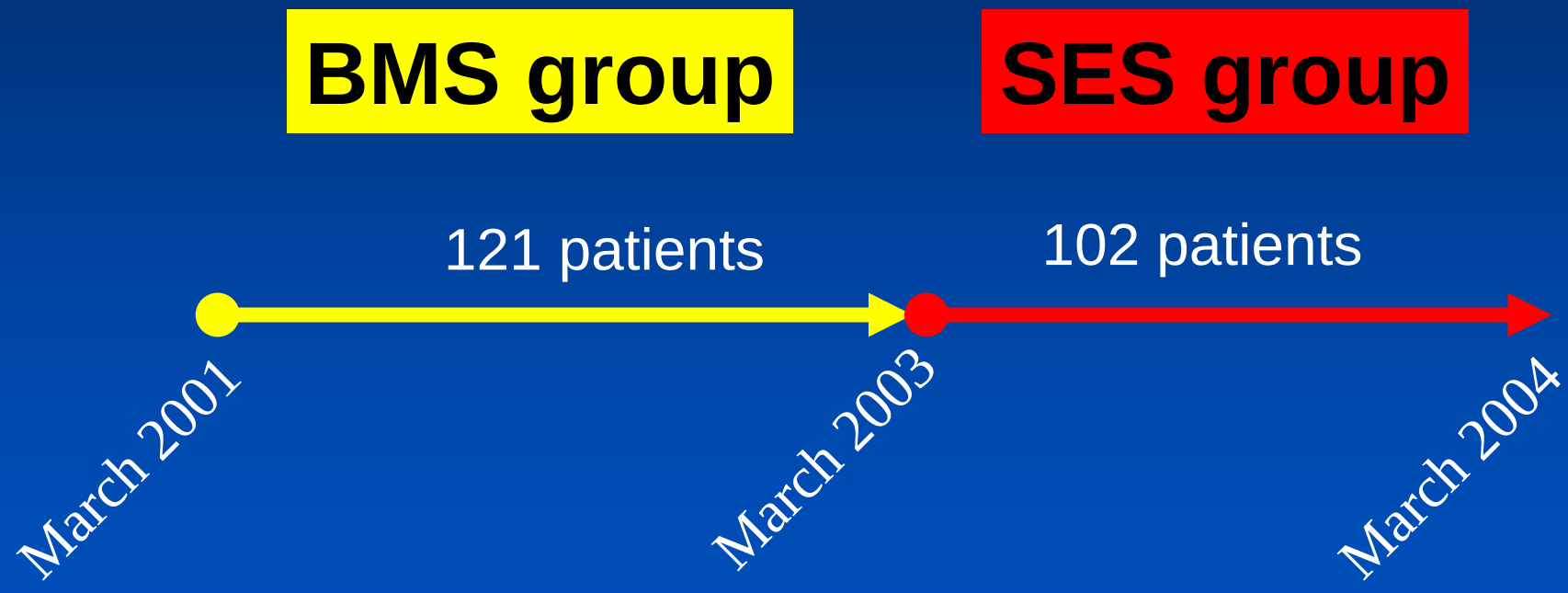
From Feb 2003 till Dec 2004

Total 178 patients

Proximal involvement	**47 (26 %)**
Ostium	**41**
Shaft	**6**
Distal involvement	**131 (74 %)**

LMCA Intervention in AMC

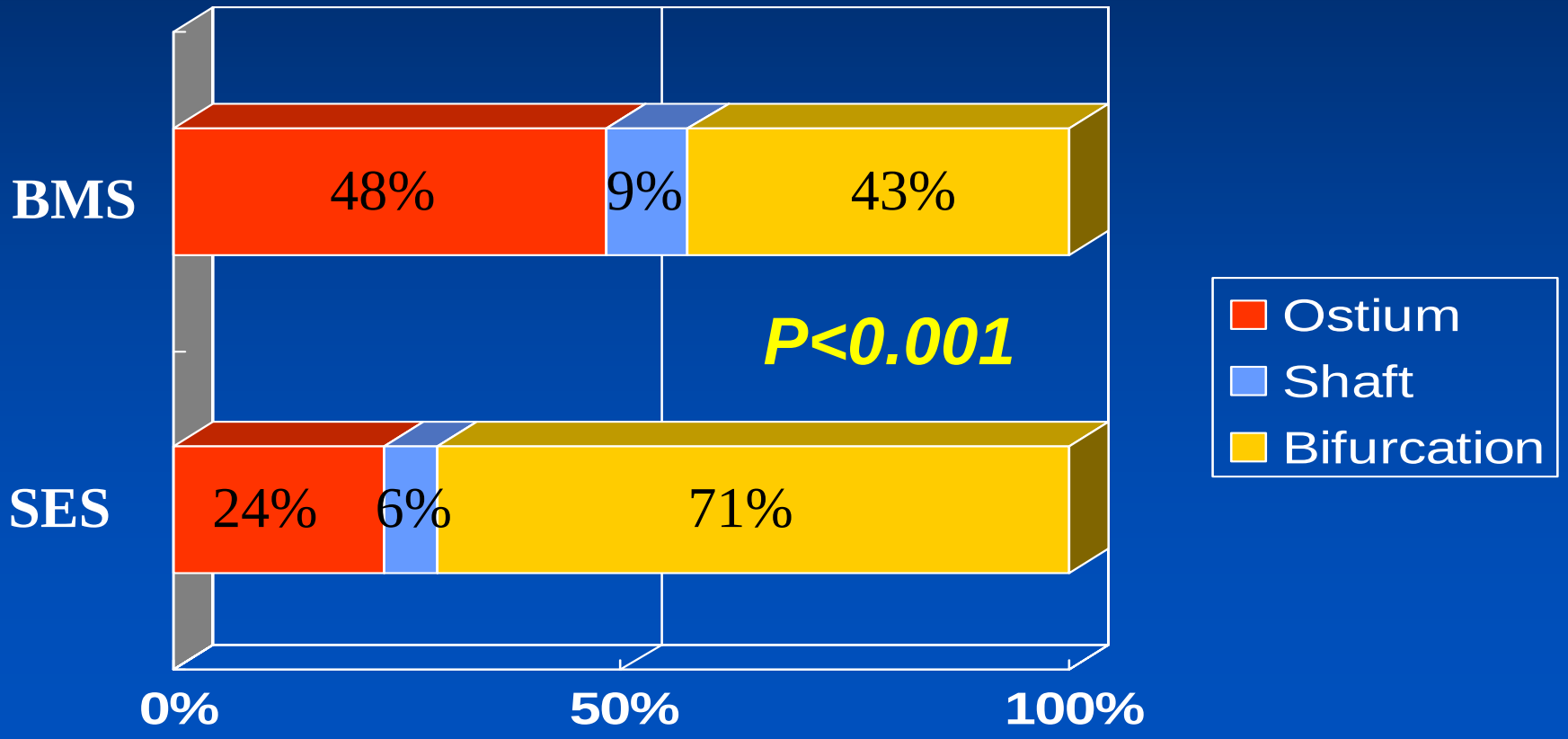
Matched Comparison with BMS



Park SJ et al, J Am Coll Cardiol 2005;45:351

More LM Bifurcation stenting…

149 pts with SES (Feb 2003-Sep 2004)
121 pts with BMS (Feb 2001-Jan 2003)



Park SJ et al, J Am Coll Cardiol 2005;45:351

Multiple & Longer Stents

	SES	BMS	P
Reference diameter, mm	3.46±0.65	3.98±0.69	<0.001
Stents per patient	2.1±1.0	1.6±0.7	<0.001
Stents per lesion	1.6±0.9	1.1±0.4	<0.001
Total stent length, mm	26.6±18.1	13.3±5.5	<0.001
Final balloon size, mm	3.90±0.44	4.39±0.55	<0.001
Inflation pressure, mm	18.5±2.8	14.0±2.6	<0.001
Balloon/Artery ratio	1.1±0.3	1.1±0.2	0.290

Park SJ et al, J Am Coll Cardiol 2005;45:351

Fewer Debulking, More Direct Stenting

	SES	BMS	P
Patients	149	121	
Multivessel PCI	63 (42.3)	42 (34.7)	0.254
Direct stenting	67 (45.0)	21 (17.4)	<0.001
Debulking atherectomy	3 (2.0)	40 (33.1)	<0.001
IVUS guidance	129 (86.6)	91 (75.2)	0.039
GP IIb/IIIa inhibitor	10 (6.7)	6 (5.0)	0.376
IABP support	6 (4.0)	5 (4.1)	0.782

Park SJ et al, J Am Coll Cardiol 2005;45:351

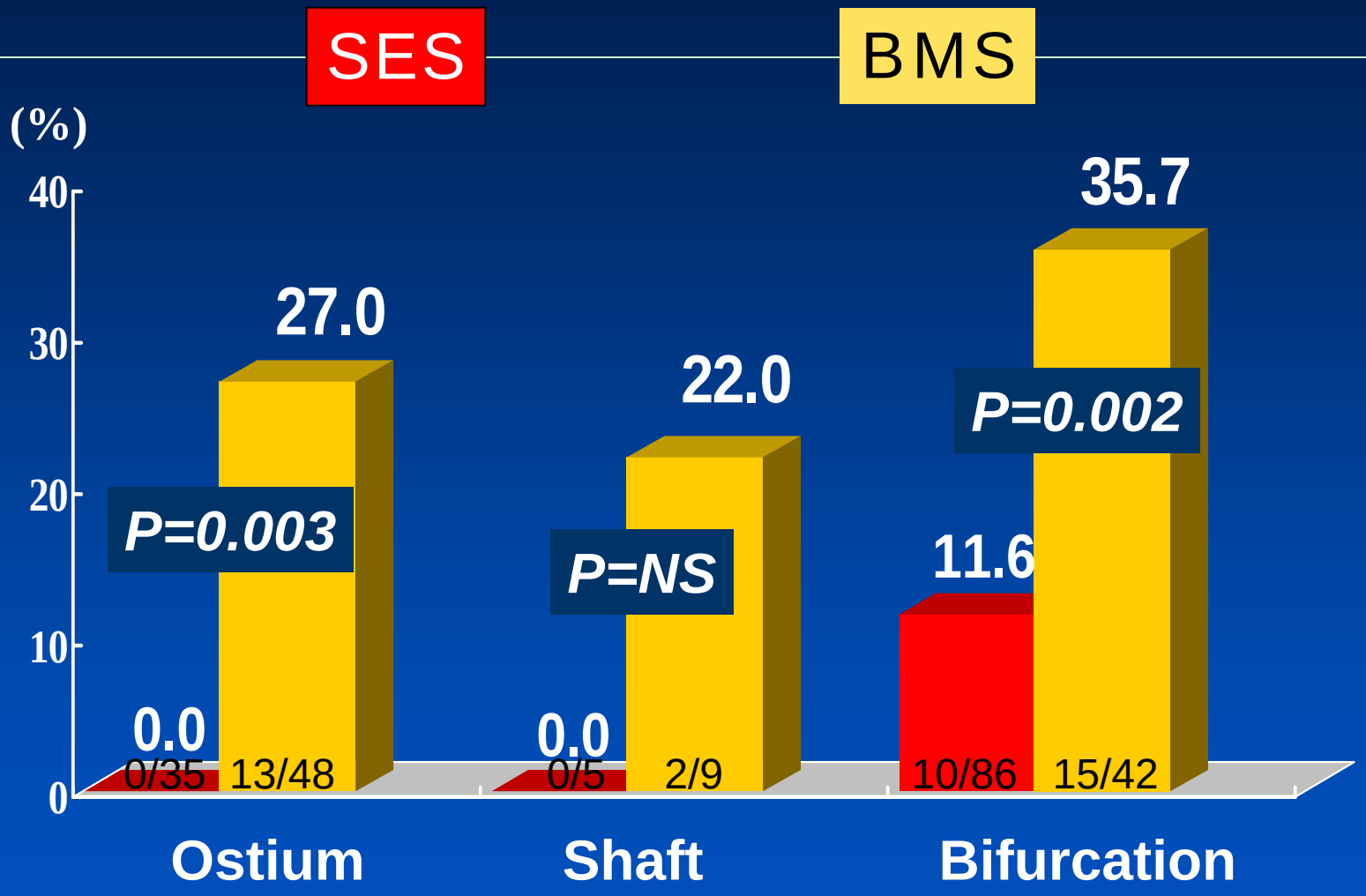
In-Hospital Outcomes

	BMS N=121	SES N=149
Procedure Success (%)	**100**	**100**
Death	**0**	**0**
Q MI	**0**	**0**
Non-QMI	**10 (8.3%)**	**11 (7.4%)**
SAT	**0**	**0**
Emergent CABG	**0**	**0**
Repeat PCI	**0**	**0**

* All procedure related, CK-MB ≥ 3 times normal value

Park SJ et al, J Am Coll Cardiol 2005;45:351

Overall Restenosis Rate : 7.9 %



Park SJ et al, J Am Coll Cardiol 2005;45:351

Left main stenting with DES

Ostial and Shaft lesions intervention

LM ostial or shaft lesions

Total 47 patients	
Age	61 ± 13
Male	28 (60%)
Hypertension	17 (36%)
Diabetes	12 (26%)
Smoking	11 (23%)
Hypercholesterolemia	10 (21%)
Previous PCI	10 (21%)
Acute coronary syndrome	27 (57%)
LV EF (%)	60 ± 10

Procedural Findings

Used stent	Single in all pts
IVUS guidance	38 (81%)
Stent size	
3.0 mm	10 (21%)
3.5 mm	37 (79%)
Mean stent length, mm	13.6±5.3
Maximal device diameter, mm	4.0±0.4
Cutting balloon	1 (2.1%)
Use of reopro	1 (2.1%)
Debulking atherectomy	1 (2.1%)

Angiographic Analysis

Lesion length, mm	9.3 ± 5.4
Reference, mm	3.49 ± 0.53
Minimal lumen diameter, mm	
Before procedure	1.37 ± 0.6
After procedure	3.55 ± 0.37
At follow-up	3.53 ± 0.35
Acute gain, mm	2.18 ± 0.66
Late loss, mm	0.02 ± 0.23
Restenosis	0 (0%)

Clinical Outcome

Mean F/U duration, months	13.1 ± 6.8
Death	0
Myocardial infarction	
Q-wave	0
Non-Q-wave *	2 (4.3%)
Stent thrombosis	0
Target lesion revascularization	0

* procedure-related, no event after discharge

DES for Ostial and Shaft LMCA stenosis

No Mortality

No Restenosis

No TLR rate

Left main stenting with DES

Bifurcation lesions intervention

103 patients with LMCA bifurcation lesions

Demographic data

Age, yr	59.6±10.6
Male	79 (78%)
Hypertension	48 (47%)
Diabetes mellitus	29 (28%)
Hypercholesterolemia	23 (22%)
Current smoking	26 (25%)
Previous PCI	15 (15%)
Acute coronary syndrome	57 (55%)
Multivessel except LMCA	55 (53%)
Left ventricular ejection fraction, %	60.4±7.7

Different Treatment Strategy

Unprotected Left Main Bifurcation Stenting

Stenting Cross Over

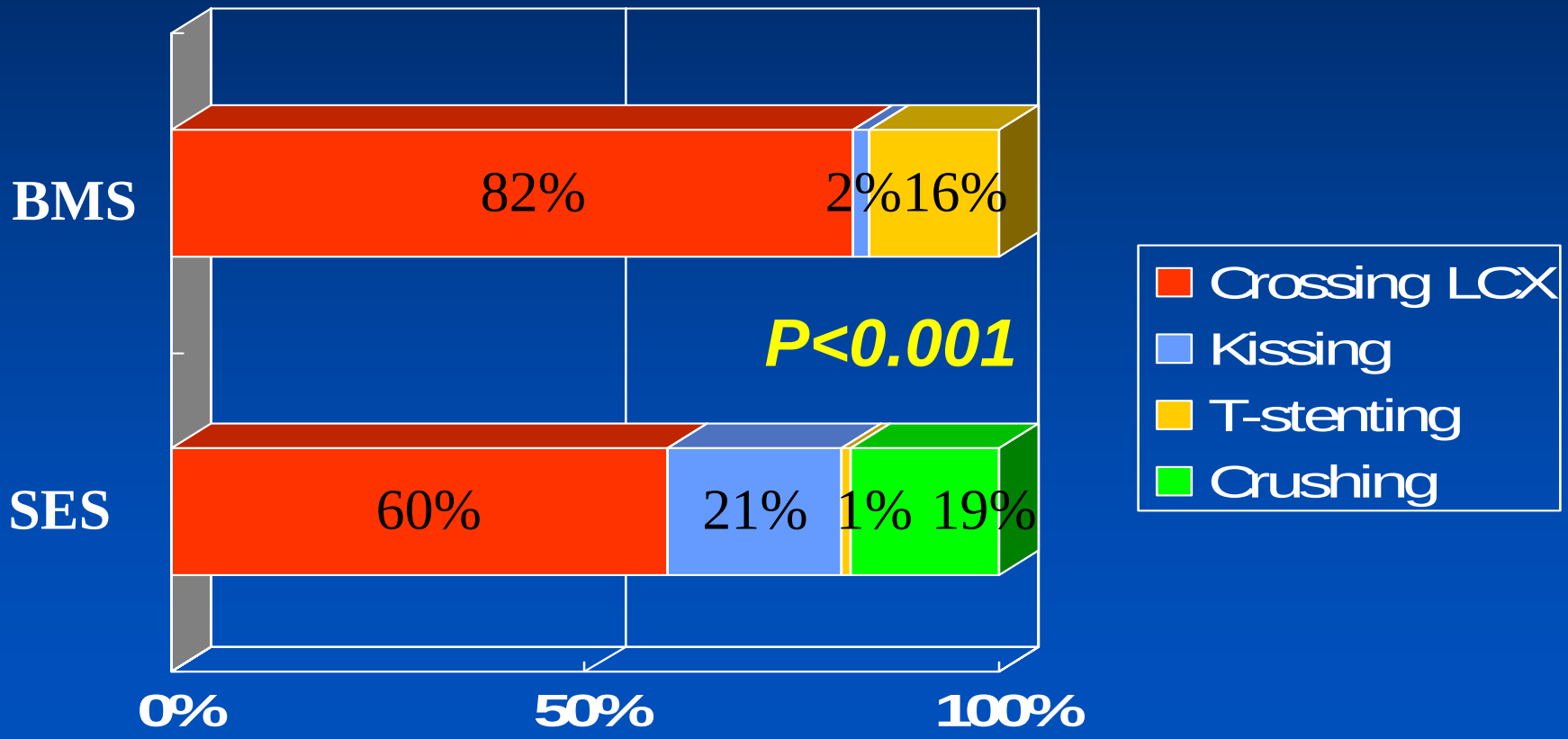
Kissing Stenting

Stent Crushing

T-stent technique

More Complex LM Bifurcation Stenting

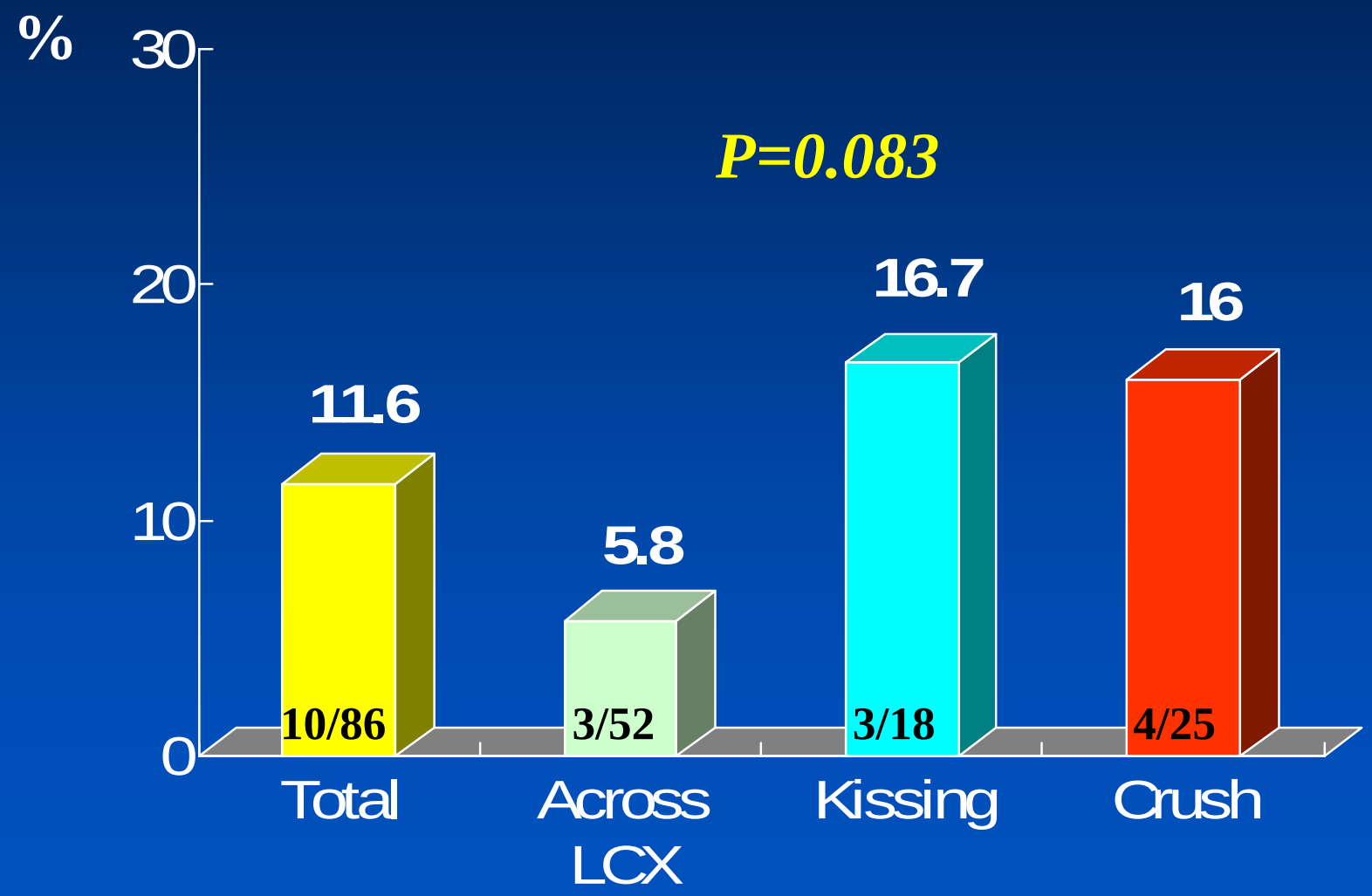
103 pts with SES vs. 51 pts with BMS for bifurcation LM disease



Park SJ et al, J Am Coll Cardiol 2005;45:351

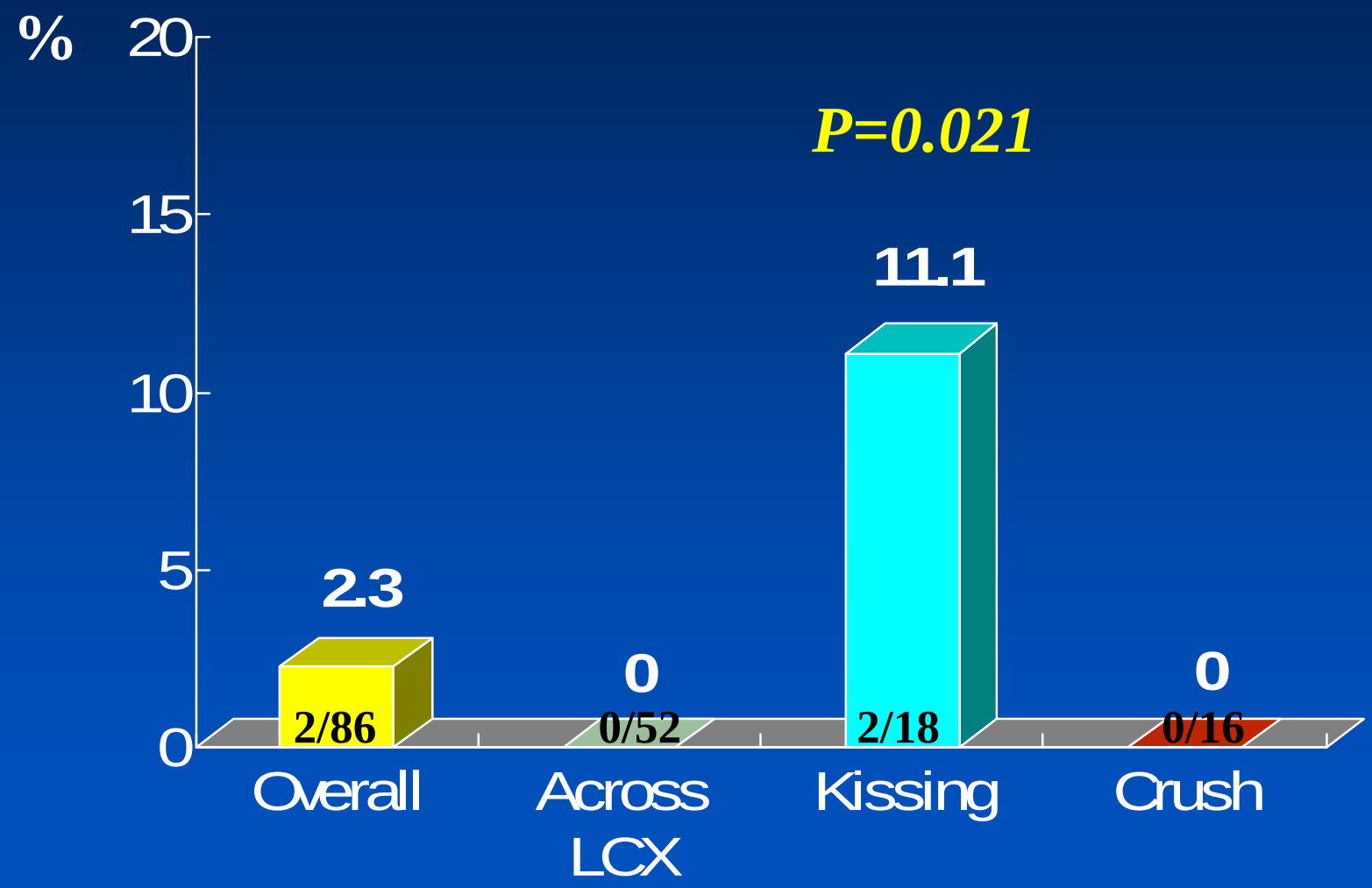
Restenosis Rate of Bifurcation

Overall



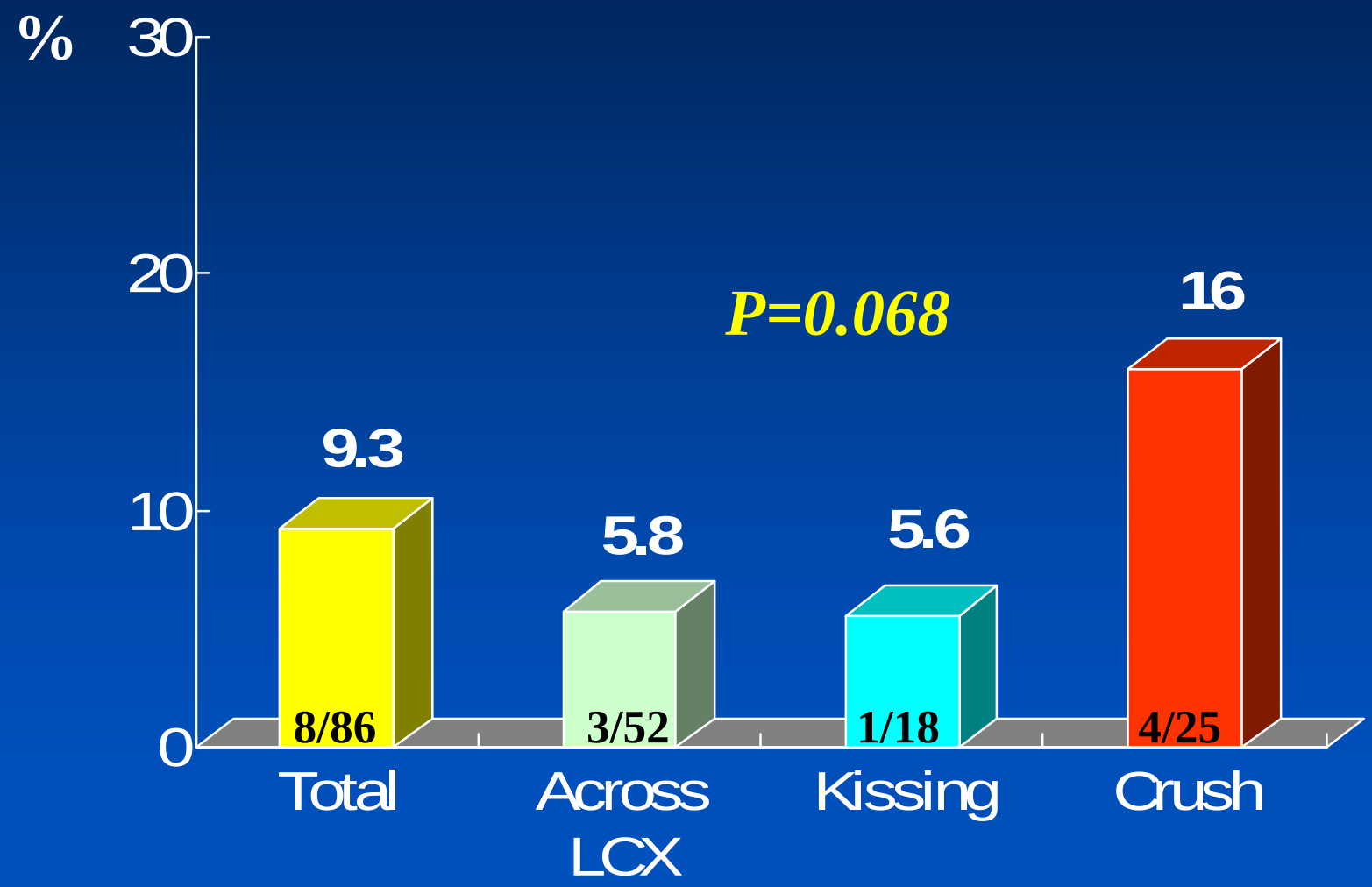
Restenosis Rate of Bifurcation

Main Vessel



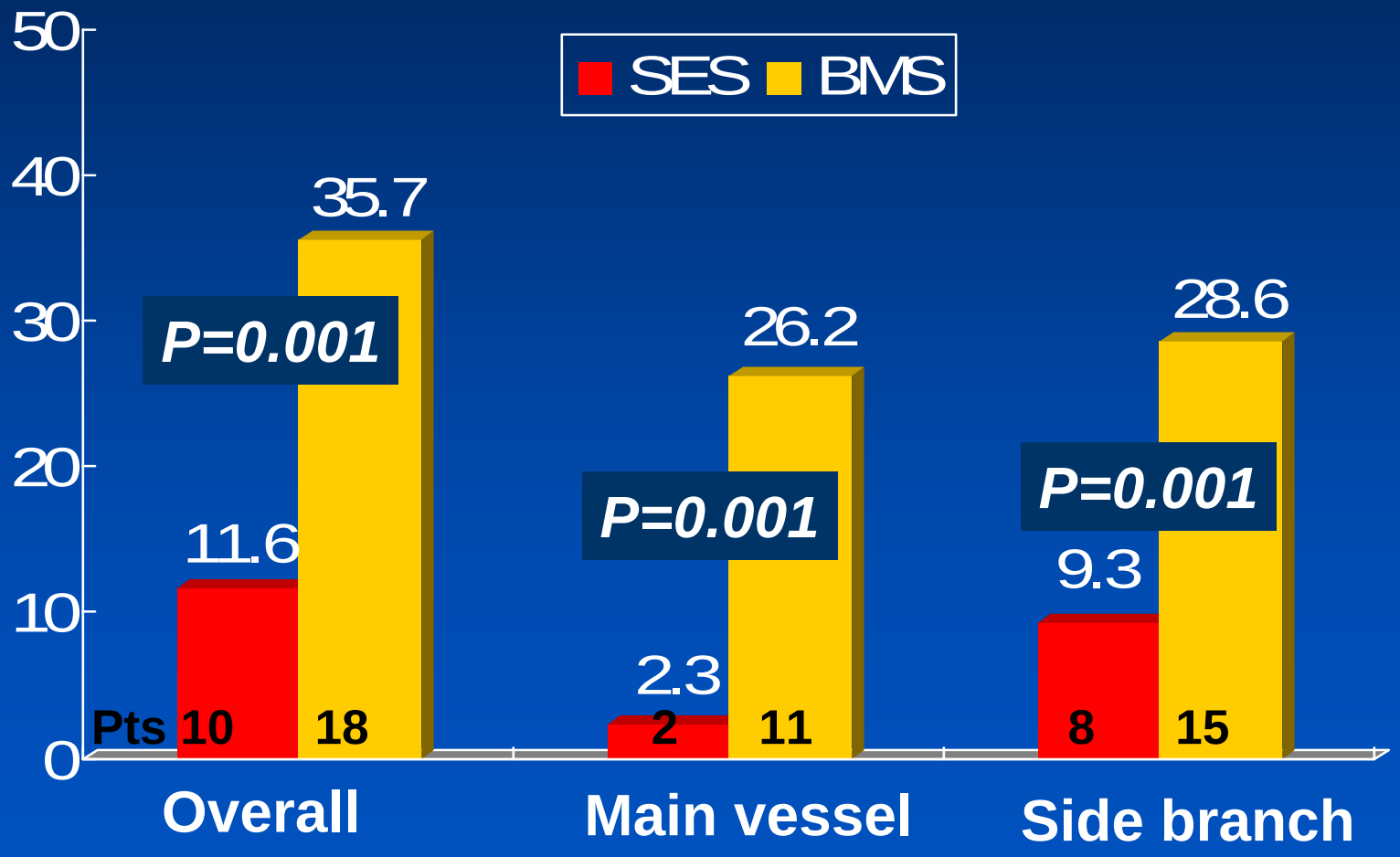
Restenosis Rate of Bifurcation

Circumflex Ositum



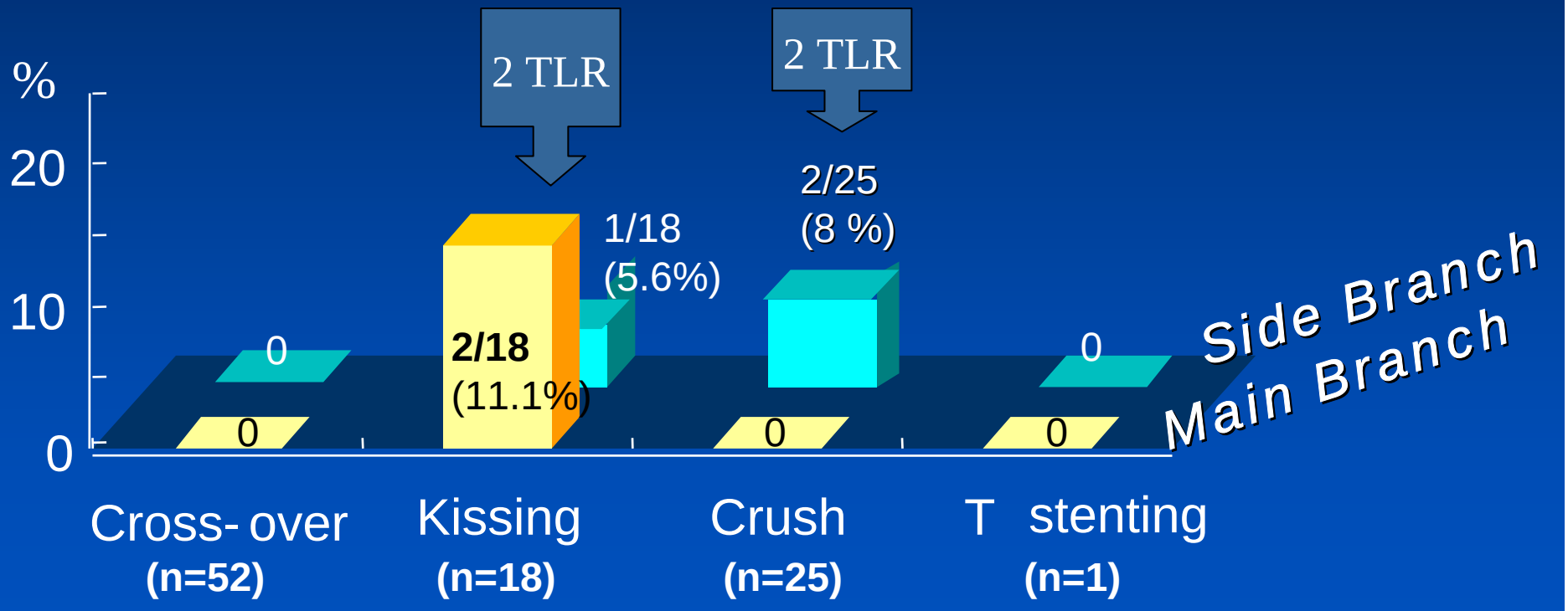
Restenosis Rate of LM Bifucation
DES vs BMS

86 pts with SES vs. 42 pts with BMS



TLR : 4.7% in LM Bifurcation PCI

4/ 86 patients



Left main stenting with DES

Over-all

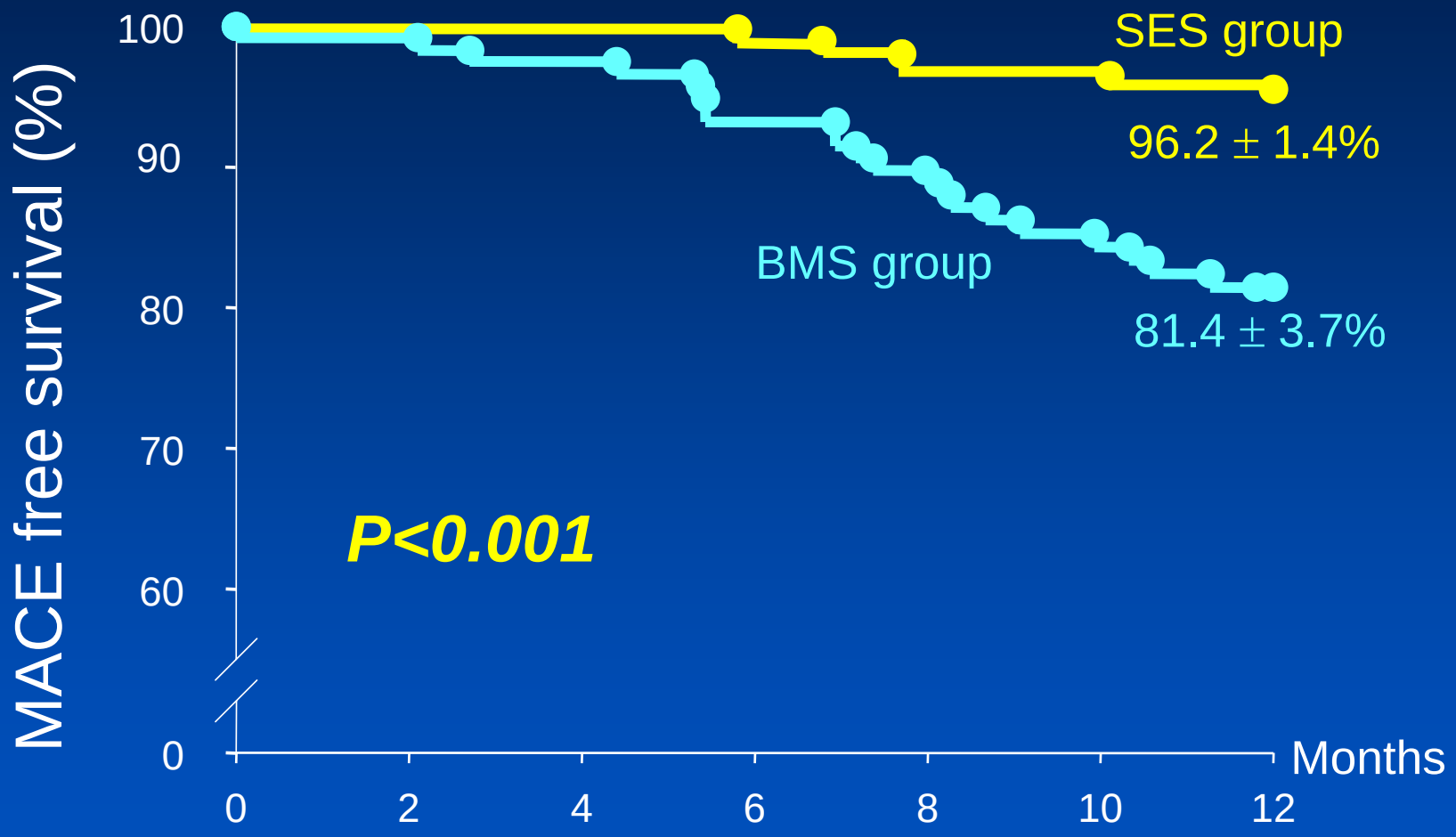
6-months Clinical Outcomes

	BMS N=121	SES N=126
Death	0	0
Q MI	0	0
Non-QMI	0	0
SAT	0	0
TLR *	24 (19.8%)	4 (3.1%)
CABG	13	2
PCI	11	0

* p<0.001

Park SJ et al, J Am Coll Cardiol 2005;45:351

MACE free Survival at 1 year



Park SJ et al, J Am Coll Cardiol 2005;45:351

PCI for LMCA disease…

- Simple technique,
- Acceptable overall restenosis and TLR rate (7.9% and 3.1%)

PCI may be more effective alternative to bypass surgery if we could do appropriate treatment with DES

Restenosis and TLR rate (11.8% and 4.7%) in AMC data were acceptable

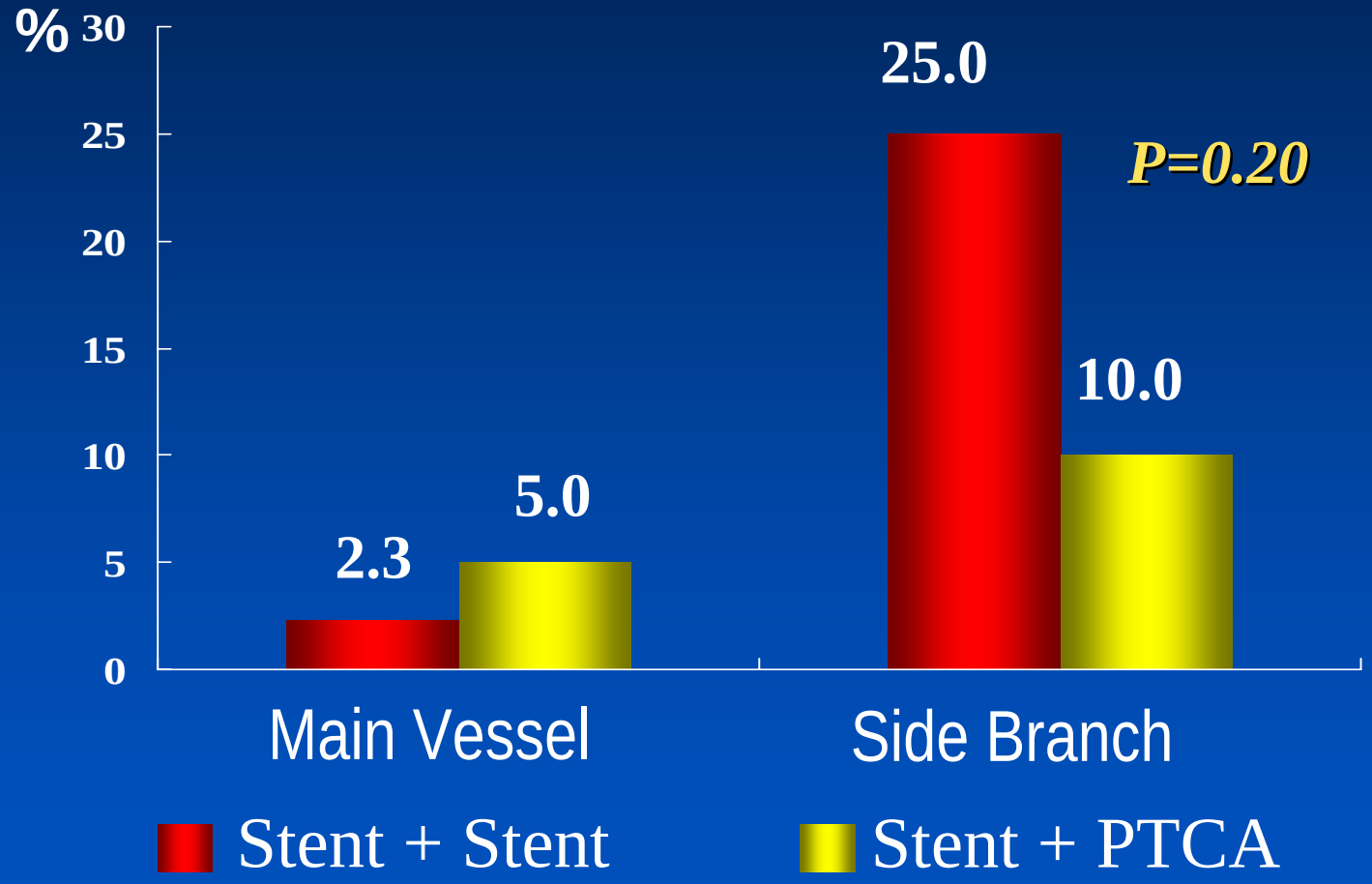
Efficacy Concerns

Bifurcation Lesions

Is DES
a final solution
for bifurcation ?

In-Segment Restenosis

SIRIUS Bifurcation



A Colombo, et al. Cir 2004;109:1244

RESEARCH Bifurcation

SES (n=127) or PES (n=72)

- Subacute thrombosis 2.5 %
- TLR 7 %
- TVR 9 %
- Binary Restenosis
  - Main vessel 9 %
  - Side branch 14 %

Serruys et al, ACC 2004

DES is a solution for bifurcation ?

- **Main branch** — **Certainly, Yes**
- **Side branch** — **Not certain, yet**

We should focus on the treatment of side branch in bifurcation PCI with DES.

Simple vs. Complex

Simple Stenting Technique

1. Stent placement in the main branch only

And

1) Optional kissing balloon inflation
2) Provisional T stenting
3) Provisional reverse Crush technique

Complex Stenting Technique

At least 2 stents

1. **Modified T stenting**
2. **Crush technique**
3. **Y stenting**
4. **V stenting**
5. **Kissing stenting**

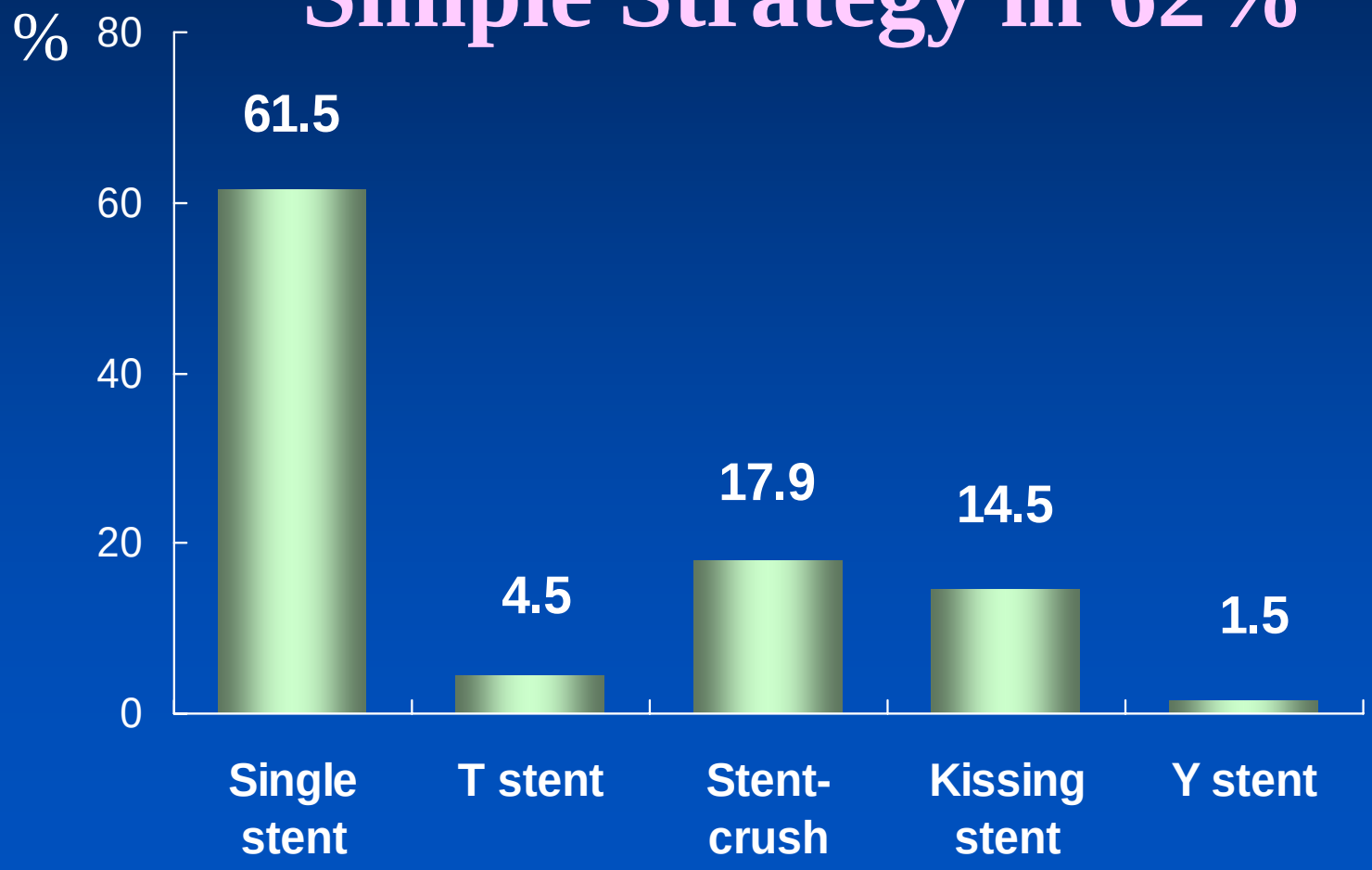
AMC Experience

DES
For Bifurcation

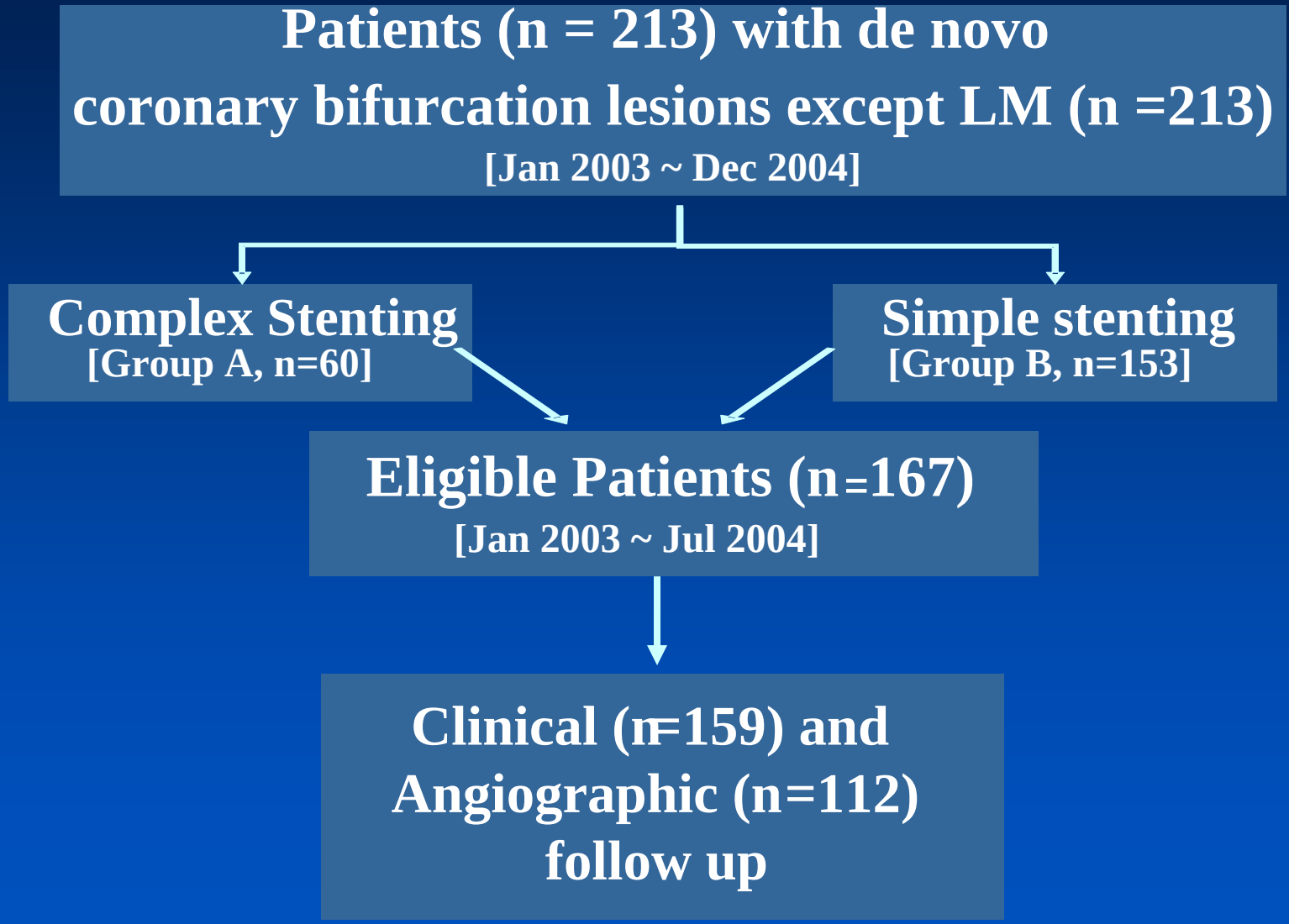
Total 330 lesions with side branch ≥ 2.0mm

Bifurcation Lesions PCI in AMC

Simple Strategy in 62%



Complex vs Simple technique



Procedural Findings

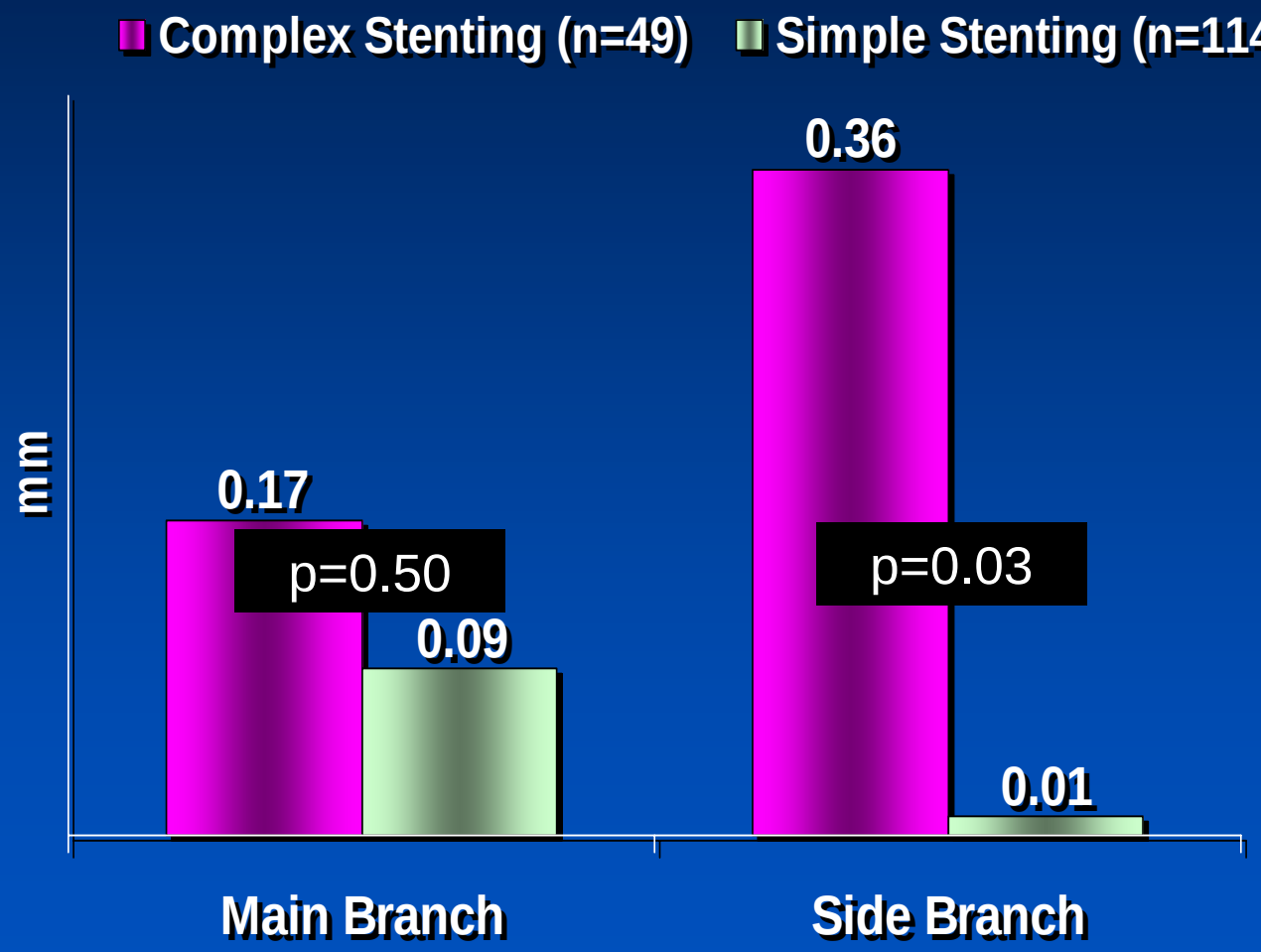
	Complex Stenting (N=60)	Simple Stenting (N=153)	*P*
MB			
Balloon size, mm	3.84 ± 0.39	3.66 ± 0.51	0.09
Balloon/artery ratio	1.23 ± 0.23	1.20 ± 0.16	0.37
SB			
Balloon size, mm	3.07 ± 0.43	2.98 ± 0.32	0.42
Balloon/artery ratio	1.21 ± 0.26	1.19 ± 0.18	0.40
Success Rate*, %	99.2	94.3	0.75
Kissing balloon %	86.7	78.5	0.36

In-Hospital Outcomes

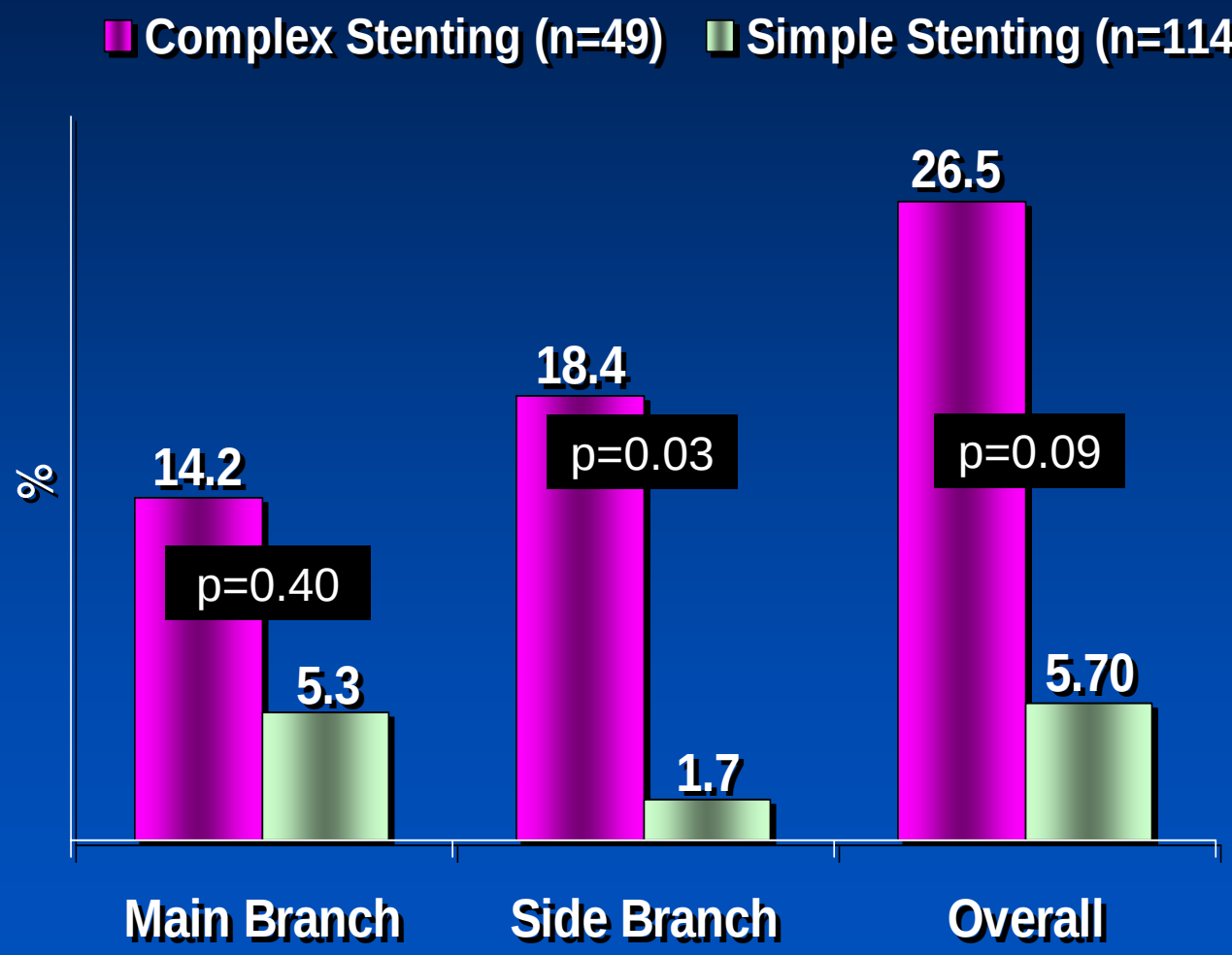
	Complex Stenting	Simple Stenting	P
Patients	60	153	
Death	0	2*	…
MI			
Q MI	0	0	…
Non-Q MI	4 (6.7%)	6 (3.9%)	0.47
Stent thrombosis	0	0	…
TLR	0	0	1.0

MB= Main Branch; SB= Side Branch; * Due to gall bladder cancer and traffic accident, respectively.

Late Loss at 6 Months

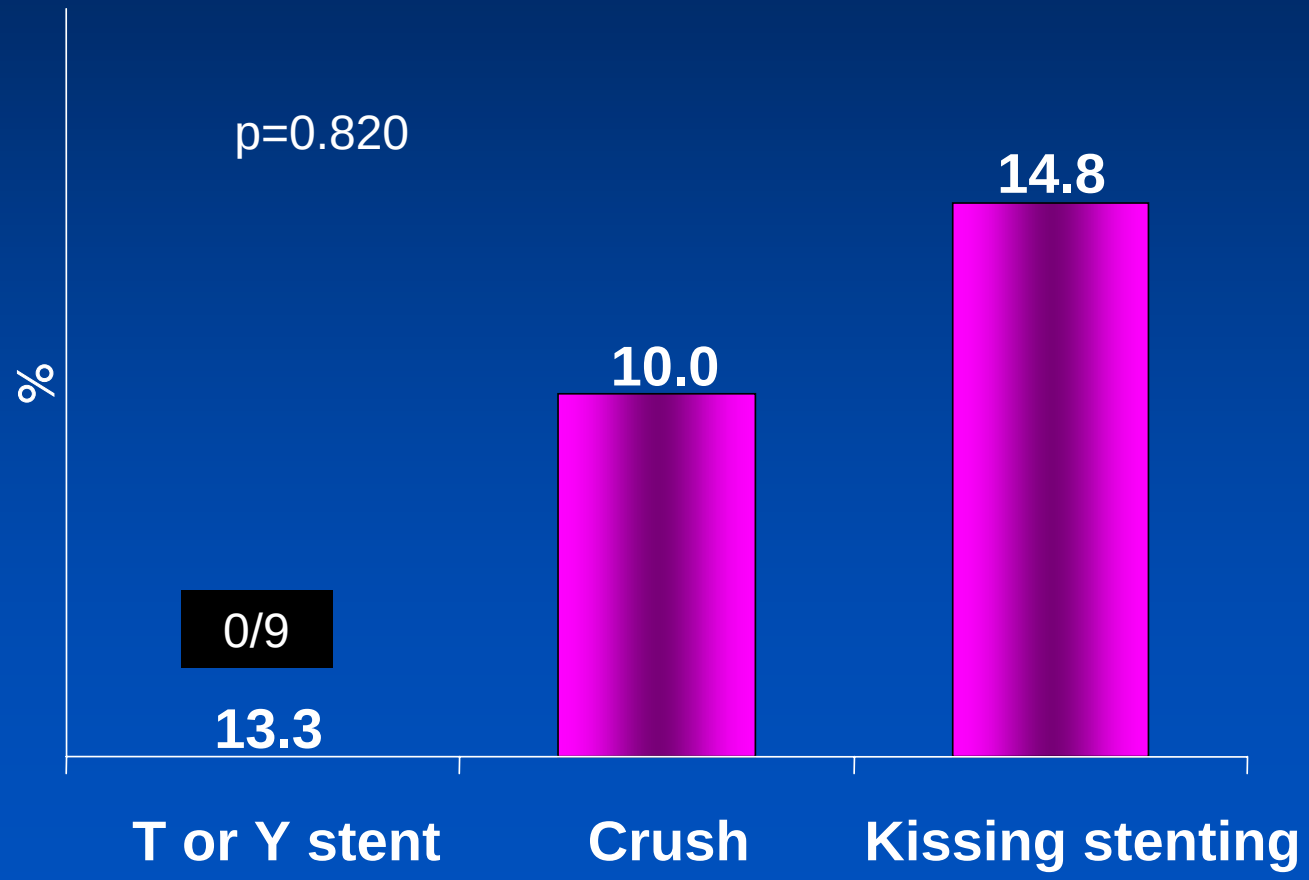


Restenosis Rate at 6 Months



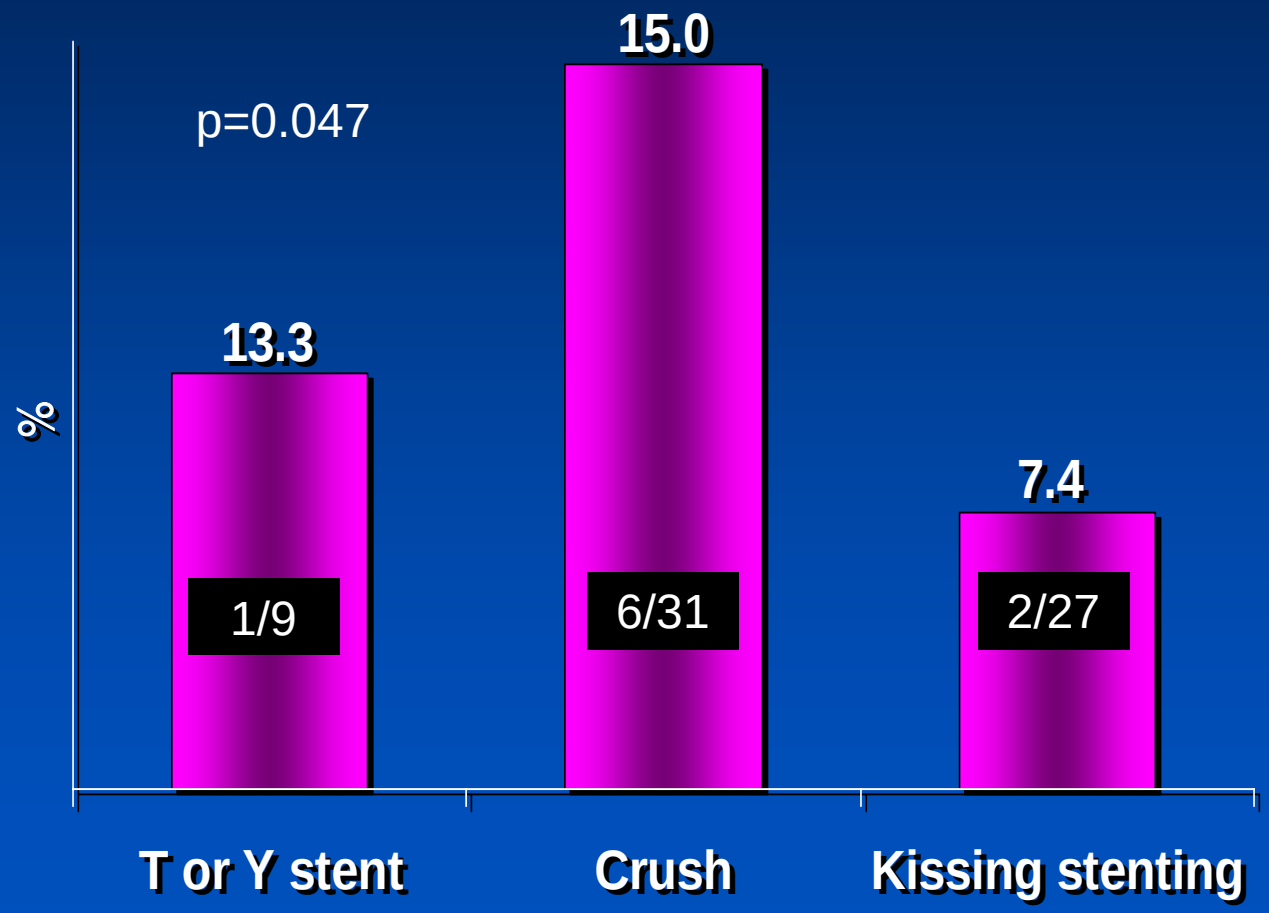
Restenosis Rate at 6 Months

Main branch



Restenosis Rate at 6 Months

Side branch



Clinical Outcomes at 9 Months

	Complex Stenting (n=58)	Simple Stenting (n=145)	P
Death	0	2*	...
MI	0	0	...
Stent thrombosis	0	0	...
TLR	4 (6.9%)	3 (2.1%)	0.46
MACE	4 (6.9%)	5 (3.4%)	0.43

* Due to gall bladder cancer and traffic accident, respectively.

Simple vs. Complex Stenting

- Simple stenting technique crossing the side branch should be preferred in bifurcation lesions with non-diseased side branch.
- Final kissing balloon dilatation improves immediate outcome of the side branch.
- Provisional T stenting can be used when the side branch narrowing was deteriorated after stenting in the main branch.

Efficacy Concerns

In-Stent Restenosis

ISR in AMC

183 lesions with DES Implantation

Focal	62 (34 %)
Diffuse	88 (48 %)
Proliferative	19 (10 %)
Total occlusion	14 (8 %)

Lesion length : 27.3 ± 15.3 mm

6-Month Restenosis : 4.9 %

	81 eligible lesions (75%)
Reference vessel (mm)	2.73 ± 0.48
MLD (mm)	2.36 ± 0.60
Late loss (mm)	0.48 ± 0.45
Diameter stenosis (%)	11.6 ± 28.6
Binary restenosis (%)	4 (4.9%)

AMC-ISR

Randomized Comparison of RT vs. SES for Diffuse ISR from Multicenter Study in Korea

Compared the efficacy and safety of sirolimus-eluting stent implantation versus β-radiation therapy with ^{188}Re-MAG$_3$- filled balloon for diffuse ISR in a prospective randomized manner.

Brachytherapy vs SES for ISR

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, RTx group)**

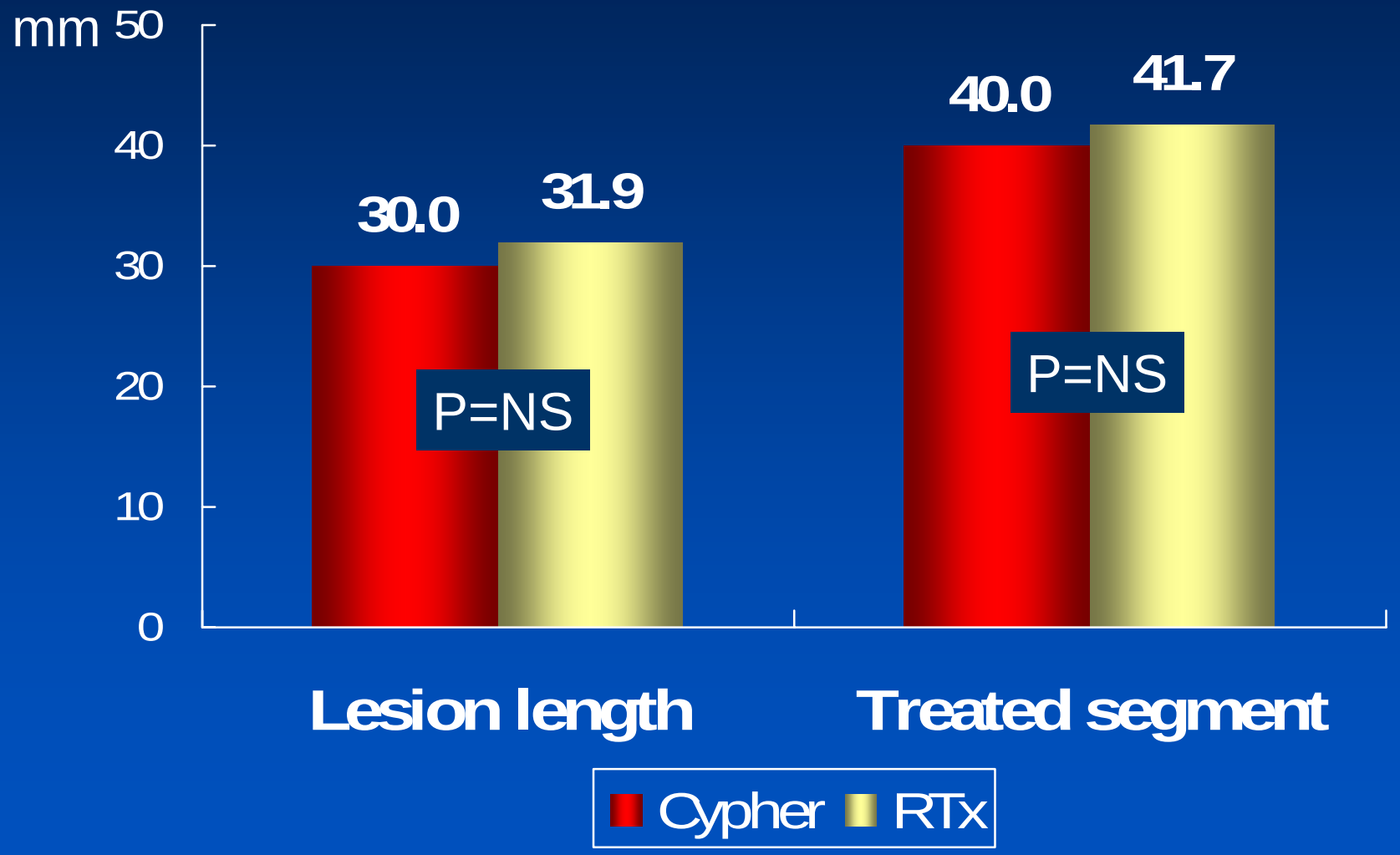
Angiography follow-up
Clinical follow-up

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

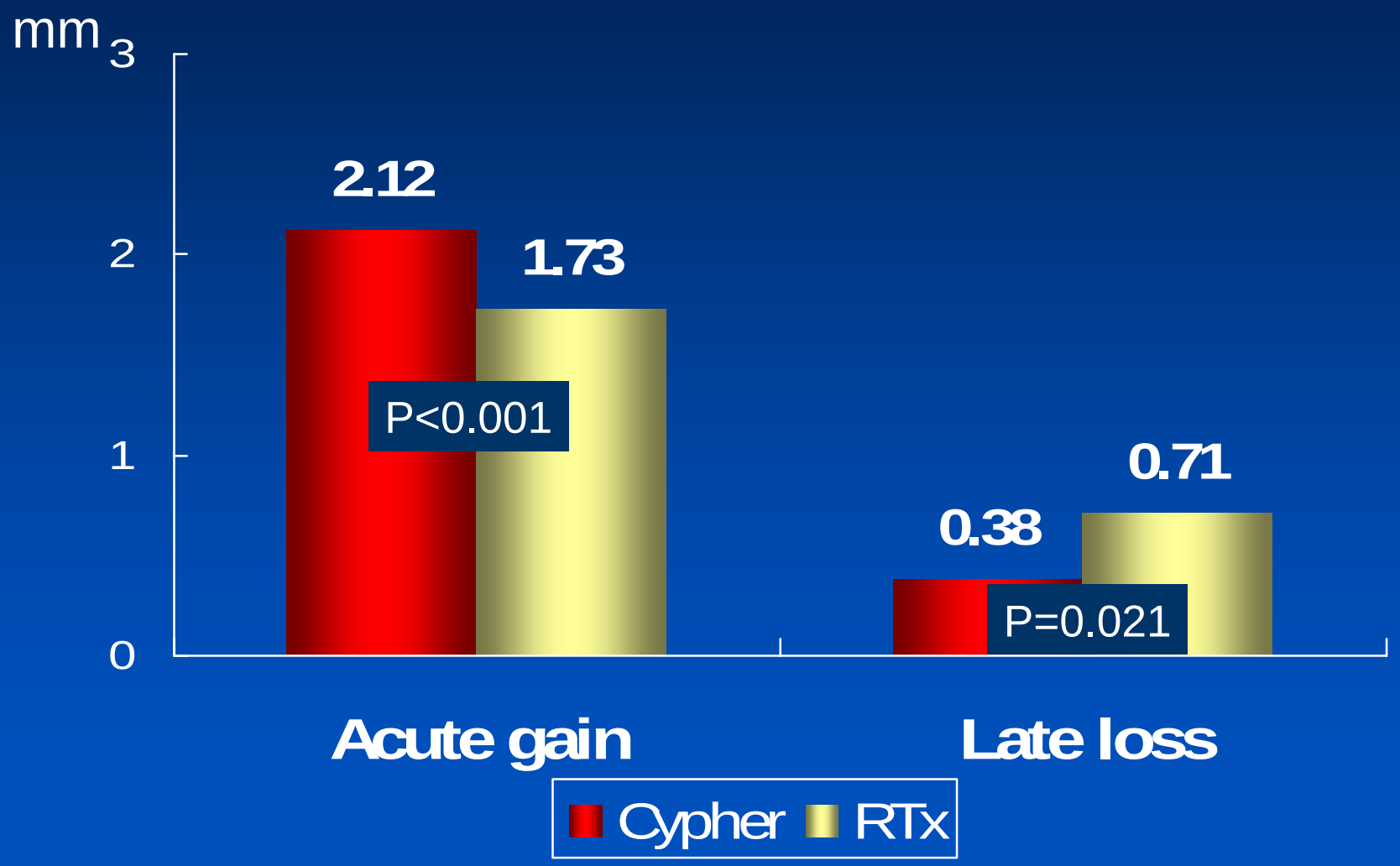
In-Hospital Outcomes

	SES	RTx	P
Patients	65	64	
Angiographic success	63 (97)	58 (91)	0.164
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

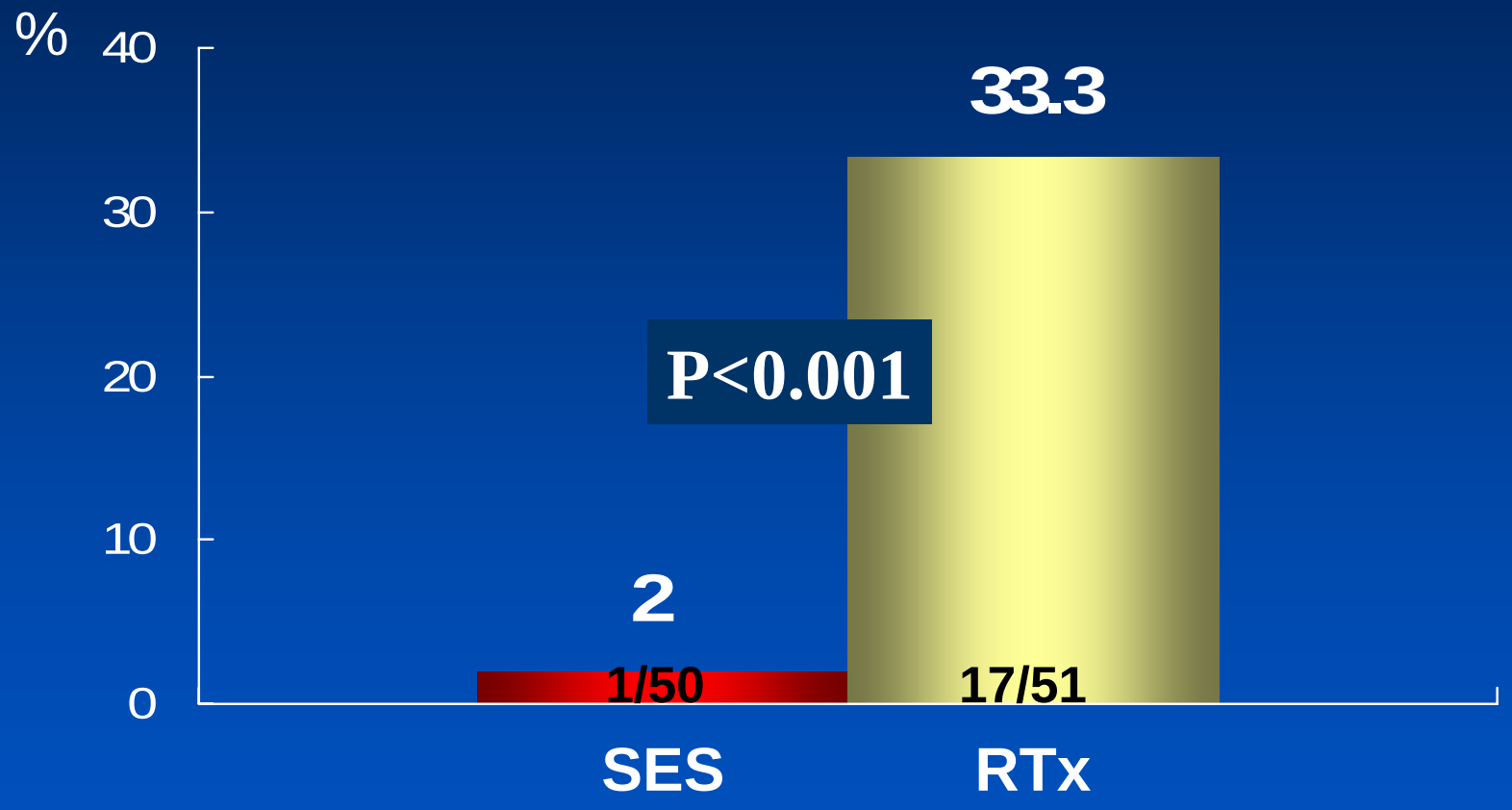
Lesion Length & Treated Segment



Acute Gain & Late Loss



Restenosis Rate at 6 Months



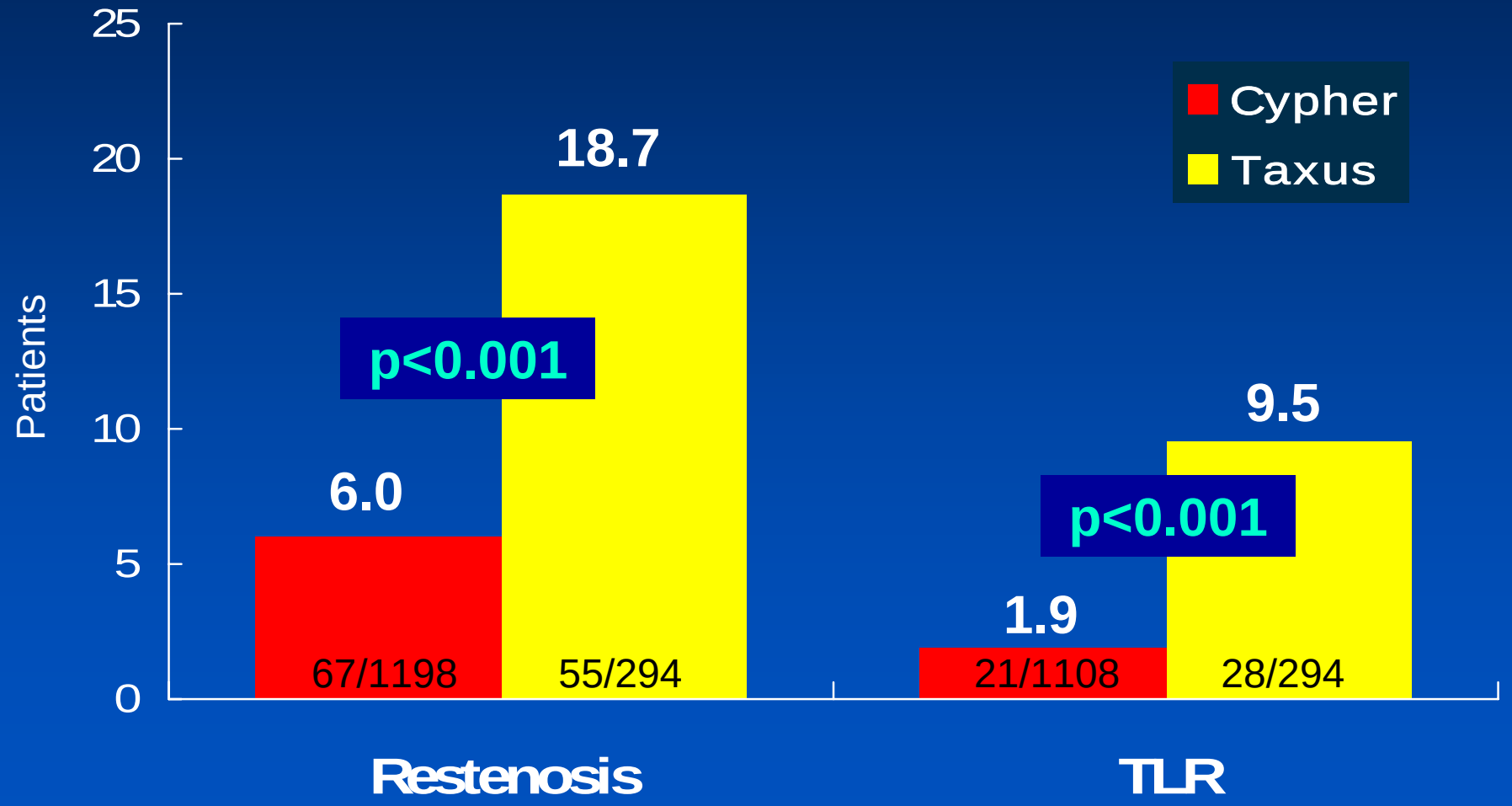
Summary

- DES improves clinical and angiographic outcomes of ISR treatment versus conventional angioplasty.
- Recurrent restenosis after SES implantation in ISR reported has not been frequent in the current reports.
- Sirolimus-eluting stent appears to be a promising and more effective alternative to intracoronary brachytherapy for the treatment of diffuse ISR.
- Lower angiographic restenosis and late loss in SES group may be related to a greater acute gain and inhibition of neointima accumulation, compared to coronary brachytherapy.

DES failure

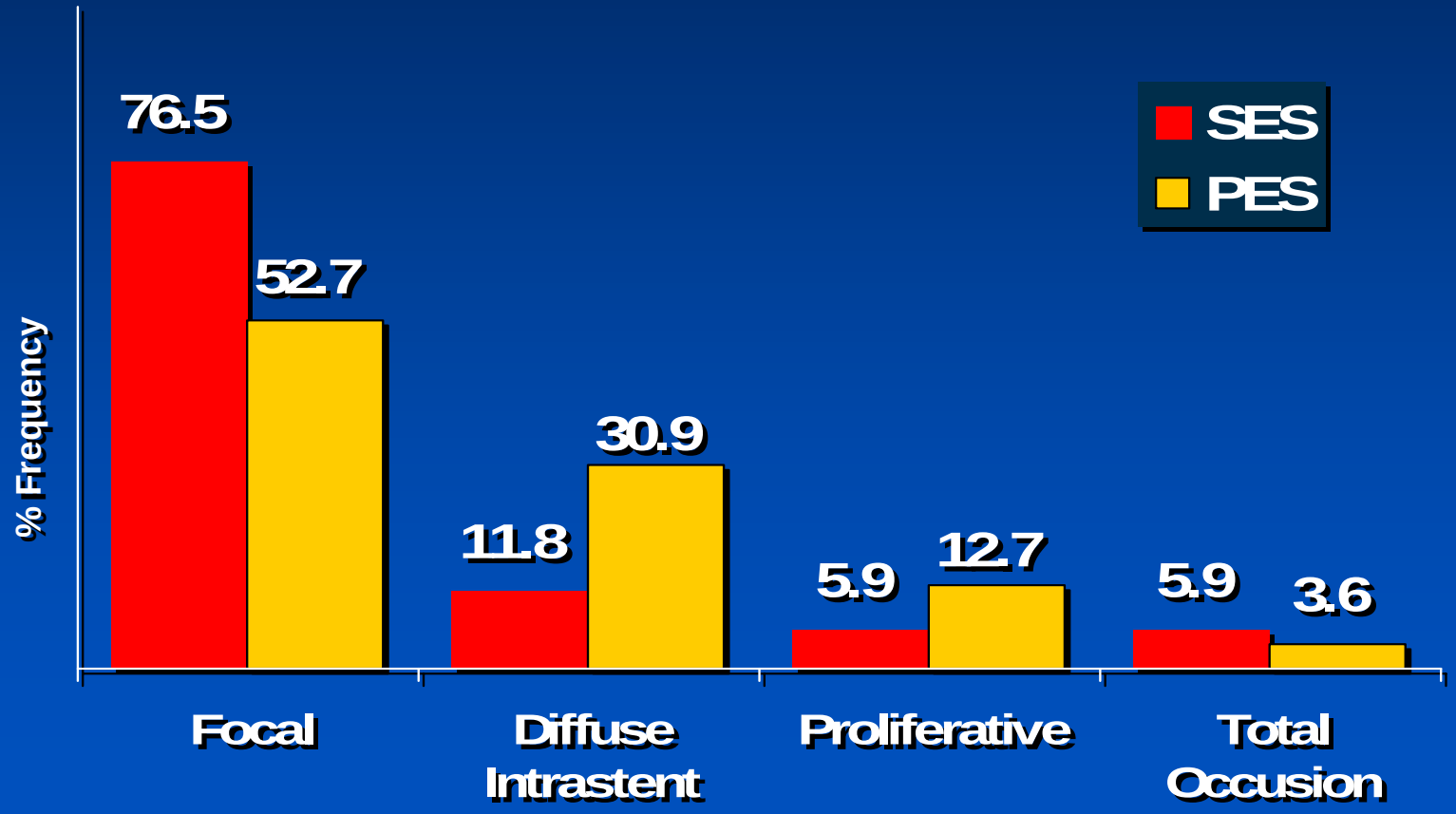
ISR after DES Implantation

Feb 2003 ~ Nov 2004



Patterns of ISR

Total 67(SES) / 55 (PES) restenosis lesions



ISR patterns and TLR strategies

Total

Cypher	13	14	3	2	0	**32 (50.8%)**
RT	0	4	5	3	0	**12 (19.0%)**
Cutting	1	7	1	0	0	**9 (9.5%)**
CABG	2	2	2	2	2	**10 (15.9%)**
	16 (25.4%)	**24 (42.9%)**	**11 (17.5%)**	**7 (11.1%)**	**2 (3.2%)**	**63**

Summary

- Focal ISR pattern was most frequent after SES implantation and was easily treated by repeat SES stenting or cutting balloon.
- Until now, no statement can be made regarding the most appropriate treatment strategy for SES failure.
- Therefore, treatment decision should depends on each patient and each lesion.

Efficacy Concerns

Very Long Lesions

Three Study Arms

From March 2003 - to February 2004

De-novo Lesions
(≥ 24mm)

637 patients, 739 lesions

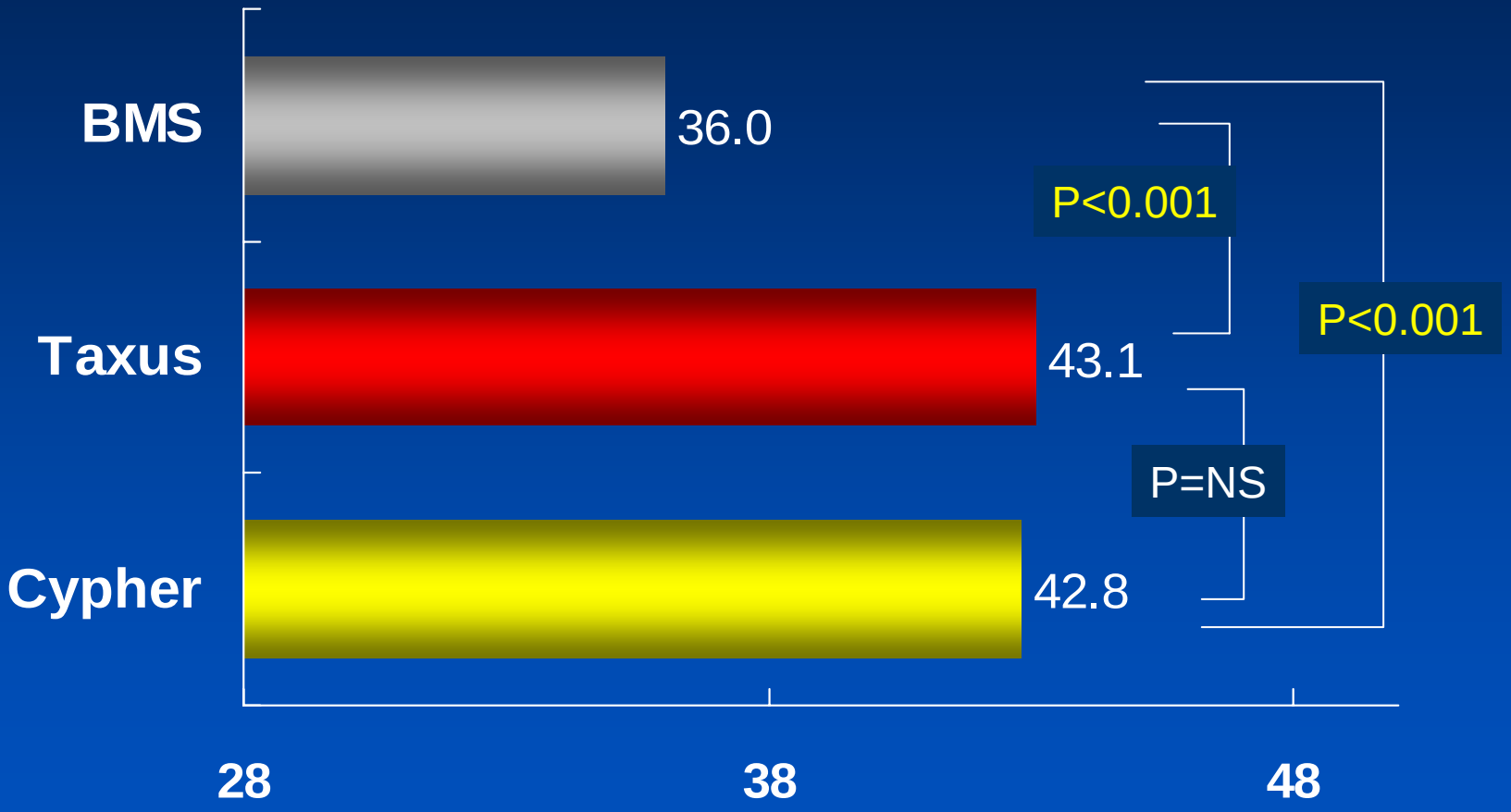
CYPHER (≥ 28mm)	**TAXUS** (≥ 28mm)	**Bare Metal** (≥ 28mm)
294 patients 344 lesions	166 patients 194 lesions	177 patients 201 lesions

Lesion Length: 35mm

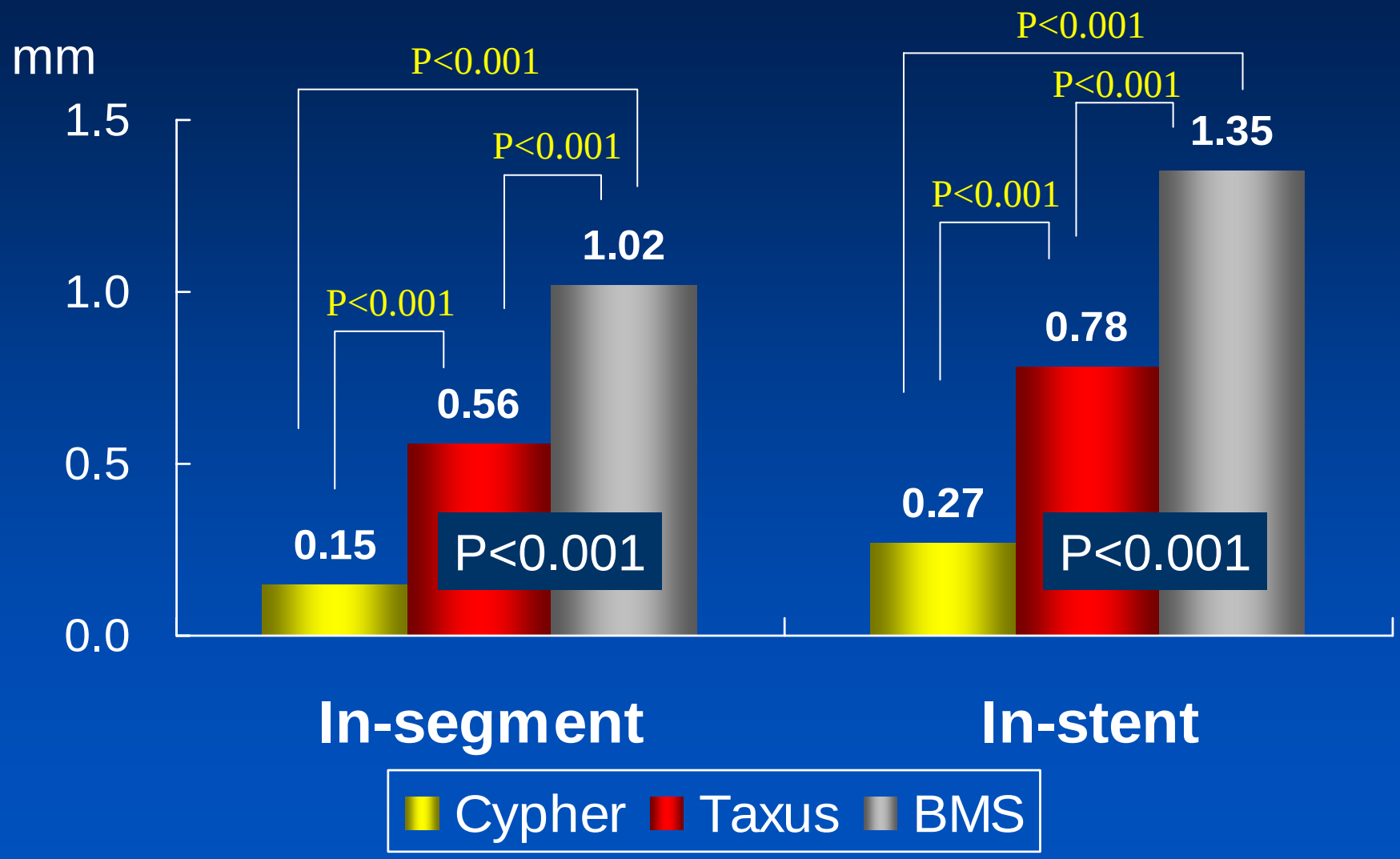
	Cypher (n=337)	Taxus (n=194)	BMS (n=201)	P value
Reference, mm				
Proximal	**3.01±0.49 #**	**3.10±0.49 ****	**3.27±0.55**	<0.001
Distal	**2.59±0.45 * #**	**2.71±0.53**	**2.84±0.57**	<0.001
Mean	**2.80±0.41 * #**	**2.90±0.48 ****	**3.10±0.54**	<0.001
Lesion length, mm	**35.3±14.3 ***	**36.3±14.5 ****	**32.0±12.3**	0.004
MLD, mm	**0.76±0.47**	**0.77±0.49**	**0.78±0.54**	**0.942**
DS, %	**72.5±16.6**	**73.6±16.2**	**74.4±17.0**	**0.450**

Between groups: * p<0.025 Cypher vs Taxus; # p<0.025 Cypher vs BMS;**, p<0.025 Taxus vs. BMS

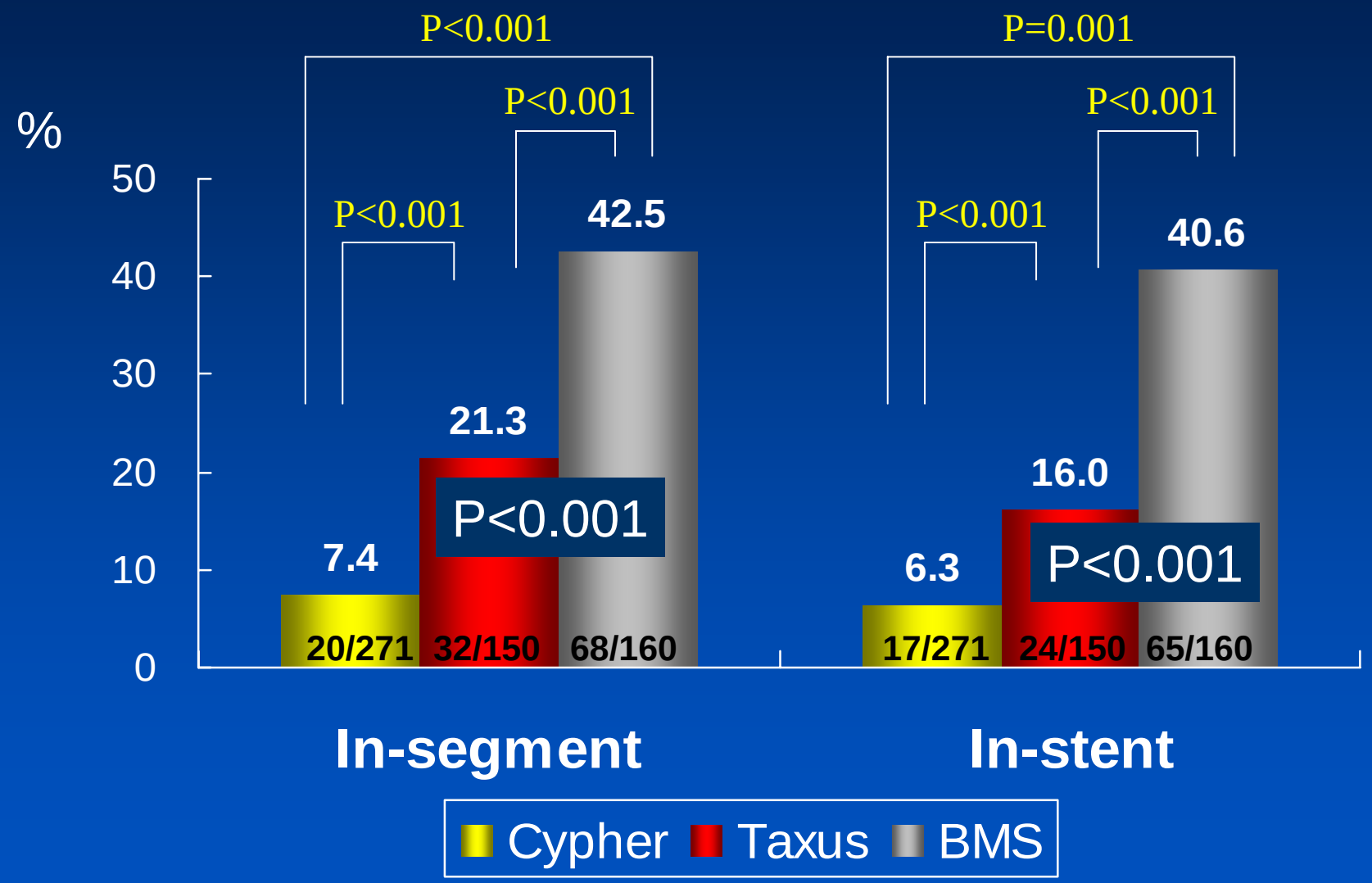
Total Stent Length: 43mm



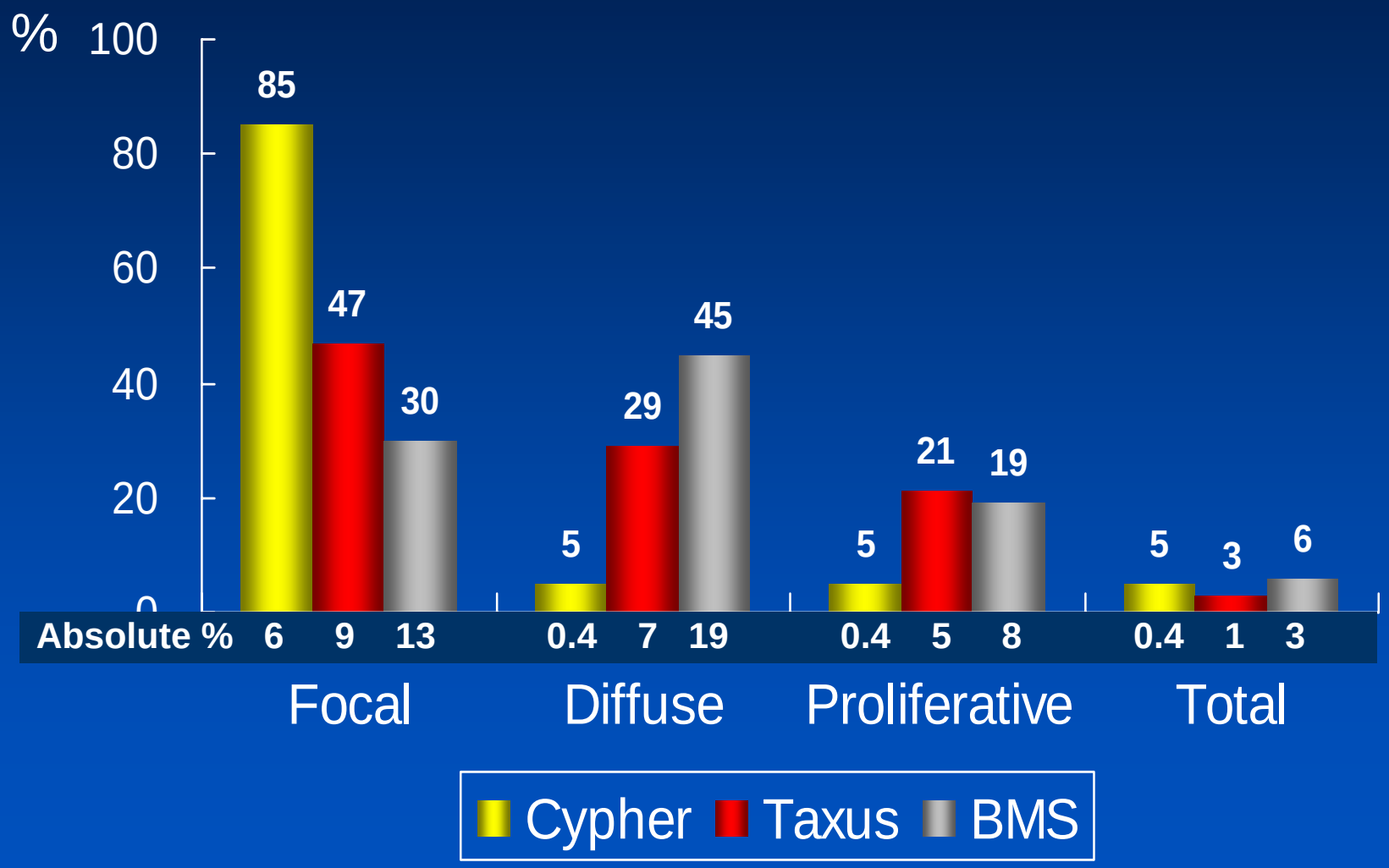
Lower Late Loss



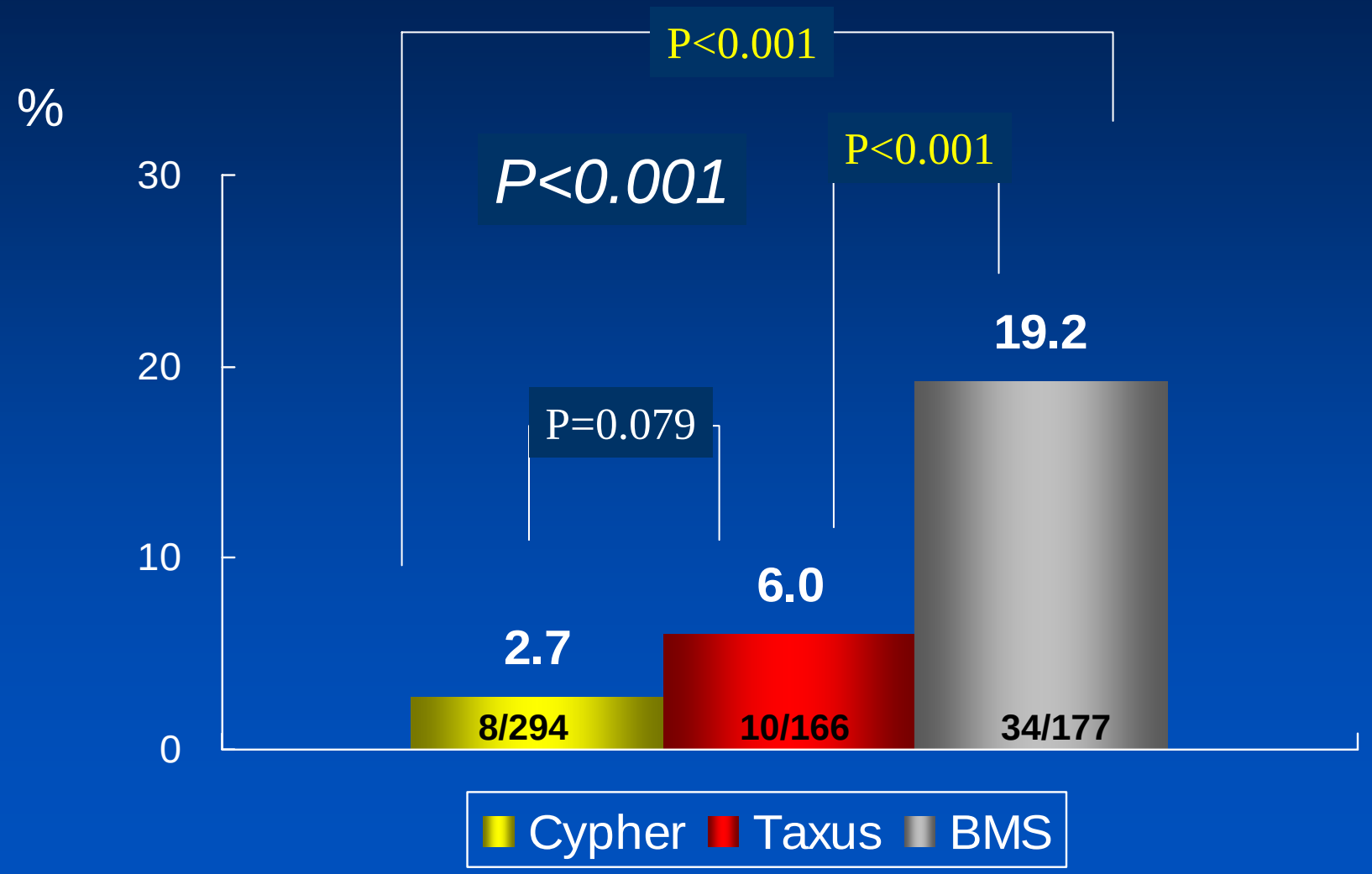
Lower Restenosis Rate



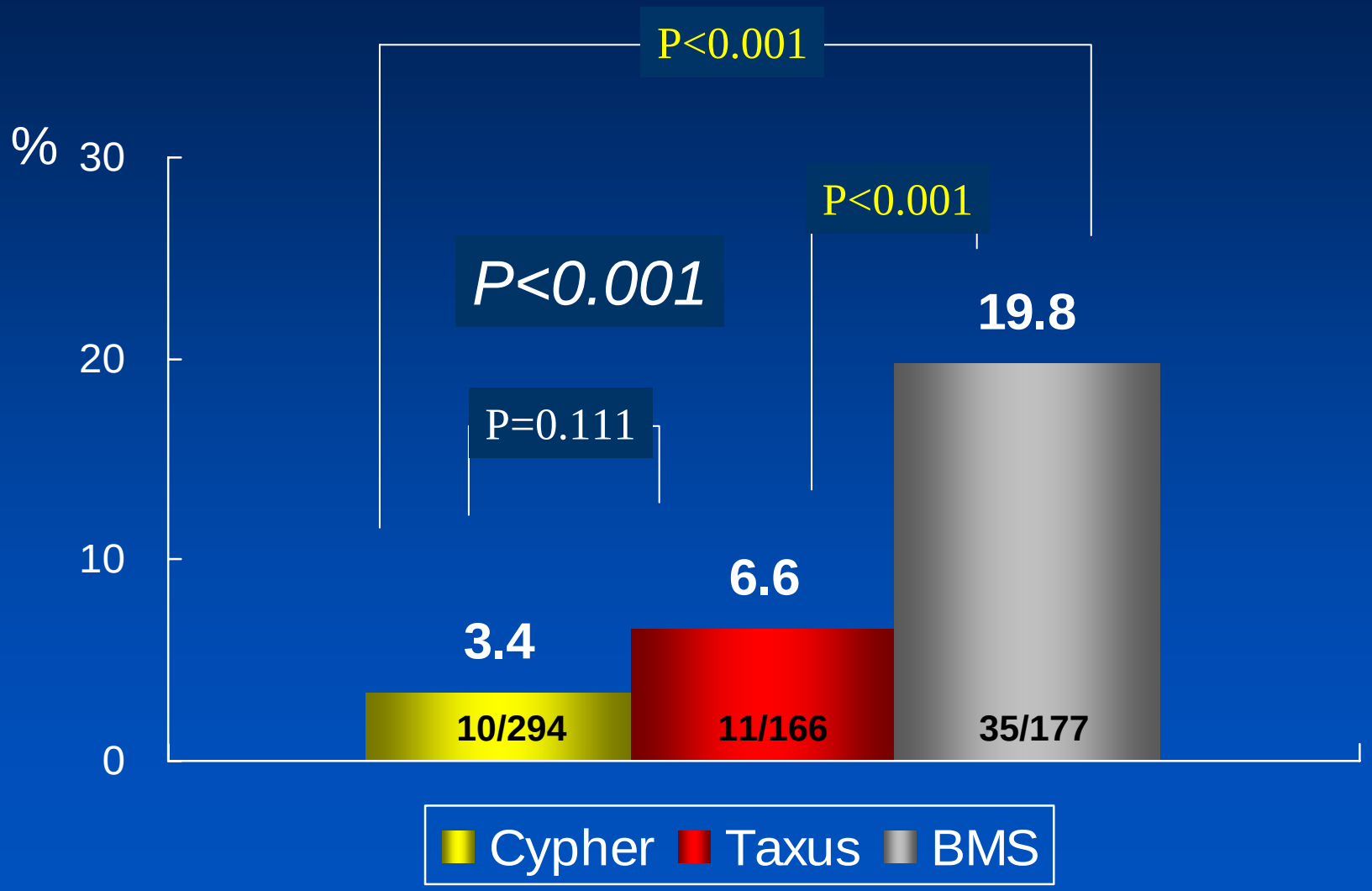
Predominantly focal ISR…



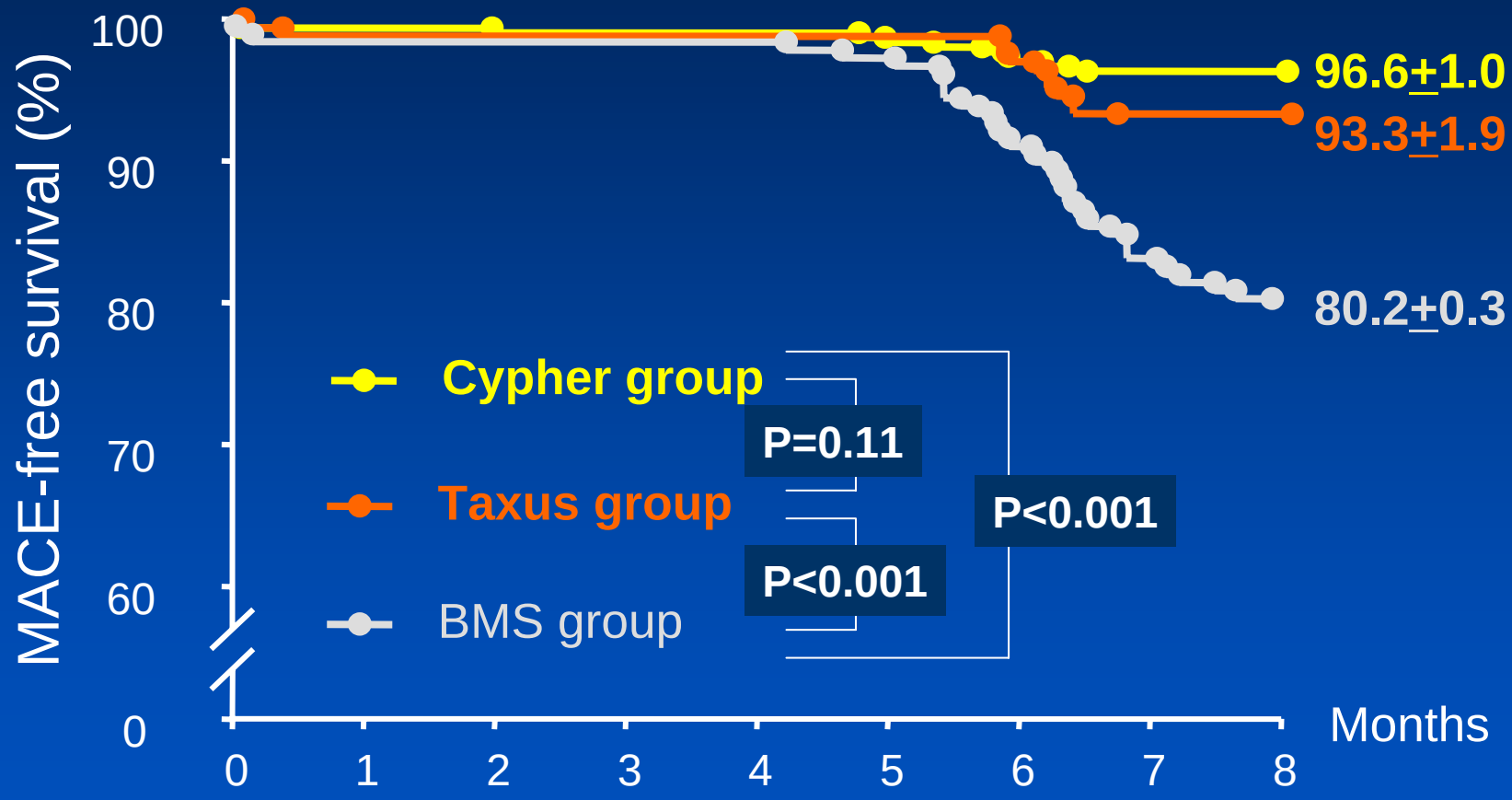
Nine-Month TLR



Nine-Month MACE

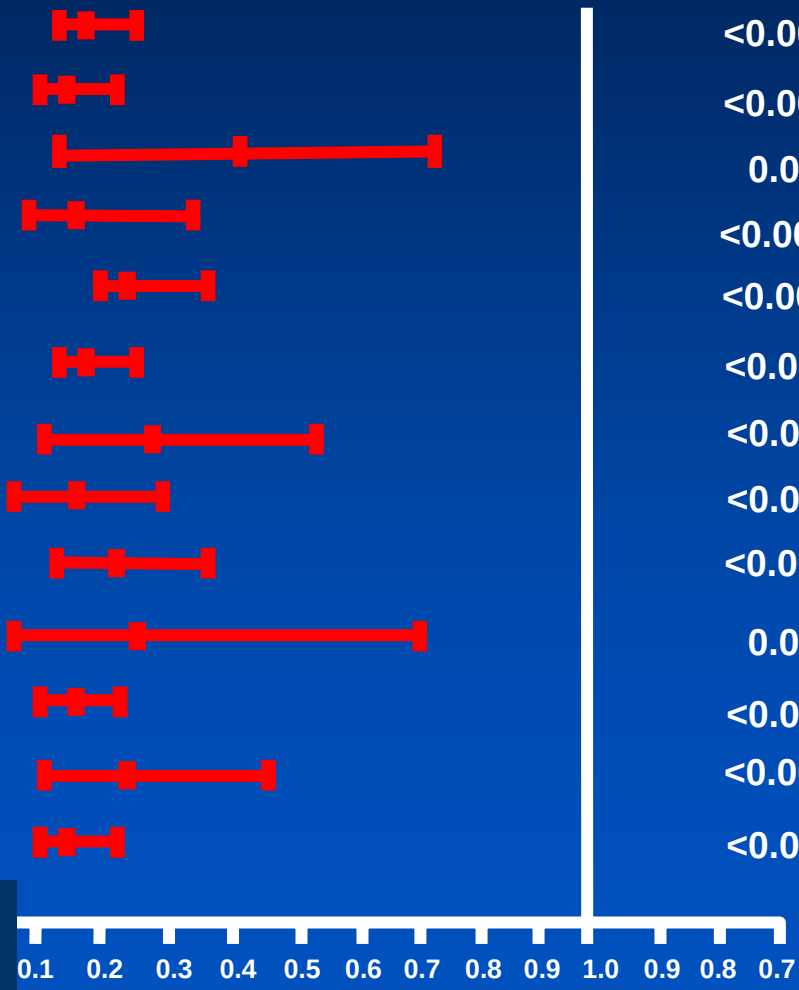


MACE-free Survival



Angiographic Restenosis : DES **vs** BMS

	DES	BMS	P-value
Overall	12.4	42.5	<0.0001
Male	12.1	45.6	<0.0001
Female	13.9	31.4	0.019
Diabetes	15.2	52.7	<0.0001
No Diabetes	11.1	37.1	<0.0001
LAD	10.3	45.9	<0.0001
Non-LAD	14.8	34.7	<0.0001
Small Vessel (≤2.75)	15.0	56.6	<0.0001
Large Vessel	10.1	35.5	<0.0001
Stent length>45mm	18.4	44.0	0.004
Stent length≤45mm	8.5	42.2	<0.0001
Multiple stent	15.8	45.2	<0.0001
Single	8.5	41.5	<0.0001



" DES Better "

Predictors of Restenosis

by Multivariate Analysis

Predictors of Restenosis
Overall

Variables	Relative Risk	95% C.I.	P value
Bare metal stent	8.01	4.90-13.11	<0.001
Lesion length (10mm)	1.29	1.10-1.51	0.002
MLD after procedure (mm)	0.32	0.19-0.53	<0.001

Predictors of Restenosis
DES subgroup

Variables	Relative Risk	95% C.I.	P value
Taxus stent	3.65	1.96-6.79	<0.001
Lesion length (10mm)	1.31	1.08-1.60	0.006
MLD after procedure (mm)	0.29	0.13-0.61	0.001

Predictors of Restenosis
Cypher or Taxus subgroup

		R.R	95% C.I.	P value
Cypher	■ Multiples stent	5.62	1.60-19.68	0.007
Taxus	■ MLD after procedure (mm)	0.19	0.05-0.57	0.004
	■ Lesion length (10mm)	1.36	1.02-1.82	0.037
BMS	■ MLD after procedure (mm)	0.31	0.15-0.64	0.001
	■ Diabetes mellitus	2.00	1.01-3.98	0.048

Summary : Restenosis Predictors

- The traditional risk factors of restenosis in the BMS era (multiple stents, lesion length, MLD after procedure) remained important determinants of restenosis in long DES implantation.

- The principles of coronary intervention in the BMS era - “the bigger, the better” or “the shorter, the better”- may be applied to the DES era in long lesion intervention. However, the clinical impact of such risk factors in the DES may not be as large as the BMS because of low absolute number of restenosis.

Restenosis Rate of Cypher : 5.4 %