SISR -- A Prospective Randomized Comparison of the Sirolimus-Eluting Stent vs Brachytherapy in Patients with Bare Metal In-Stent Restenosis

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Nothing to disclose

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, particularly the Sirolimus-eluting stent (SES), have shown promise for the treatment of in-stent restenosis
- No large-scale randomized study has compared outcomes for VBT vs. SES

Study Objective

- The main objective of this study is to demonstrate the non-inferiority or superiority of the Sirolimus-eluting Bx VELOCITY® stent (SES) compared to vascular brachytherapy (VBT) in patients with in-stent restenotic (ISR) native coronary artery lesions

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

Secondary Endpoints

- Angiographic parameters by QCA:
  - Post-procedure and 6-month* in-stent and in-lesion MLD and % DS
  - In- stent and in-lesion binary restenosis (≥ 50% DS) and late loss at 6 months* post-procedure
- Stent lumen and stent volume obstruction by IVUS at post-procedure and 6 months in a subset of patients

*Analysis at 6 months chosen to allow “borrowing data” from GAMMA I/II using Bayesian statistical methods

Secondary Endpoints (continued)

- Composite of Major Adverse Cardiac Events (MACE) at 30 days and 6, 9, and 12-months, and 2, 3, 4, and 5 years post-procedure
  - Defined as death, MI (Q wave and non-Q wave), emergent bypass surgery, or repeat target lesion revascularization
  - TLR & TVF at 9 months post-procedure
- Rate of late thrombosis

Statistical Analysis

Primary Endpoint:

- Assumed rates of TVF at 9 months
  - Active + Historical Control VBT arm: 30.5%
  - Sirolimus-eluting stent arm: 15.3%
- Bayesian statistical methods used for trial design and for primary analysis
- Test for non-inferiority and then superiority of SES over VBT at the 0.05 level of significance
- Safety evaluation and effectiveness analysis performed on intent-to-treat population
  - all patients in whom treatment attempted with the assigned device

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

Major Exclusion Criteria

- Prior thoracic radiation, VBT, or treatment with SES
- Significant (> 50%) in-stent restenoses proximal or distal to the target lesion
- Intervention of another lesion ≤ 30 days before or planned following the procedure
- Recent MI or Braunwald Class IIIB or C Unstable Angina
- Prior stent within 5mm of target lesion
- TIMI 0 Flow
- Ostial lesion
- Bypass graft (IMA or SVG) or left main coronary artery lesion
- Serum creatinine ≥ 2.0mg/dL

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

SISR Study

Intent-to-Treat Analyses

Lesion Characteristics

	CYPHER	Brachytherapy	P-value
# of Patients # of Lesions	259 patients 259 lesions	125 patients 125 lesions	
Mean ± SD Lesion Length (mm)	17.22 ± 7.97	16.76 ± 8.55	0.605
Lesion Length (%) 1-10 mm 10-20 mm > 20 mm	 15.9 57.1 27.0	 22.4 44.8 32.8	 0.154 0.028 0.278
Vessel Location (%) - LAD - LCx - RCA	 47.9 19.1 33.1	 44.8 19.2 36.0	 0.587 1.000 0.568
Lesion Location (%) - Ostial - Proximal - Mid - Distal	 4.7 30.7 55.6 8.9	 4.0 29.6 59.2 7.2	 1.000 0.906 0.582 0.695
Eccentric Lesion (%)	62.3	48.8	0.015

Procedural Characteristics

	CYPHER (259 lesions)	Brachytherapy (125 lesions)	P-value
Bend, Mean ± SD (degrees)	28.6 ± 20.7	26.6 ± 17.2	0.351
Any Lesion Angulation (%)			
0 - 44°	77.8	83.2	0.279
45 - 89°	12.1	10.4	0.734
≥ 90°	4.7	3.2	0.596
Tortuosity (%)			
- Moderate	6.6	4.8	0.648
- Severe	0.4	0.0	1.000
Any Calcification (%)	10.5	15.2	0.185
TIMI Grade Flow (%)			
- 0	1.6	0.8	1.000
- 1	5.1	0.8	0.042
- 2	3.5	3.2	1.000
- 3	89.8	95.2	0.080
Thrombus (%)	3.9	2.4	0.559
Total Occlusion (%)	6.7	1.6	0.043
Bifurcation (%)	28.2	34.7	0.234

Intent-to-Treat Analyses

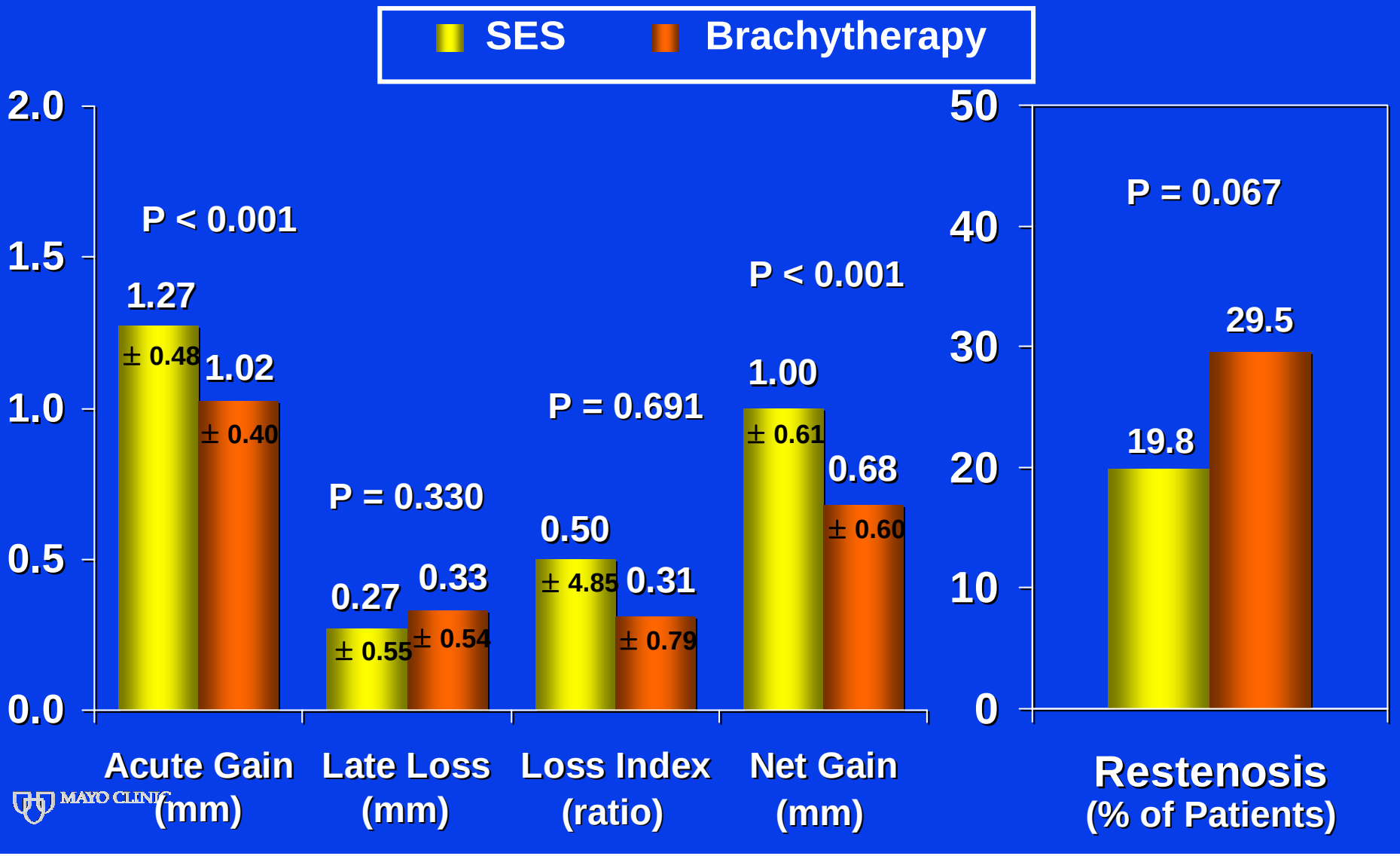
Procedural and Lesion Success

	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

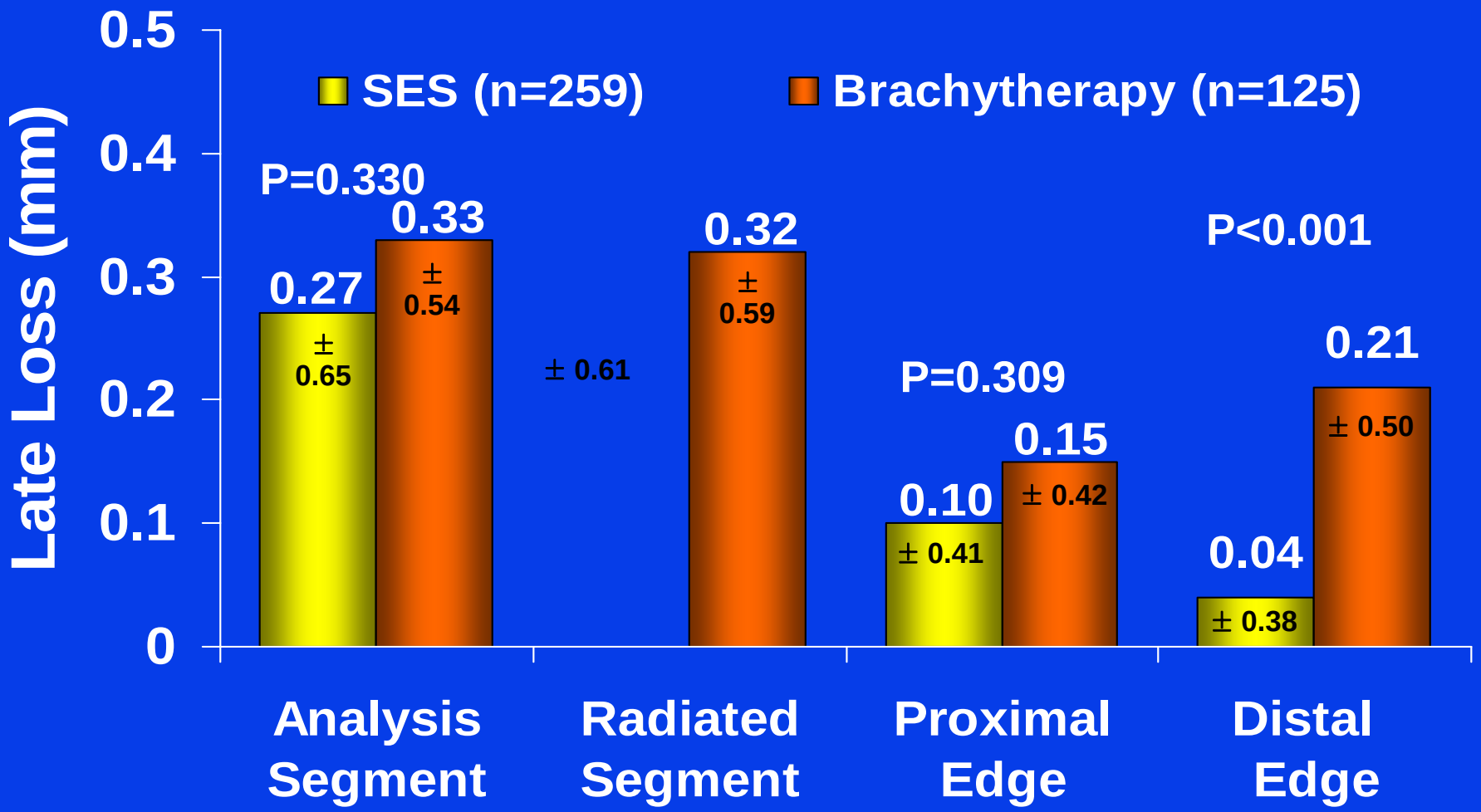
Angiographic (QCA) Definitions

- Analysis-segment:
  - All portions of the vessel within the radiation or stent zones + proximal and distal 5 mm margins
- Injury segment:
  - Comprises region of vessels injured with balloon dilatation or stent placement
- Stent segment:
  - Segment of the vessel covered with new stents
  - May not include all of previously stented segment
- Radiation segment:
  - Region of vessel treated by radiation, determined by radiographic markers on the brachytherapy catheter
  - Does not include 5 mm proximal or distal margins

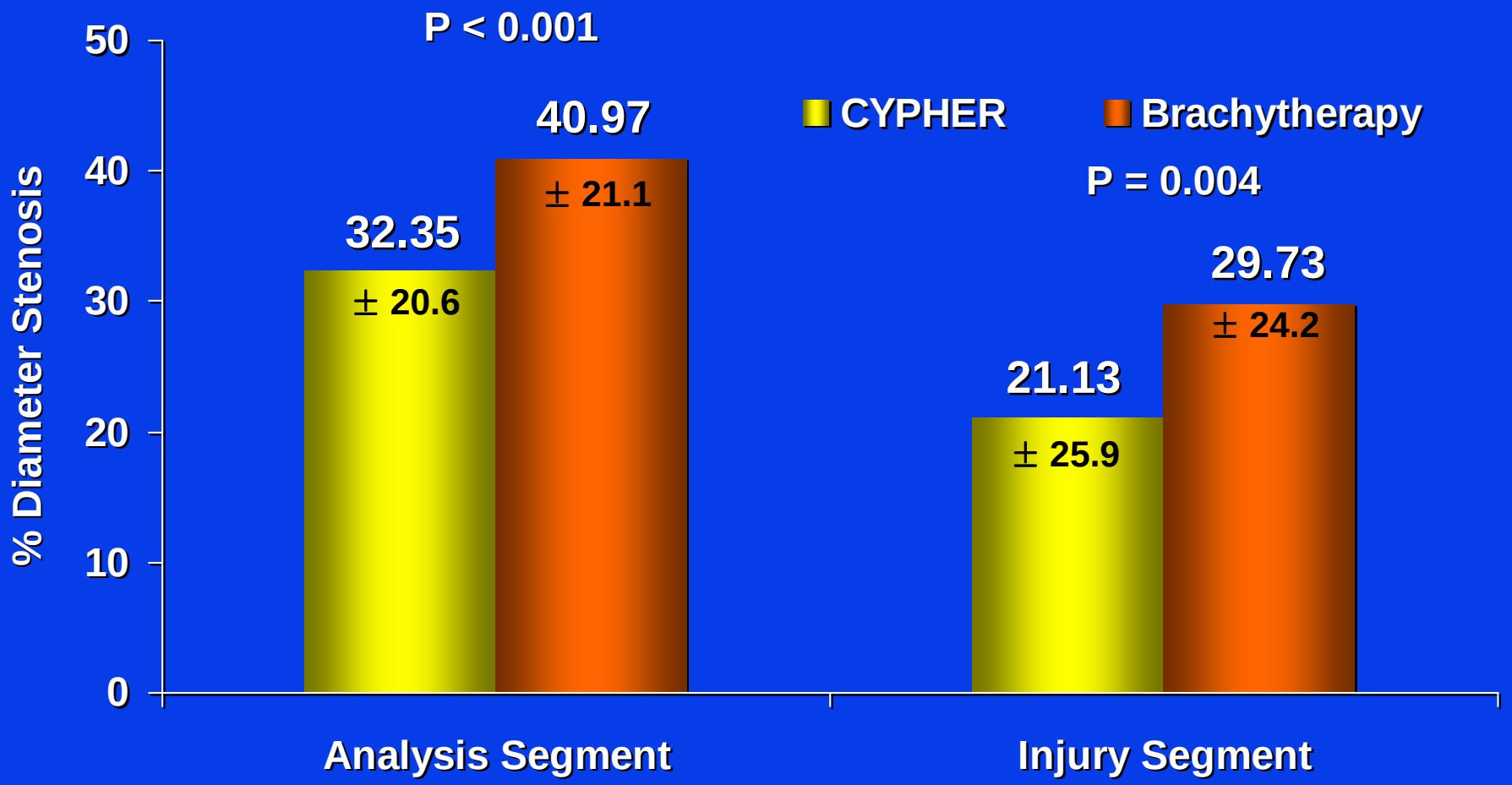
Angiographic Outcomes Through 6-Months (Analysis Segment)



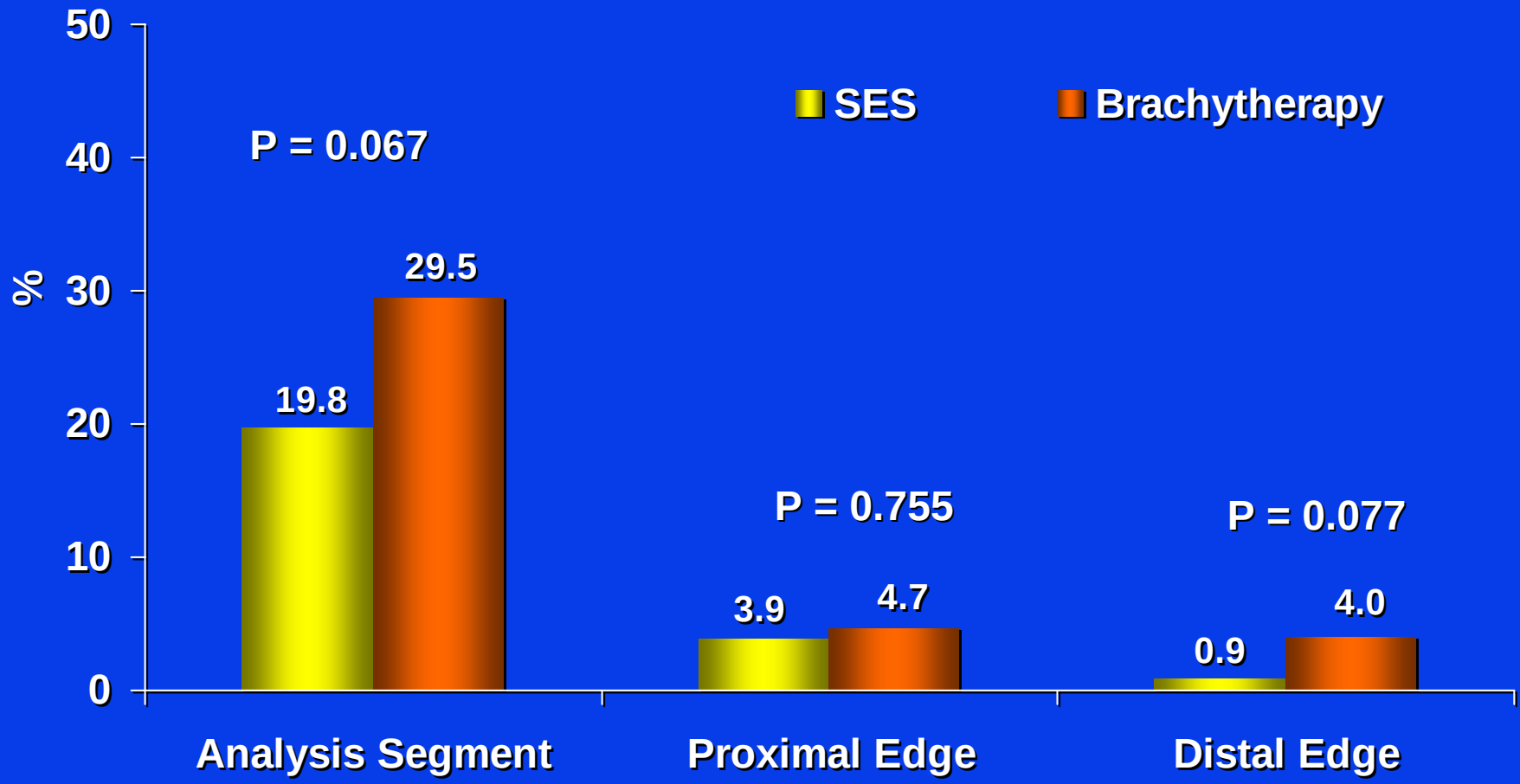
SISR: 6-month Late Loss



% Diameter Stenosis at 6 Month Follow-Up



Binary Angiographic Restenosis at 6-Month Follow-Up



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:

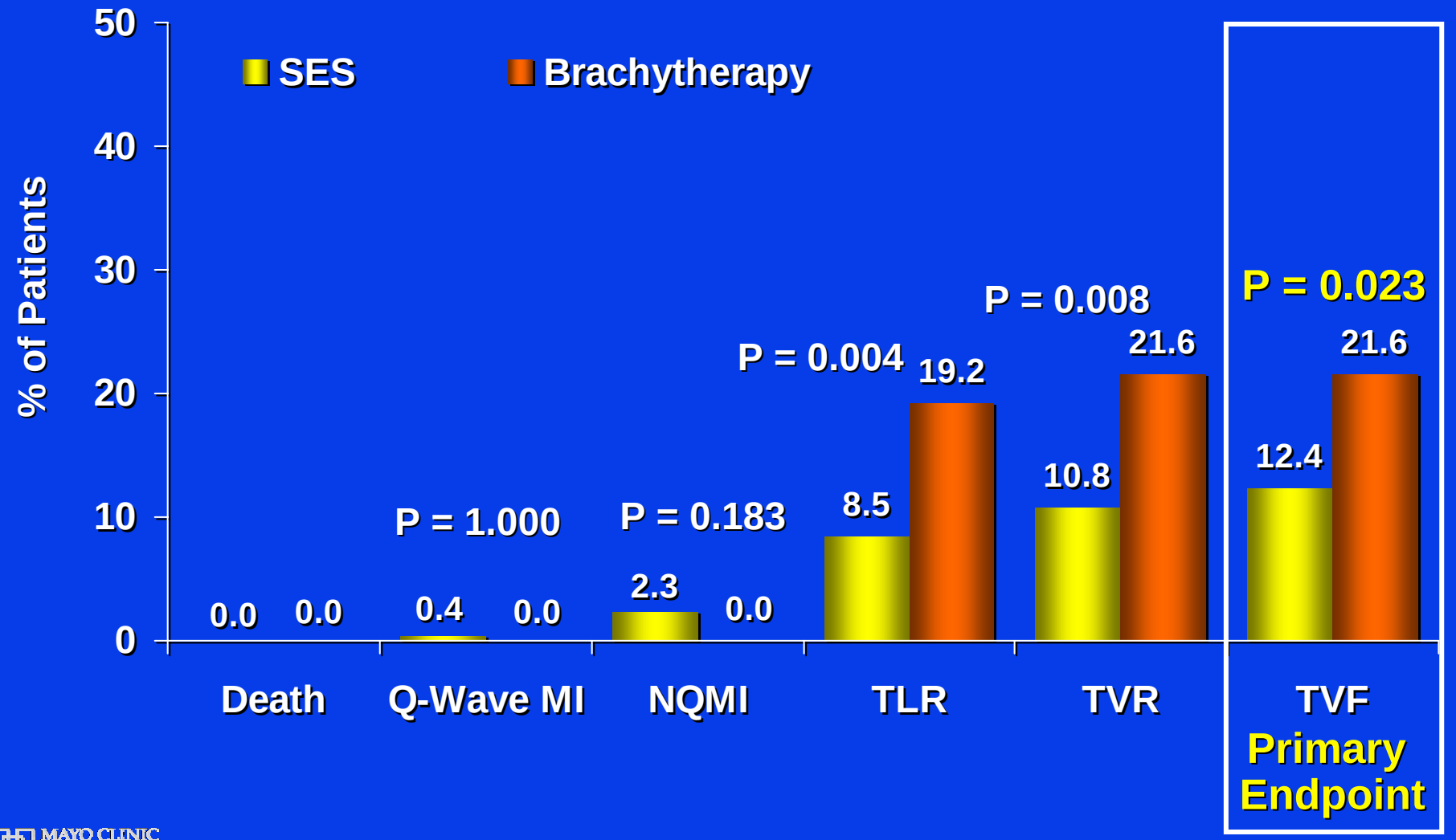
1b: Margin restenosis involving the margin of the stent

1c: Focal body in-stent restenosis

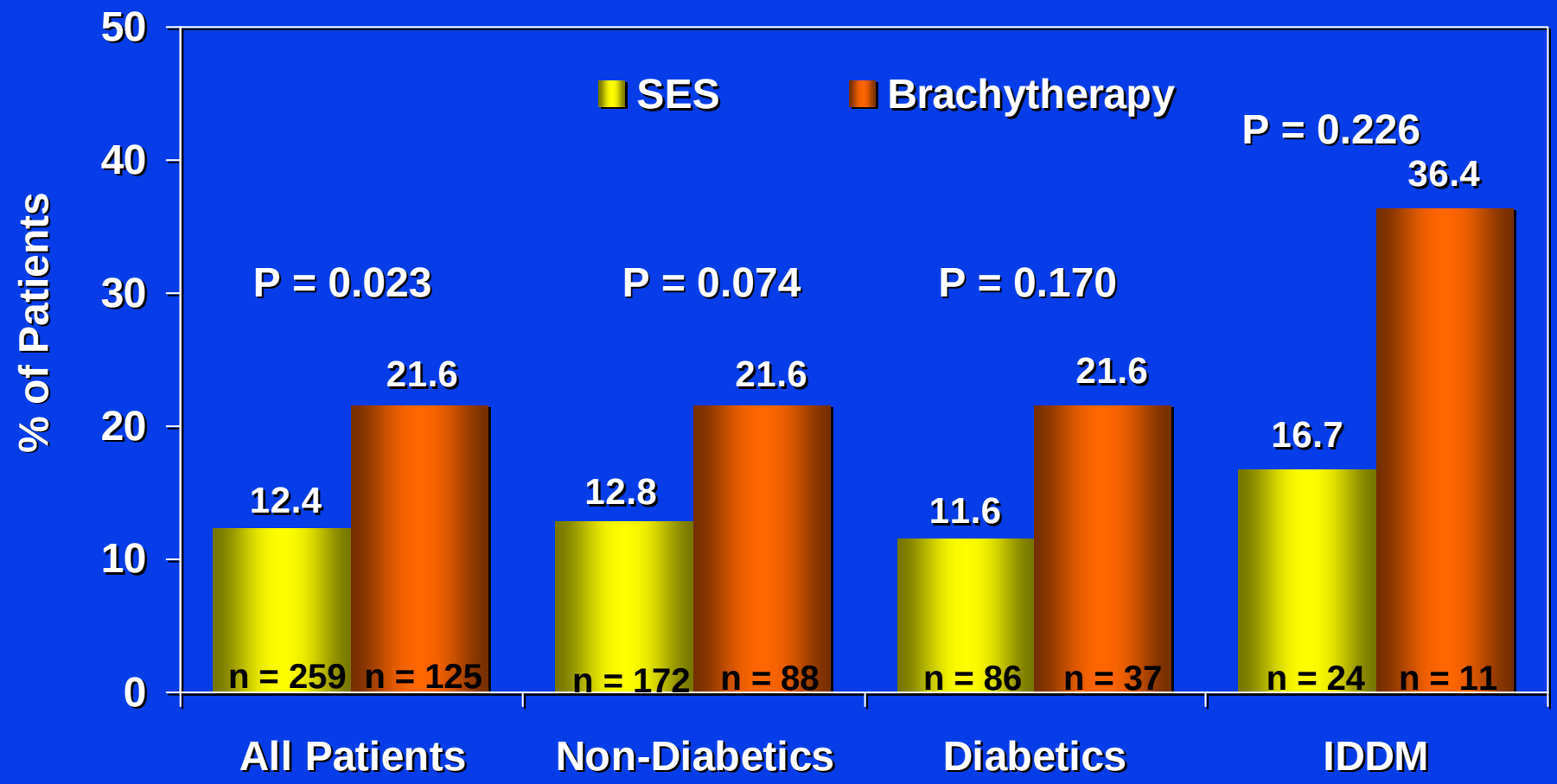
2: Restenosis >10 mm extending to the margins of the stent

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

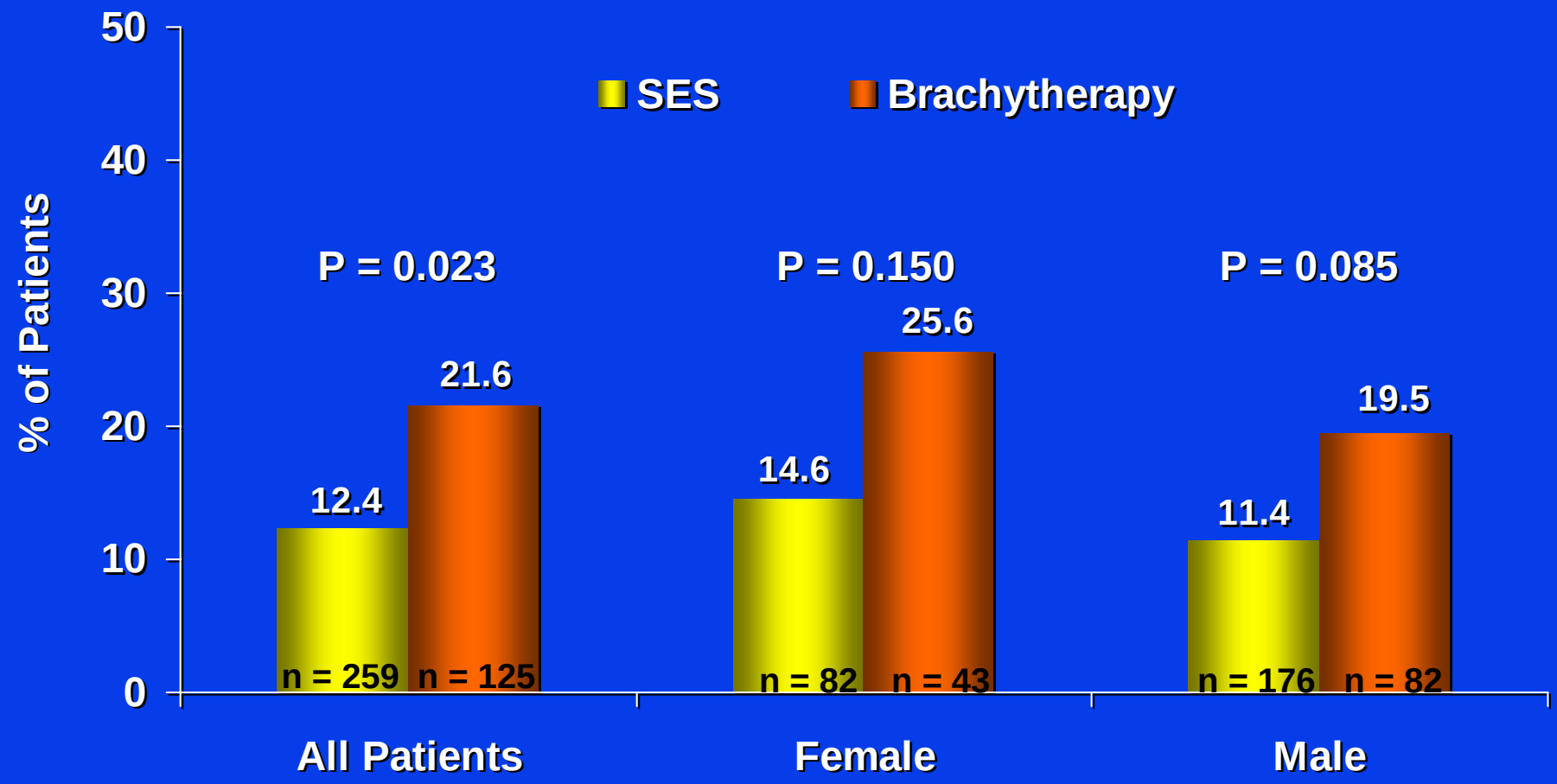
Clinical Outcomes Through 9-Months



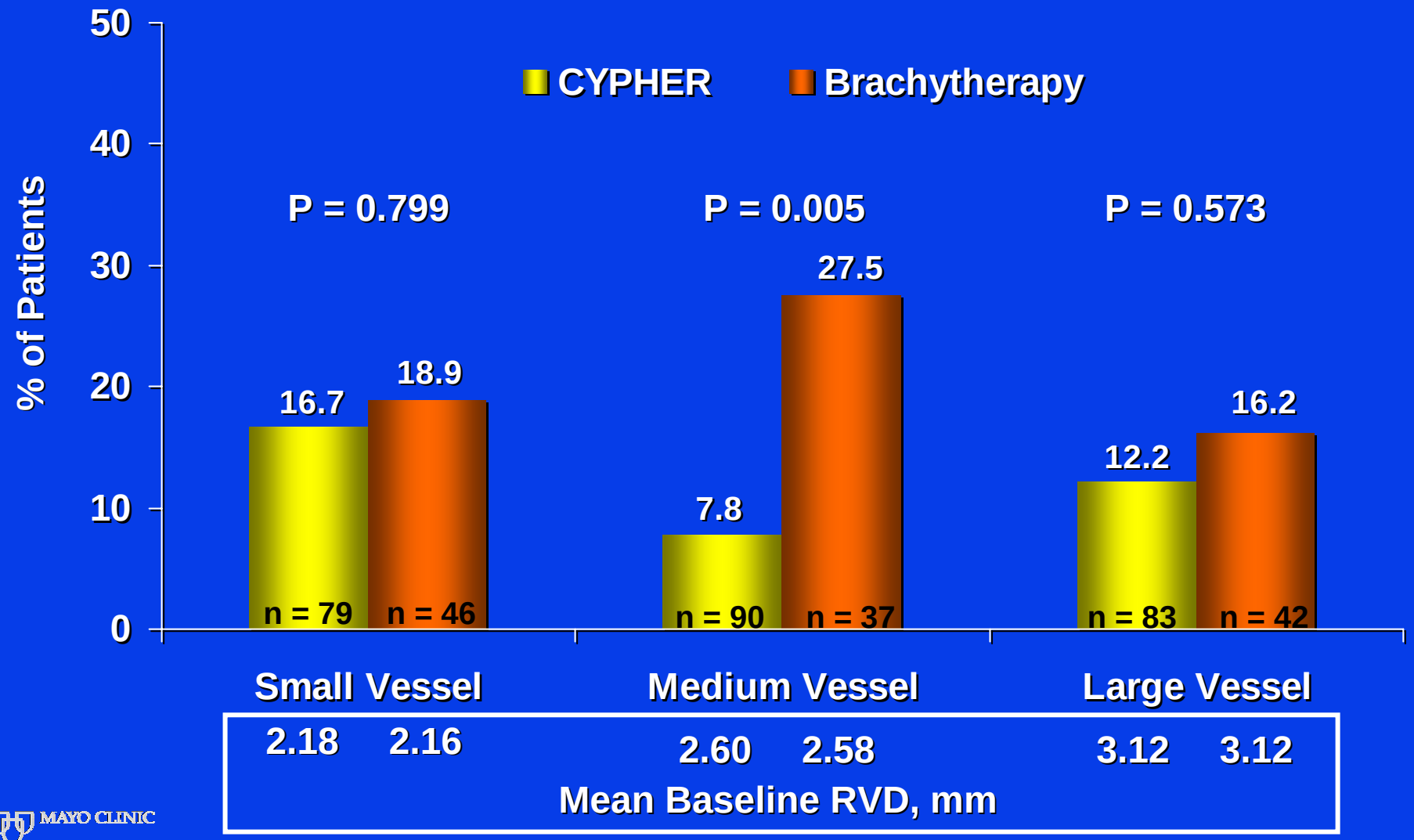
TVF by Diabetic Status



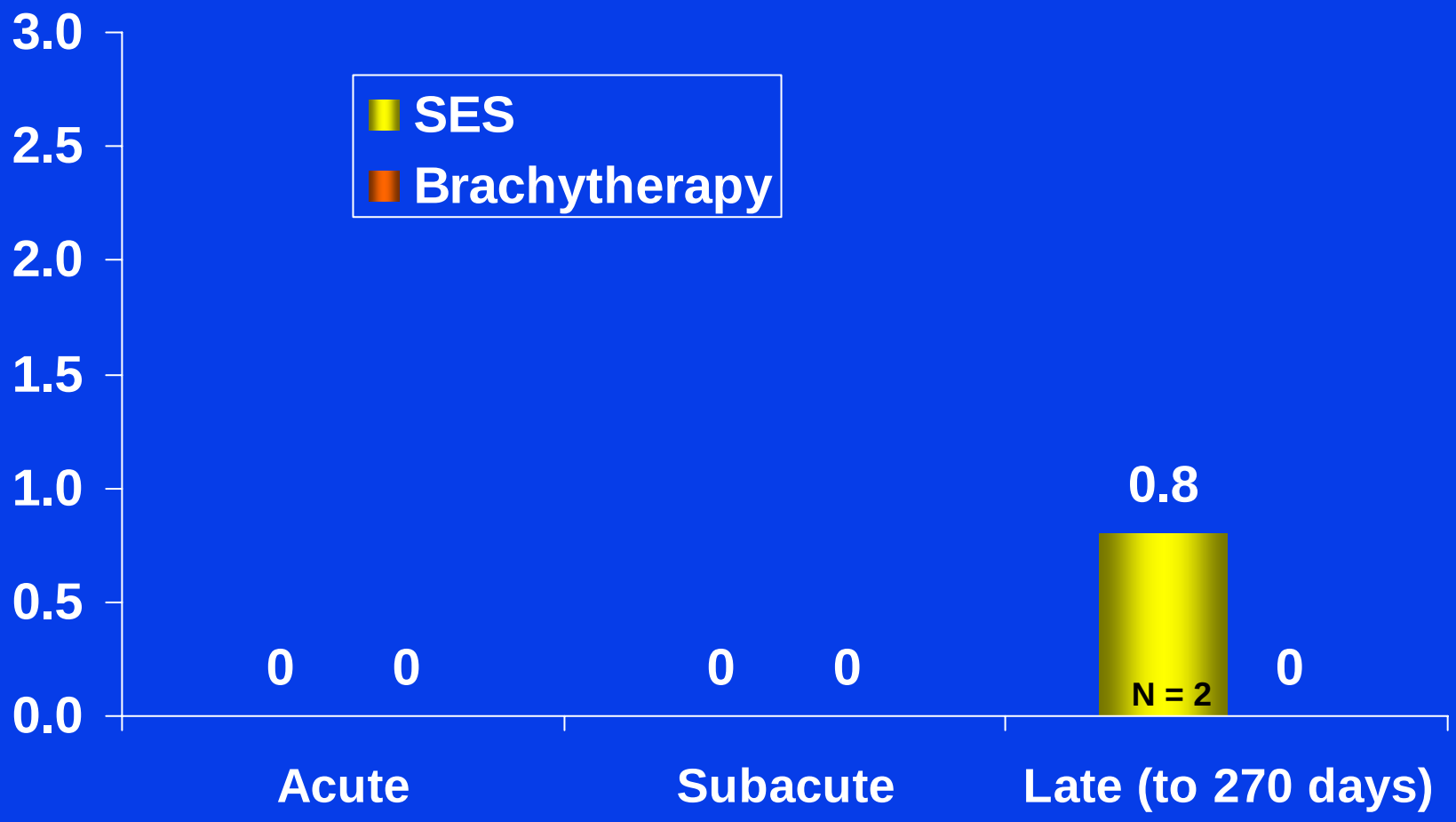
TVF by Gender



TVF by Baseline Vessel Size Tercile Analysis



Stent Thrombosis at 9-Month Follow-Up



Conclusions

- Both treatments were effective in reducing neointimal hyperplasia within the treated region
- However, 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 for SES-treated lesions measured by both angiography & IVUS
- SES treatment resulted in a significantly lower TLR than VBT
- The relative % improvement in TVF with SES treatment was the same for both diabetic and non diabetic subgroups (42%)
- The Sirolimus-eluting stent was superior to vascular brachytherapy in reducing the primary endpoint of Target Vessel Failure

BACK-UP SLIDES

Procedural Characteristics

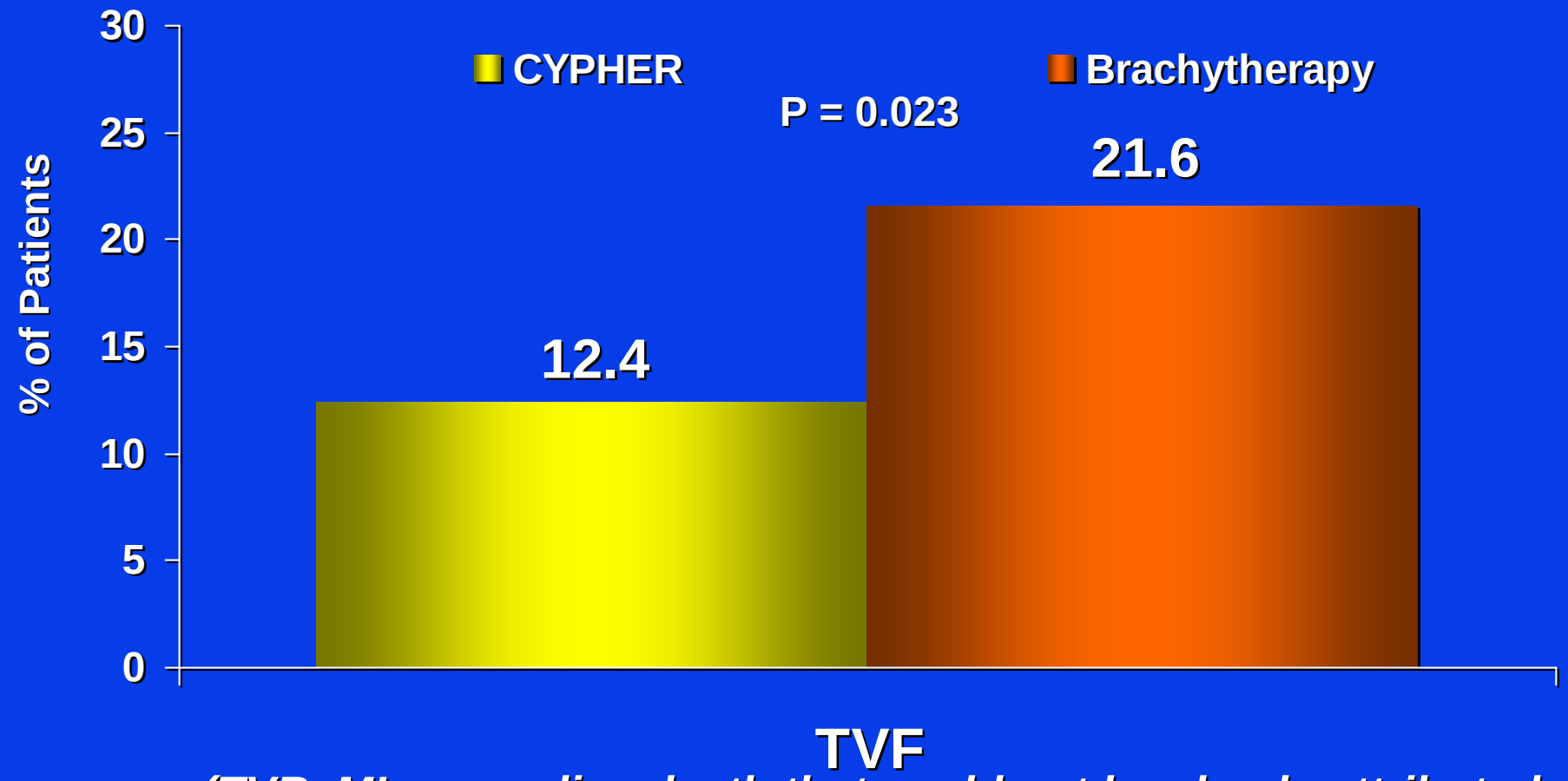
	CYPHER	Brachytherapy	P-value
Post-Procedure Hospital Length of Stay - Mean ± SD	1.1 ± 0.5	1.1 ± 0.4	0.325
IIb/IIIa During Procedure (%)	31.1	36.8	0.297

Statistical Analysis

Primary Endpoint:

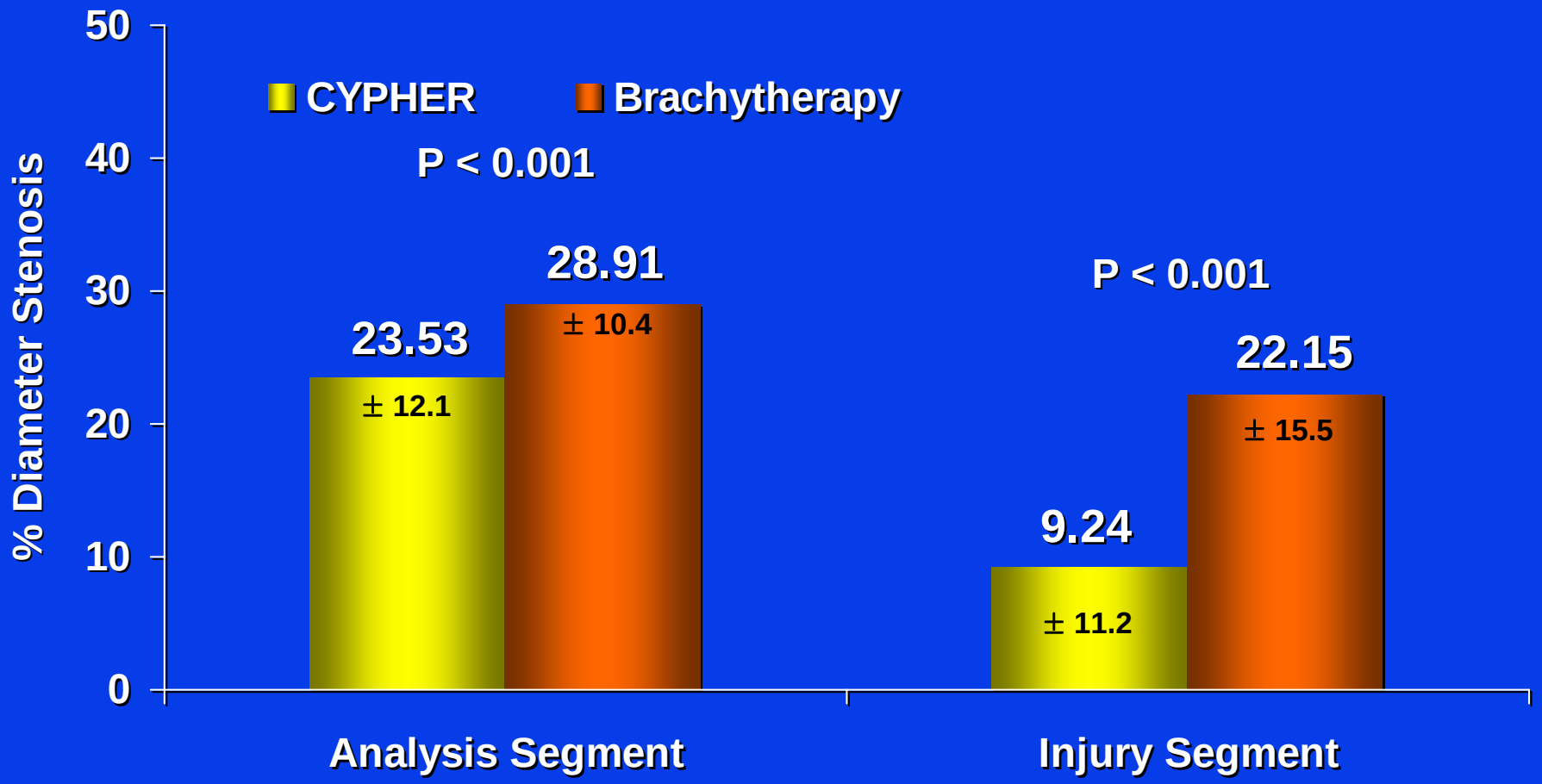
- To establish a more precise estimate of the objective performance criterion, applicable data from the Gamma I (N=131) and Gamma II (N=125) trials will be combined with the active control (brachytherapy) using Bayesian statistical methods
- The analysis will adjust for the following confounding variables:
  - 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

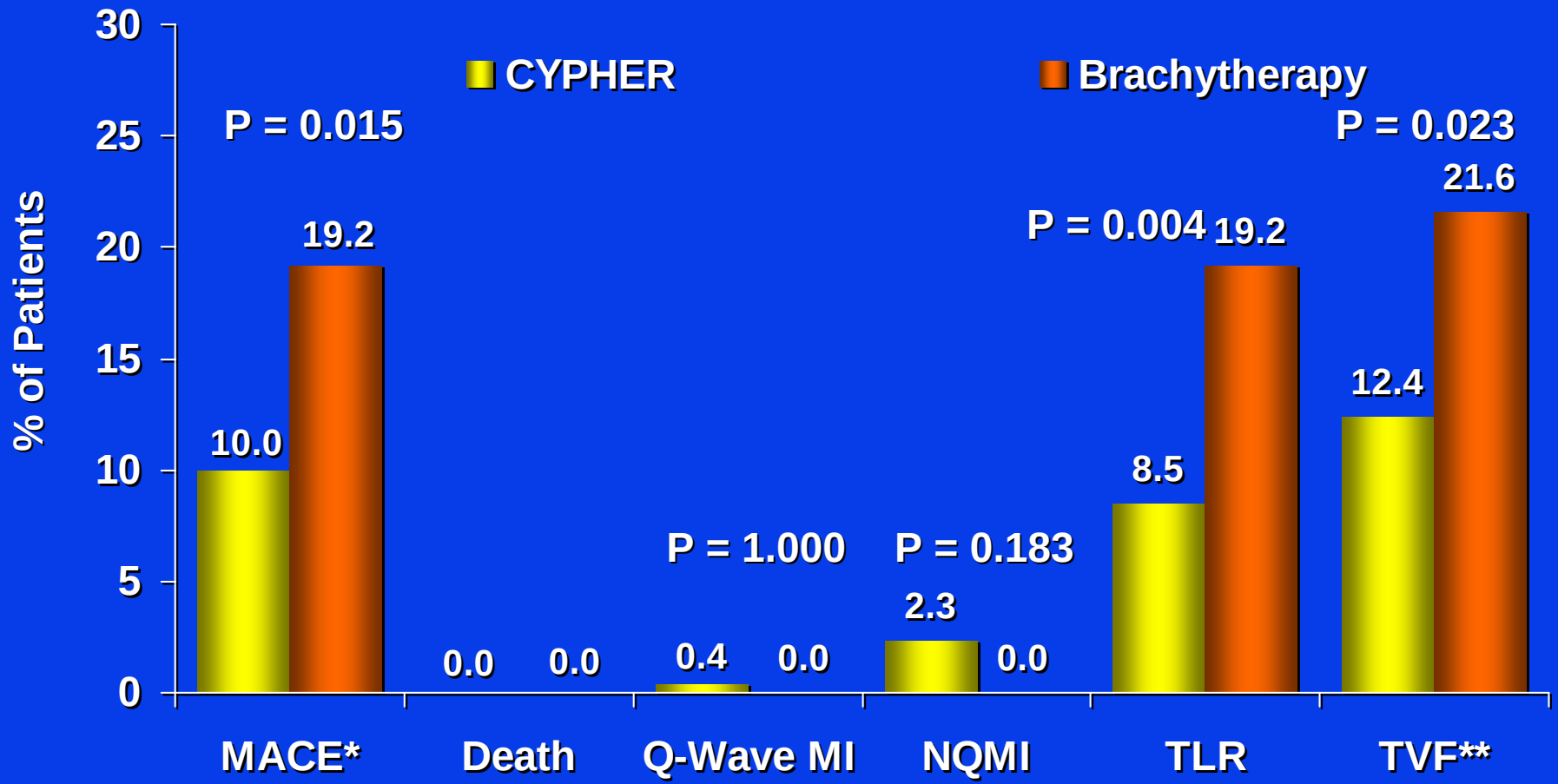


(TVR, MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel)

% 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

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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 $p<0.05$)

Logic Flow for Angiographic data:

- 1. Acute gain higher with SES than with VBT
- 2. Late loss similar with SES and VBT
- 3. Loss index lower with SES than with VBT
- 4. Net gain better with SES than with VBT
- 5. Analysis segment better with SES than with VBT
- 6. It is the analysis segment that correlates with Clinical endpoints
- MAY WANT TO USE SUMMARY SLIDE (NEXT) RATHER THAN INDIVIDUAL SLIDES TO ILLUSTRATE THESE POINTS

Not necessarily to be included in final slide set

TAXUS vs ISR

- Multicenter RCT
- 396 patients with ISR of a bare metal stent
- Randomization to Beta VBT or PES
- Primary endpoint:
  - Ischemia driven TVR at 9 months

Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR
Baseline Characteristics

	VBT (n = 201)	PES (n = 195)	P
Age (y)	63 (54-73)	63 (54-70)	.62
Men	141 (70.1)	121 (62.1)	.09
DM (requiring medication)	61 (30.3)	78 (40.0)	.04
Insulin	21 (10.4)	38 (19.5)	.01
Noninsulin	40 (19.9)	40 (20.5)	.88
Hypertension	159 (79.1)	165 (84.6)	.16
Hyperlipidemia	184 (91.5)	177 (90.8)	.79
Current smoker	30 (14.9)	27 (13.8)	.76
Prior MI	106 (52.7)	101 (51.8)	.85
Unstable angina	56 (27.9)	55 (28.2)	.94
Time since BMS implant (d)	316 (177-644)	281 (158-658)	.43

Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR
Baseline Characteristics

	VBT (n = 201)	PES (n = 194)	P
Target lesion cor. artery			
Left ant. descending	67 (33.3)	76 (39.2)	.23
Left circumflex	54 (26.9)	45 (23.2)	.40
Right	78 (38.8)	72 (37.1)	.73
Left main (protected)	2 (1.0)	1 (0.5)	>.99
Diameter, mm			
Reference vessel	2.61 (2.32-2.93))	2.68 (2.35-2.94)	.29
Minimal lumen	0.83 (0.61-1.01)	0.80 (0.55-1.04)	.51
Stenosis (%)	68.0 (59.4-5.4)	68.5 (60.3-77.8)	.25
Lesion length, mm	15.0 (10.0-23.3)	15.9 (11.8-22.8)	.14

Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR
Baseline Characteristics

	VBT (n = 200)	PES (n = 194)	P
Restenosis pattern			
Focal	58 (29.0)	36 (18.6)	.02
Diffuse	94 (47.0)	118 (60.8)	.006
Proliferative	47 (23.5)	37 (19.1)	.28
Total occlusion	1 (0.5)	2 (1.0)	.62

Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR
Clinical Results in the Randomized Study Population

	VBT (n = 201)	PES (n =195)	Unadjusted RR (95% CI)	P
30-d adverse events	(n = 199)	(n = 194)		
Any death	0	0		
Cardiac death	0	0		
MI	3 (1.5)	3 (1.5)	1.03 (0.21-5.02)	>.99
Q-wave	0	1 (0.5)		.49
Non Q-wave	3 (1.5)	2 (1.0)	0.68 (0.12-4.05)	>.99
TVR	3 (1.5)	2 (1.0)	0.68 (0.12-4.05)	>.99
Any MACE	5 (2.5)	4 (2.1)	0.82 (0.22-3.01)	>.99

Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR

Clinical Results in the Randomized Study Population

	VBT (n = 201)	PES (n =195)	Unadjusted RR (95% CI)	P
9 mo. adverse events	(n = 194)	(n = 191)		
Any death	1 (0.5)	0		>.99
MI	9 (4.6)	7 (3.7)	0.79 (0.30-2.08)	.63
Q-wave	0	1 (0.5)		.50
Non Q-wave	9 (4.6)	6 (3.1)	0.68 (0.25-1.87)	.45
Ischemic TLR	27 (13.9)	12 (6.3)	0.45 (0.24-0.86)	.01
Isch. non-target lesion TVR	12 (6.2)	10 (5.2)	0.85 (0.37-1.91)	.69
Ischemic TVR	34 (17.5)	20 (10.5)	0.60 (0.36-1.00)	0.46
Non-ischemic TLR	13 (6.7)	3 (1.6)	0.23 (0.07-0.81)	.01
Non-ischemic TVR	13 (6.7)	3 (1.6)	0.23 (0.07-0.81)	.01
Any TLR	39 (20.1)	15 (7.9)	0.39 (0.22-0.68)	<.001
Any TVR	46 (23.7)	23 (12.0)	0.51 (0.32-0.80)	.003
Target vessel failure	38 (19.6)	22 (11.5)	0.59 (0.36-0.96)	.03
Any MACE	39 (20.1)	22 (11.5)	0.57 (0.35-0.93)	.02

Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR
Clinical Results in the Randomized Study Population

	VBT (n = 194)	PES (n =191)	Unadjusted RR (95% CI)	P
Target vessel thrombosis	5 (2.6)	3 (1.6)	0.61 (0.15-2.50)	.72
In hospital	0	0		
Postdischarge thru 1 mo	1 (0.5)	1 (0.5)	1.03 (0.06-16.28)	>.99
Between 1 & 6 mo	3 (1.5)	2 (1.0)	0.68 (0.12-4.04)	>.99
Between 6 & 9 mo	1 (0.5)	0		>.99

Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR
Angiographic Results in the Randomized Study Population

	VBT (n = 170)	PES (n =172)	Unadjusted RR (95% CI)	P
Binary restenosis				
In stent	NA	12 (7.0)		
Injury segment	34 (20.1)	12 (7.0)	0.35 (0.19-0.65)	<.001
Proximal edge	8 (6.5)	11 (7.2)	1.11 (0.46-2.69)	.81
Distal edge	6 (4.0)	4 (2.4)	0.60 (0.17-2.08)	.53
Analysis segment	53 (31.2)	25 (14.5)	0.47 (0.30-0.71)	<.001

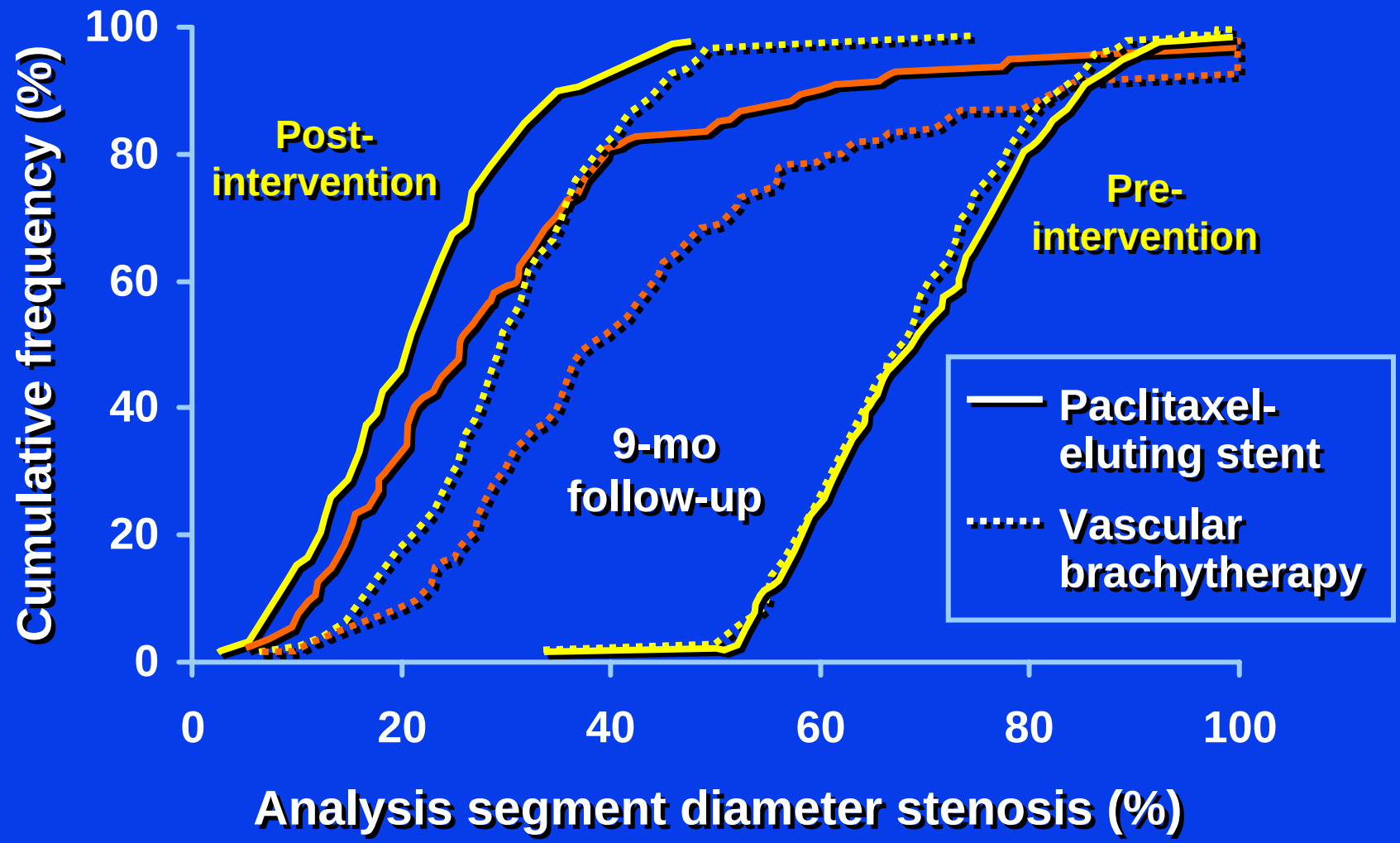
Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR

Treatment of bare metal ISR with PES reduces clinical and angiographic restenosis at 9 months compared with VBT

Stone GW, JAMA 2006; 295:1253-63

TAXUS vs ISR



Stone et al: JAMA 295:1253, 2006

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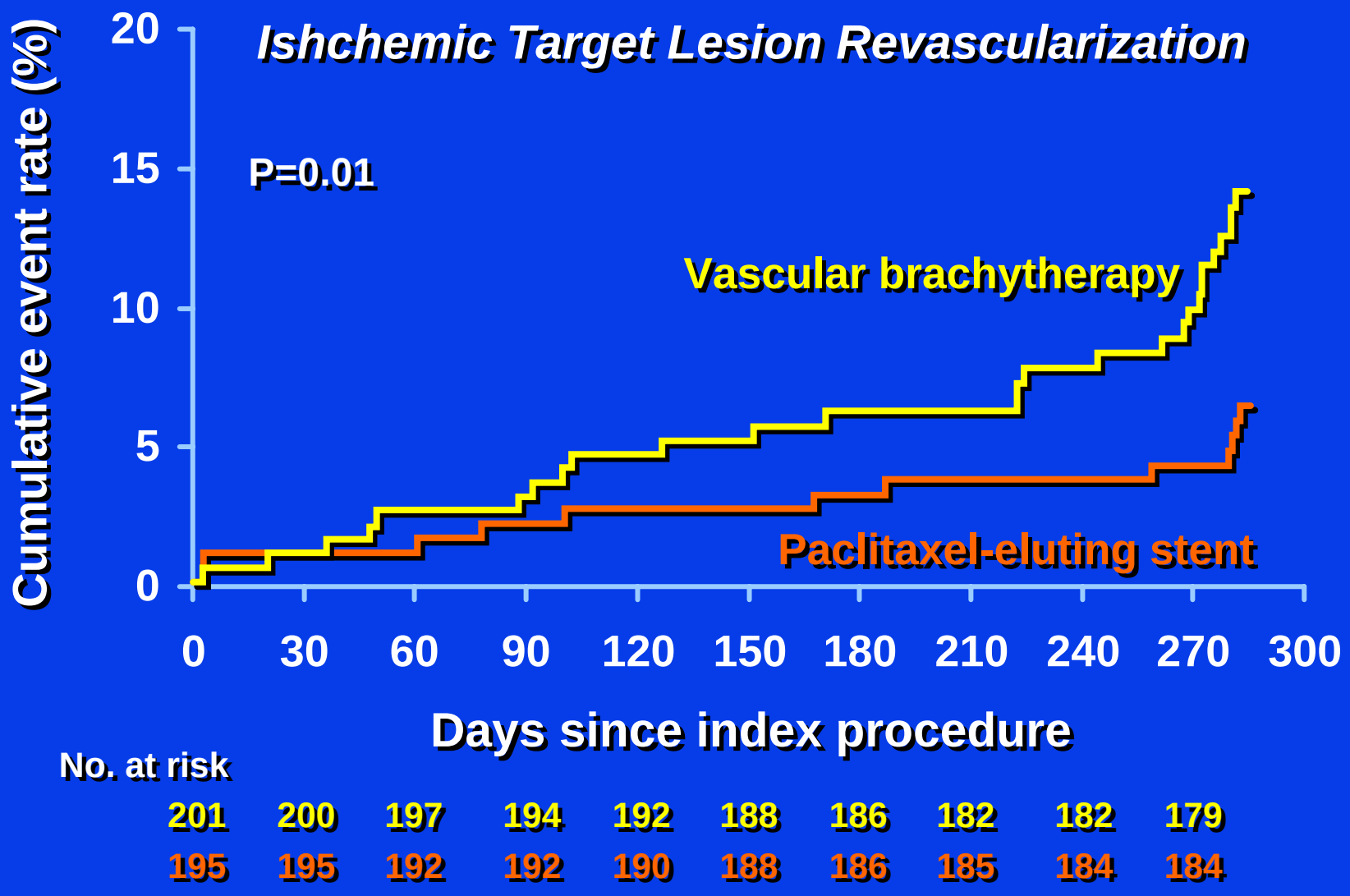
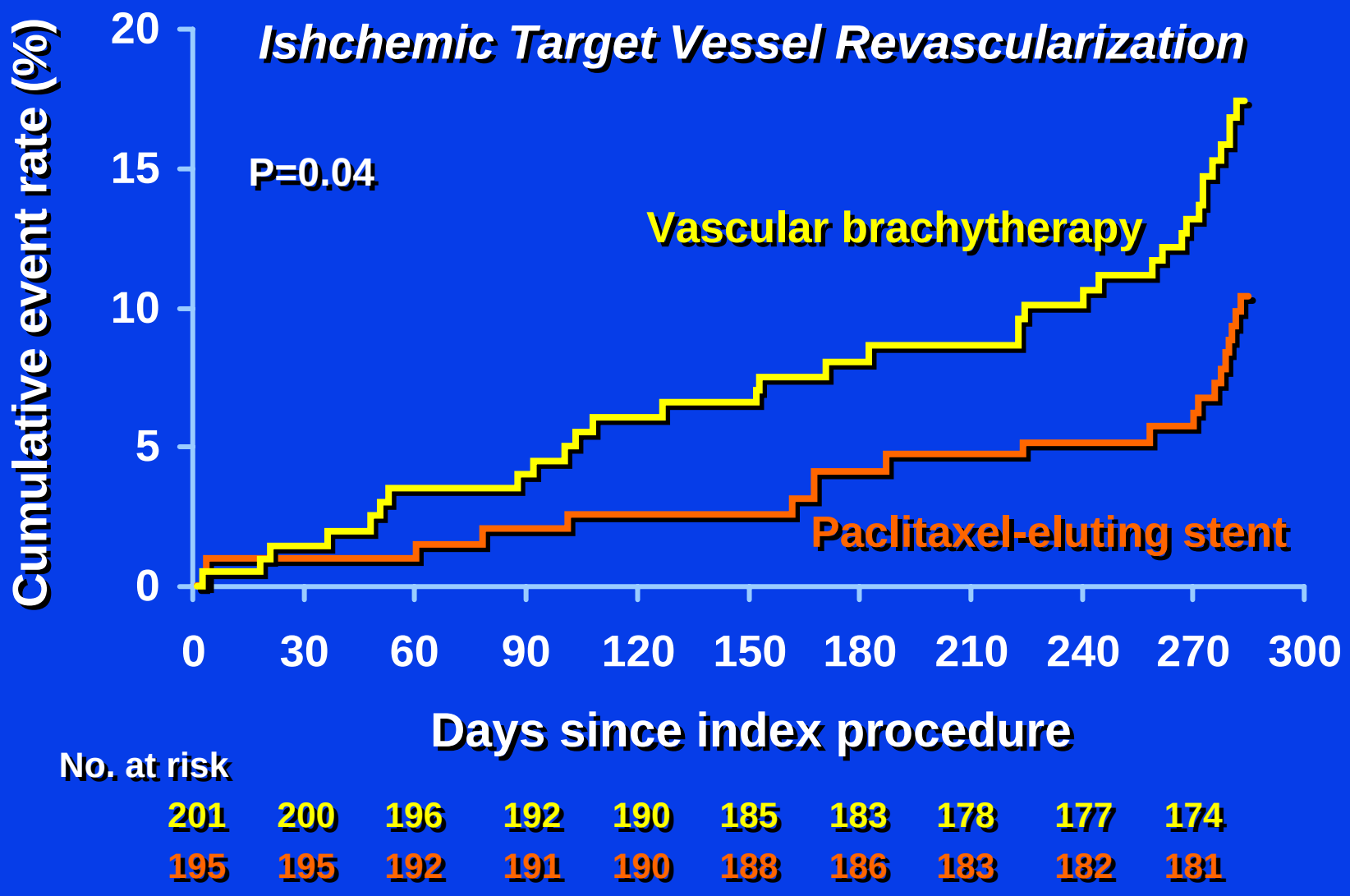
TAXUS vs ISR



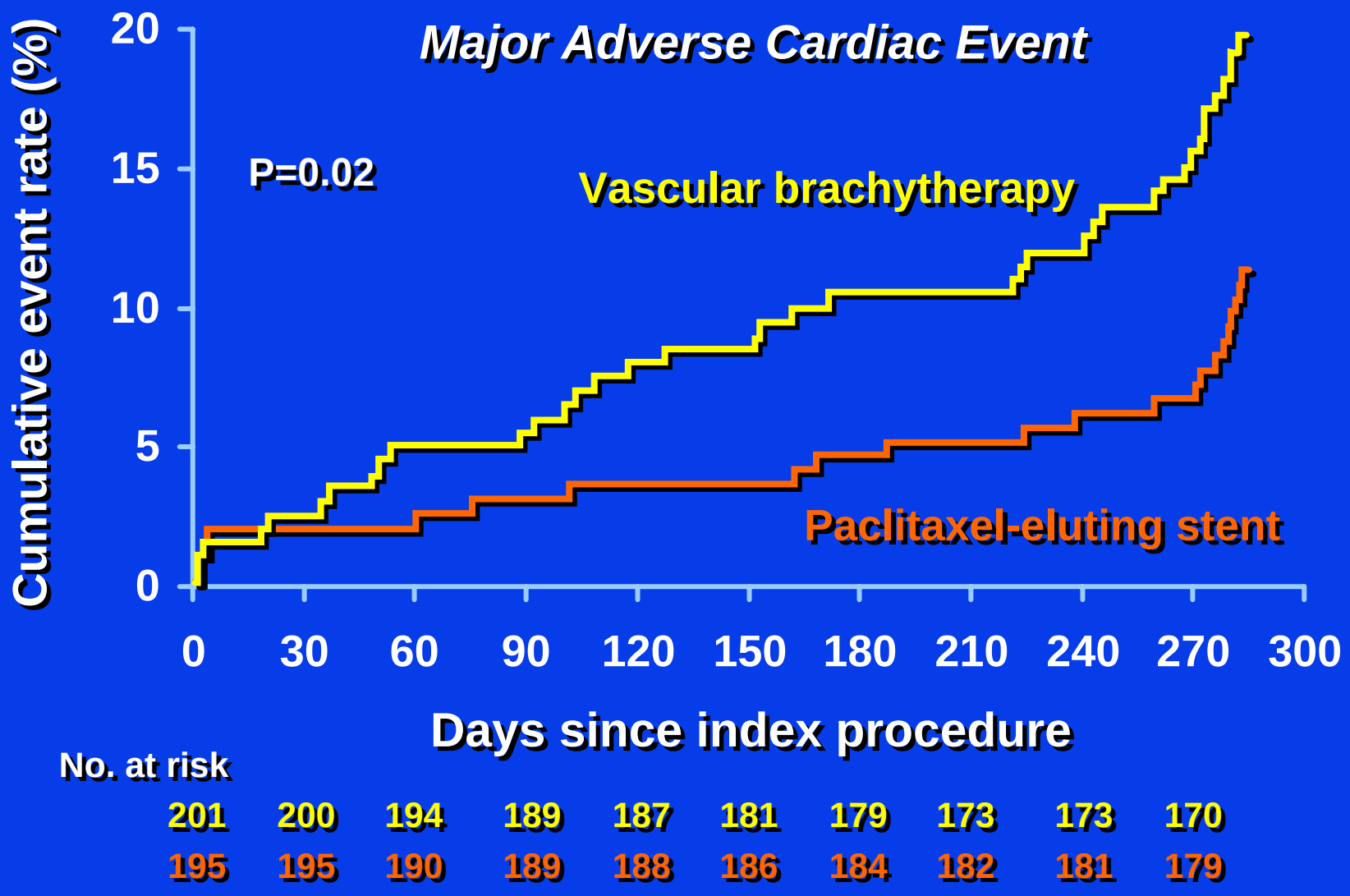
Stone et al: JAMA 295:1253, 2006

TAXUS vs ISR



Stone et al: JAMA 295:1253, 2006

TAXUS vs ISR



Stone et al: JAMA 295:1253, 2006

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