Evidence-based Overview of DES in CTO Revascularization

Clinical Trials and Outcomes with DES Treatment of Chronic Total Occlusions

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Relevant Disclosure

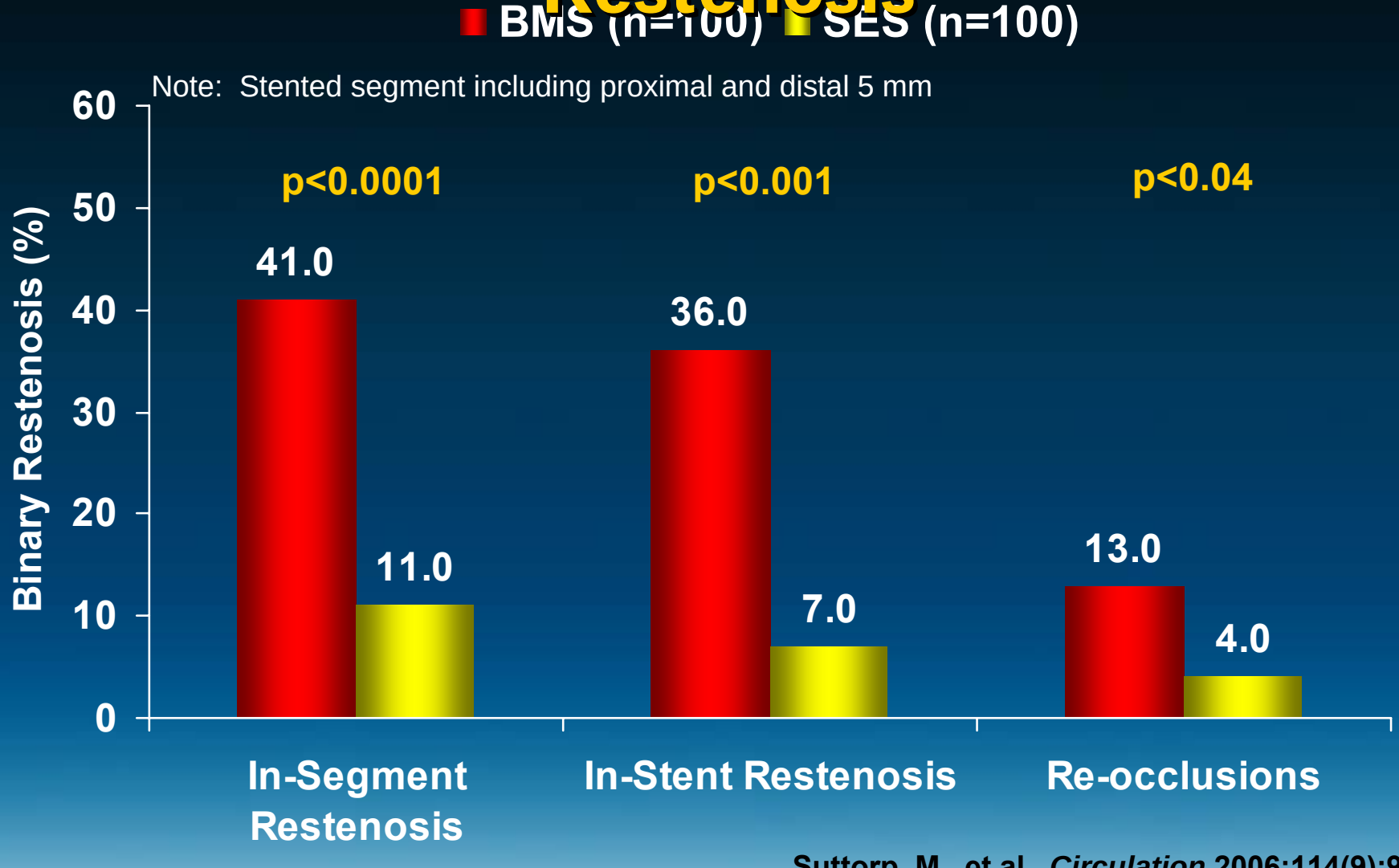
Employment: Cordis/ Johnson and Johnson

Background

Trial	N	Re-Occlusion			Restenosis			TVR		
		PTCA	Stent	p-	PTCA	Stent	p-	PTCA	Stent	p-
SICCO	114	26%	16%	NS	74%	32%	<0.01	42%	22%	0.025
GISSOC	110	34%	8%	<0.01	68%	32%	<0.01	22%	5%	0.04
Mori et al.	96	11%	7%	0.04	57%	28%	<0.01	49%	28%	<0.05
SPACTO	85	24%	3%	0.01	64%	32%	0.01	40%	25%	NS
TOSCA	410	20%	11%	0.02	70%	55%	<0.01	15%	8%	0.03
PRISON	200	7%	8%	NS	33%	22%	NS	10%	3%	<0.01
STOP	96	17%	8%	NS	71%	42%	0.032	42%	25%	NS

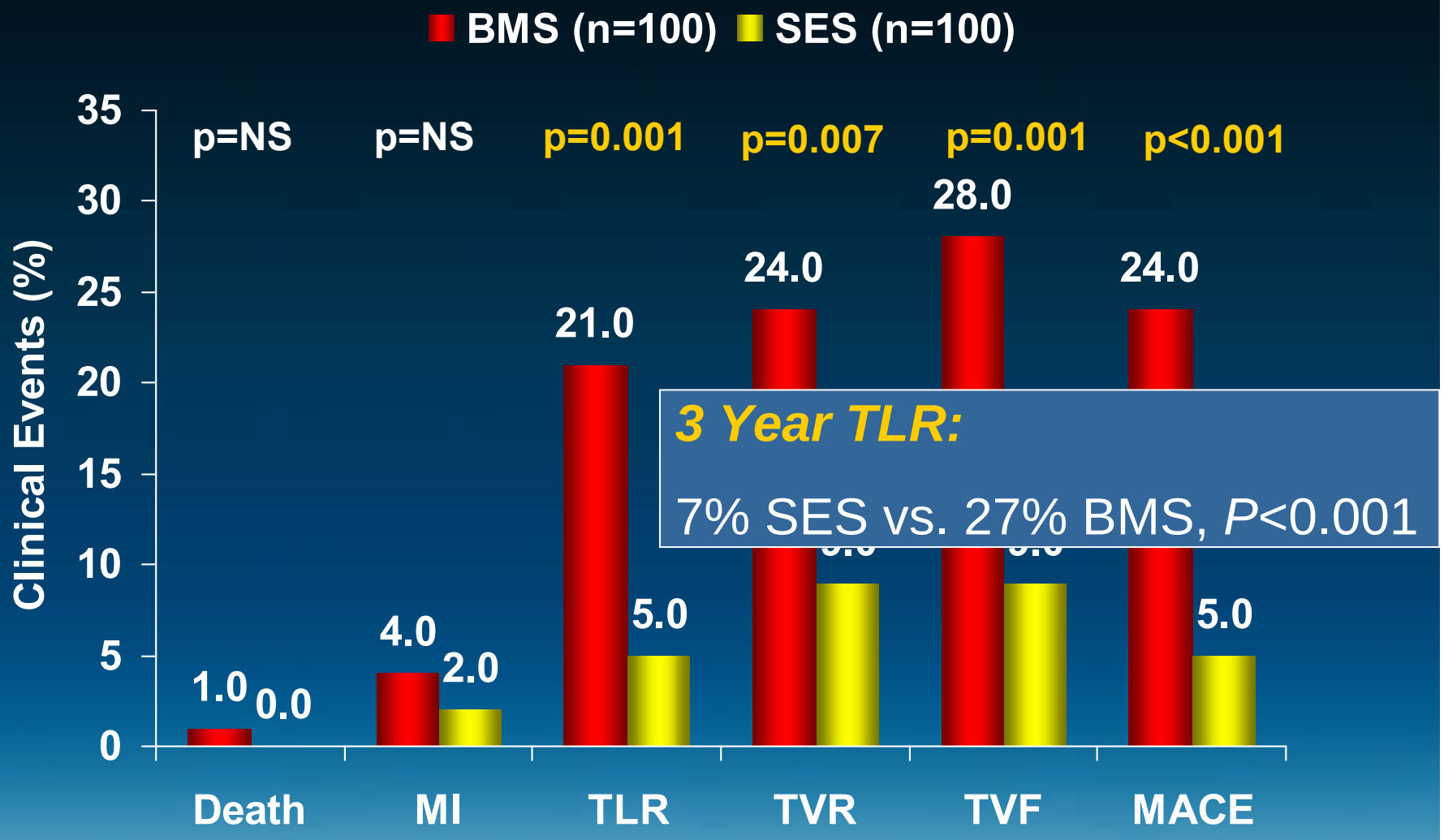
SICCO: Stenting in Chronic Coronary Occlusion
GISSOC: Gruppo Italiano di Studi sulla Stent nelle Occlusioni coronariche
SPACTO: Stent vs. Percutaneous Angioplasty in Chronic Total Occlusion
TOSCA: Total Occlusion Study of Canada
PRISON: Primary Stenting of Occluded Native Coronary Arteries
STOP: Stents in Total Occlusion for Restenosis Prevention

PRISON II
6-Month Angiographic Binary Restenosis



Suttorp, M., et al., *Circulation* 2006;114(9):921-8.

PRISON II
12-Month Clinical Follow-up



3 Year TLR:

7% SES vs. 27% BMS, *P*<0.001

Suttorp, M., et al., *Circulation* 2006;114(9):921-8.

Study Design

CYPHER® Sirolimus-eluting Stent (SES) in Non-acute Total Coronary Occlusions (CTO)

CYPHER® SES	TOSCA-I BMS Control
N = 200	N = 202

Primary Endpoint:
6-Month Angiographic Binary Restenosis (≥ 50%) within the "Treated Segment" Compared with Historic Control TOSCA-I BMS Arm

Treated Segment defined as length of contiguous target segment exposed to balloon inflation

Clinical F/U at 150 days: 197 (98.5%)
Clinical F/U at 180 days: 185 (92.5%)
Angiographic F/U: 170 (85.0%)

Secondary Endpoints

- Lesion, device and procedural success
- 6-month, in-segment and in-stent:
  - Binary restenosis (≥ 50%)
  - Late lumen loss
  - Minimum lumen diameter (MLD)
- Major adverse cardiac events (MACE) at 30 days, 6 months, and annually out to 5 years
- Target lesion revascularization (TLR) at 6 and 12 months
- Target vessel revascularization (TVR) at 6 and 12 months
- Target vessel failure (TVF) at 6 and 12 months
- Failure of sustained patency at 6 months
- Protocol- and ARC-defined stent thrombosis

Study Administration

Sponsor and Principal Investigator
David E. Kandzari, MD*
Sunil Rao, MD
Duke University Medical Center
Durham, NC

Funding:
Cordis Corporation,
a Johnson and Johnson Company
Warren, NJ

Data Coordinating Center:
Duke Clinical Research Institute (DCRI)
Durham, NC

Angiographic Core Lab:
Cardiovascular Imaging Research Core Laboratory (CIRCL)
University of British Columbia
Vancouver, BC

Medical Monitor:
Michael Cuffe, MD
Duke University Medical Center
Durham, NC

Site Monitoring:
Duke Clinical Research Institute (DCRI)
Durham, NC

** Enrollment and 6-month follow-up completed prior to employment with Cordis Corporation.*

Baseline Characteristics

	CYPHER® SES N = 200 Patients
Age (years)	62.0 ± 10.9
Male (%)	80.0
History of MI (%)	33.5
History of Previous PCI (%)	32.5
History of CABG (%)	8.5
Diabetes Mellitus (%)	24.5
History of Hyperlipidemia (%)	86.0
History of Hypertension (%)	69.5
History of Congestive Heart Failure (%)	4.0
Current Smoker (%)	17.5

Angiographic Characteristics

	CYPHER® SES 200 Lesions
Vessel Location (%)	
LAD	29.5
LCX	21.5
RCA	49.0
Moderate to Severe Calcification (%)	46.7
Side Branch Occlusion (%)	9.7
Reference Vessel Diameter (mm)	2.97 ± 0.67
Mean Treated-Segment Length (mm)	51.9 ± 24.9
Total Implanted Stent Length (mm)	48.9 ± 24.3
≥2 Stents implanted (%)	75.0
Overlapping Stents (%)	92.0

Treated Segment defined as length of contiguous target segment exposed to balloon inflation

Procedural Success

	CYPHER® SES 200 Lesions
Lesion Success (%)	99.5
Device Success (%)	98.0
Procedural Success (%)	97.9

- Lesion success: < 50% residual stenosis of target lesion using any percutaneous method
- Device success: < 50% residual stenosis of target lesion using only assigned device
- Procedural success: < 50% residual stenosis of target lesion and no in-hospital MACE

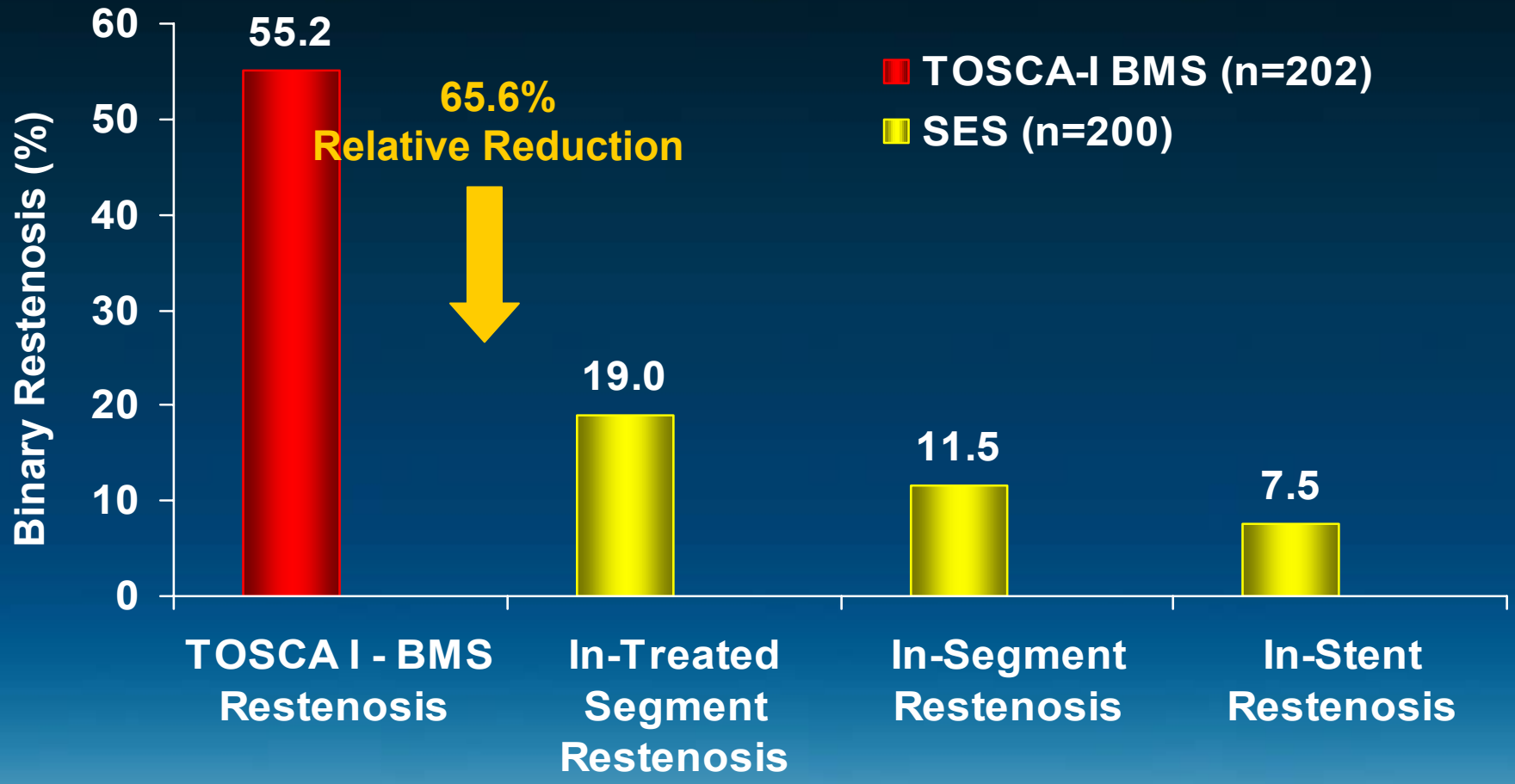
QCA at 6 Months

CYPHER® SES 200 Lesions	In-segment	In-stent	Proximal Edge	Distal Edge
MLD (mm)	1.93 ± 0.62	2.23 ± 0.67	2.87 ± 0.67	2.23 ± 0.59
% Stenosis	33.02 ± 17.45	21.28 ± 20.57	--	--
Acute Gain (mm)	1.88 ± 0.58	2.44 ± 0.45	--	--
Late Loss (mm)	0.02 ± 0.48	0.24 ± 0.63	0.10 ± 0.47	0.24 ± 0.38
Loss Index (mm)	0.23 ± 0.07	0.30 ± 0.12	--	--
TIMI Flow 0 (%)	2.4	--	--	--
TIMI Flow 1 (%)	0.6	--	--	--
TIMI Flow 2 (%)	7.7	--	--	--
TIMI Flow 3 (%)	89.4	--	--	--

ACROSS - CYPHER®

6-Month Angiographic Binary Restenosis

In treated-segment refers to length of contiguous target segment exposed to balloon inflation
In-segment includes stented area plus 5 mm proximal and distal to stent



TOSCA: *Circulation* 1999; 100:236-42.

Population Comparison Based on 10 Variables

	ACROSS-CYPHER® (N = 200)	TOSCA-1 (N = 202)	p-value (before)
Age (years)	62.0 ± 10.9	57.5 ± 10.5	<0.001
Age of Occlusion > 6 weeks	78.8% (119/151)	36.6% (48/131)	<0.001
Baseline RVD (mm)	3.0 ± 0.6	3.3 ± 0.6	<0.001
Current Smoker	17.6% (35/200)	17.8% (36/202)	0.9326
History of Diabetes	24.5% (49/200)	14.9% (30/202)	0.0158
Male	80.0% (160/200)	83.7% (169/202)	0.3415
History of Hypertension	69.5% (139/200)	34.7% (70/202)	<0.001
Target Vessel: LAD	29.5% (59/200)	38.6% (78/202)	0.0545
Stent Length (mm)	48.9 ± 24.3	29.7 ± 17.0	<0.001
Working Lesion Length (mm)	51.9 ± 24.9	35.9 ± 18.8	<0.001

Despite the more difficult to treat baseline patient and lesion characteristics, the unadjusted 6-month angiographic binary restenosis rate favored ACROSS-CYPHER®

Treatment Effect

Groups were matched using propensity score adjusted for 3 variables (diabetes, baseline reference diameter and working lesion length)

	ACROSS-CYPHER® (N = 200)	TOSCA I (N = 202)	OR and 95% CI	p-value
Angiographic Binary Restenosis	22.6% (38/168)	55.2% (107/94)	0.160 (0.090, 0.283)	<0.0001

When adjusted for 5 variables (age, current smoker, history of diabetes, baseline reference diameter and working lesion length)

	ACROSS-CYPHER® (N = 200)	TOSCA I (N = 202)	OR and 95% CI	p-value
Angiographic Binary Restenosis	22.6% (38/168)	55.2% (107/94)	0.167 (0.093, 0.300)	<0.0001

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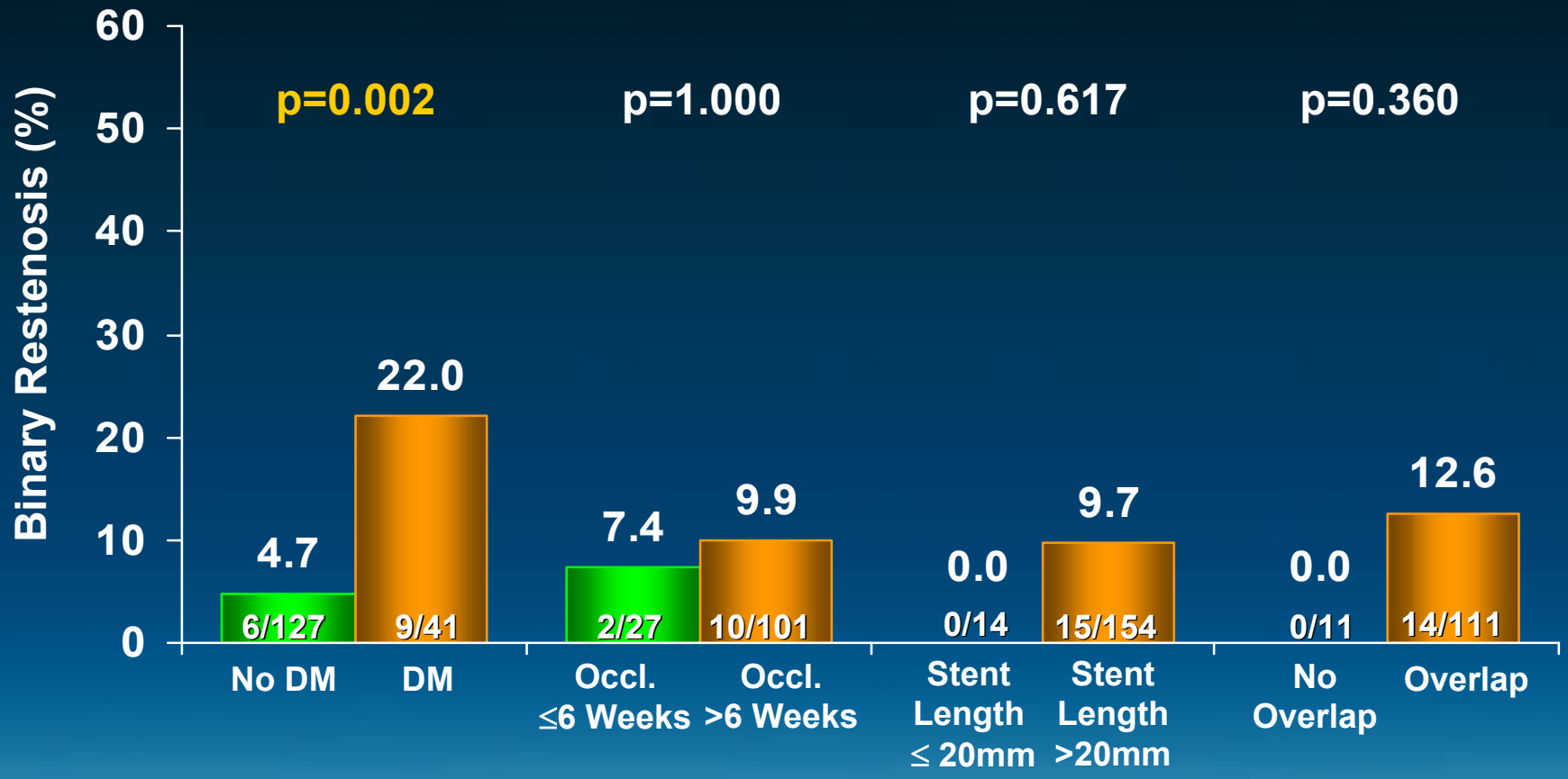
6-Month In-Stent Binary Restenosis in Subgroups



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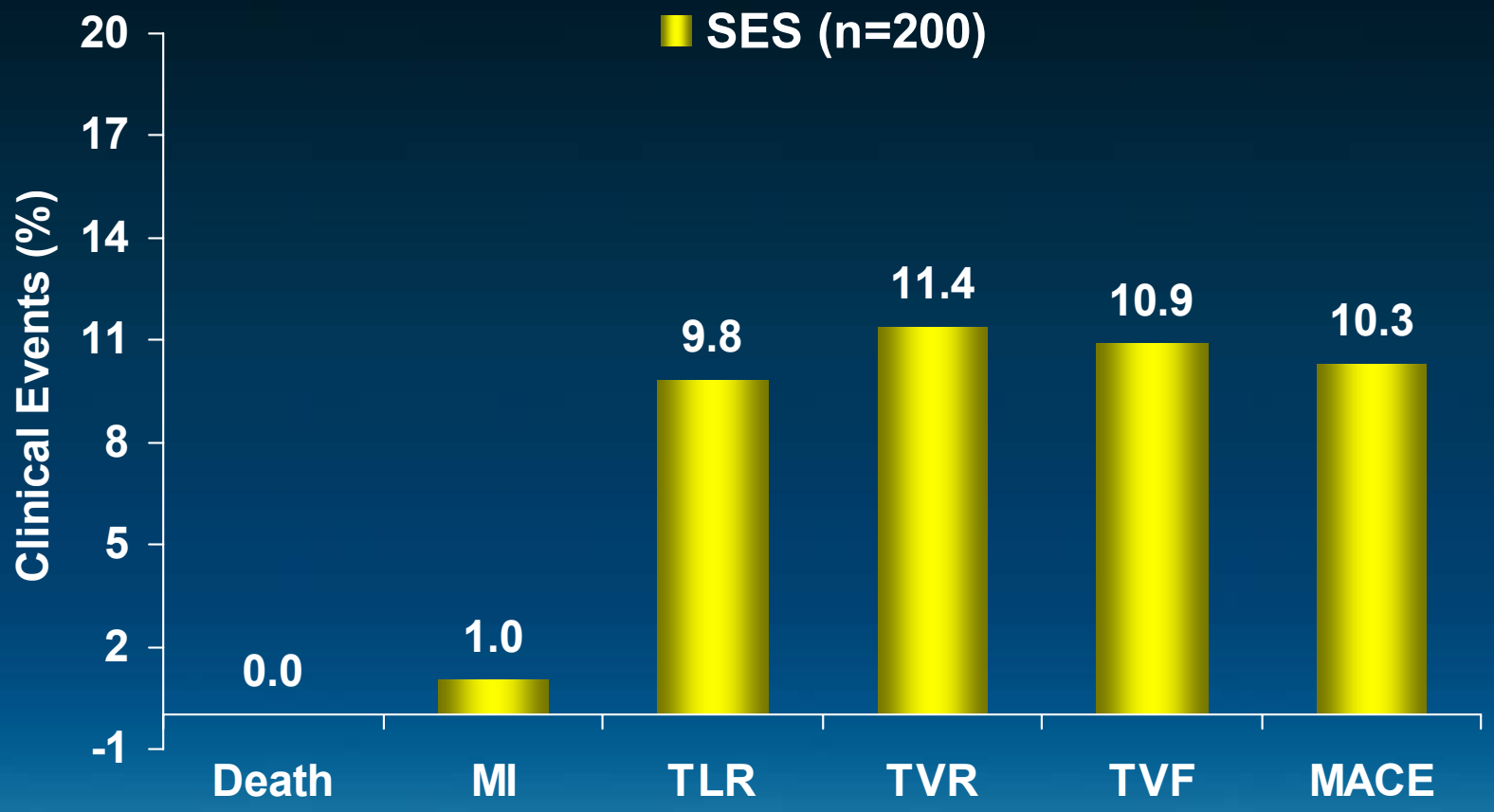
1 Year Clinical Outcomes



MACE defined as death, MI (Q- and non-Q-wave), emergent bypass surgery, or repeat TLR

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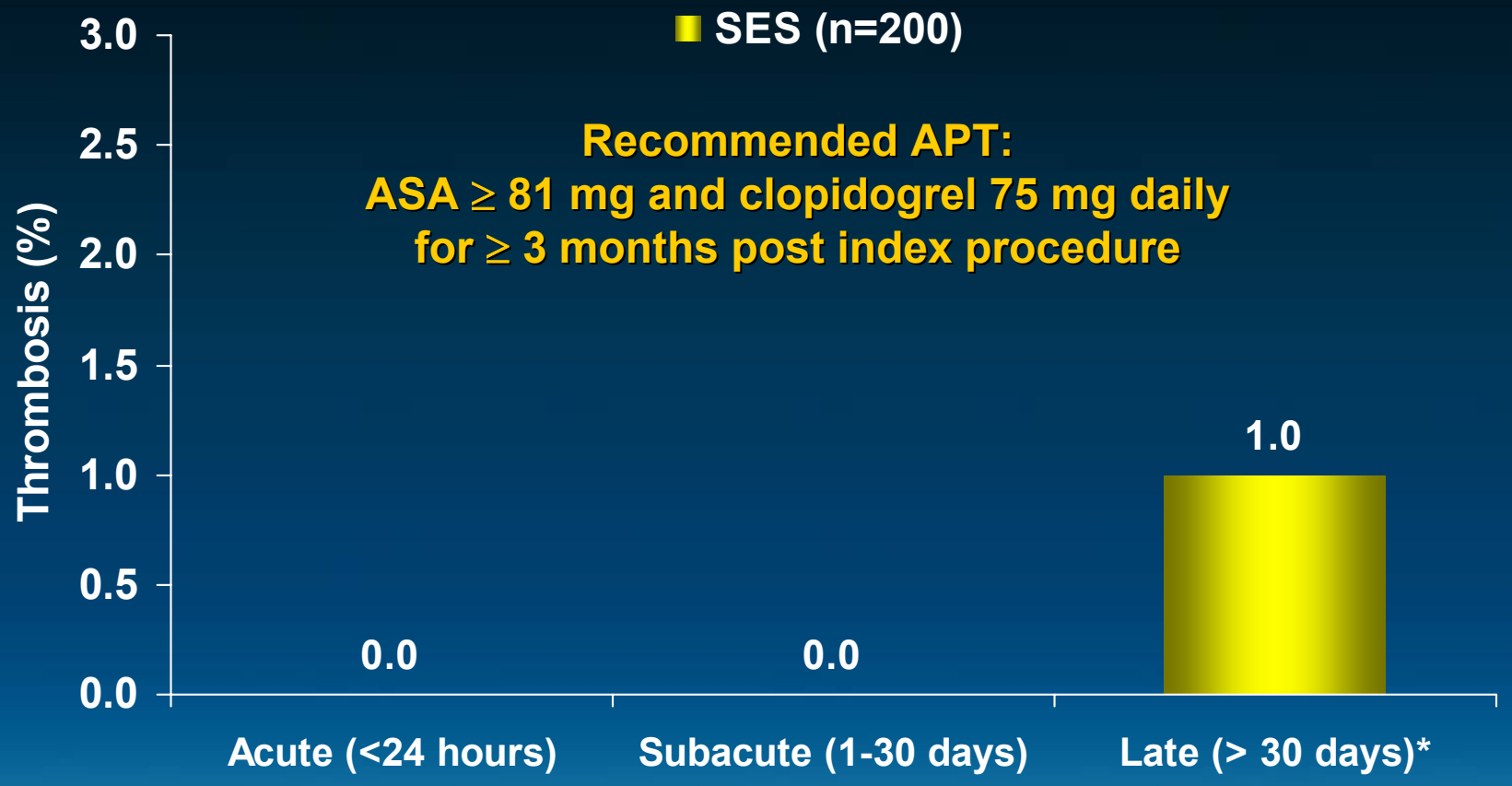
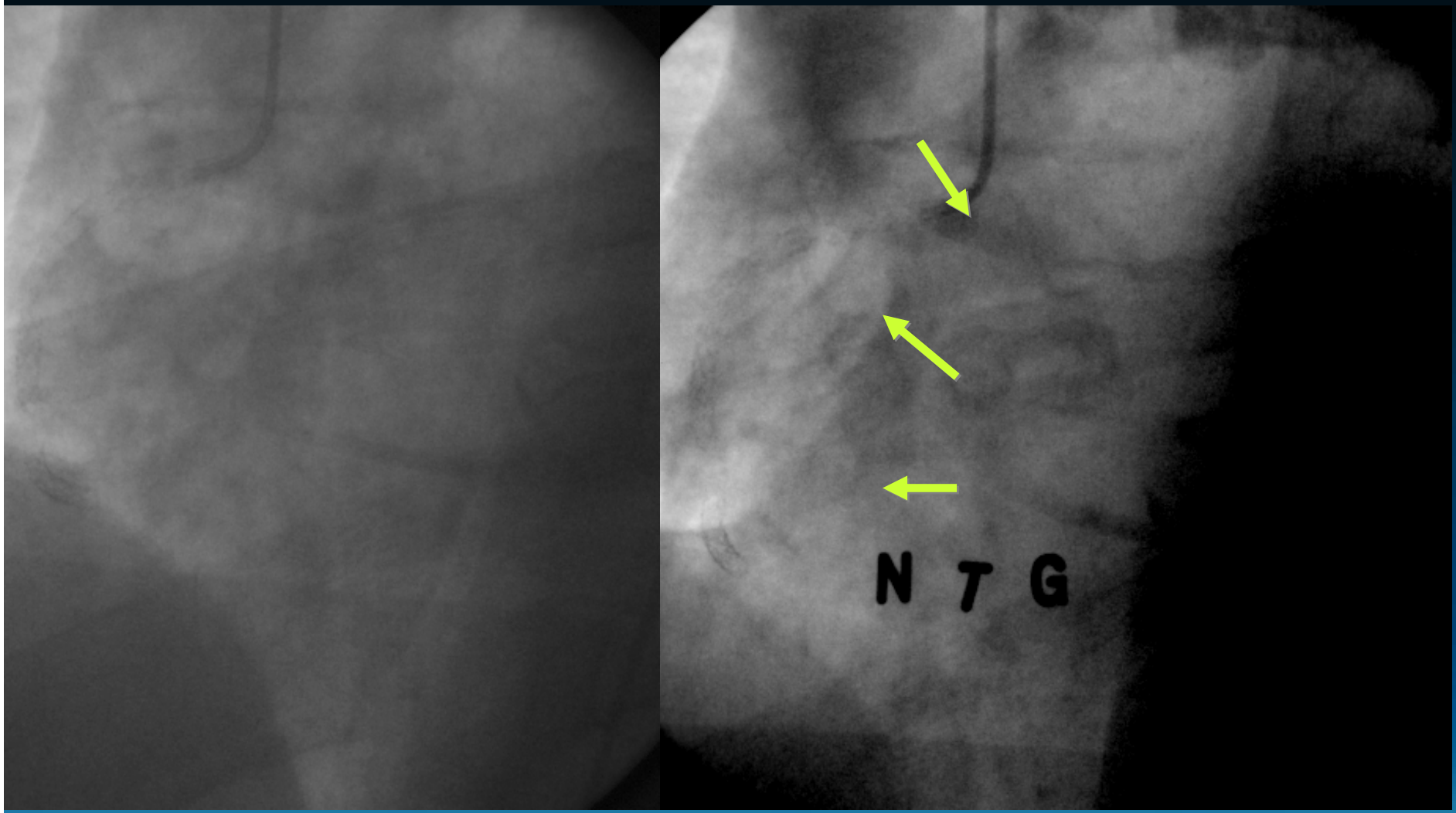
1 Year Stent Thrombosis



Dual APT compliance at 6 months 177/189 (93.7%)

** In one patient, thrombus was noted in a side branch of the RCA (index vessel) which was considered the working length of the RCA.*

7 month angiographic follow-up



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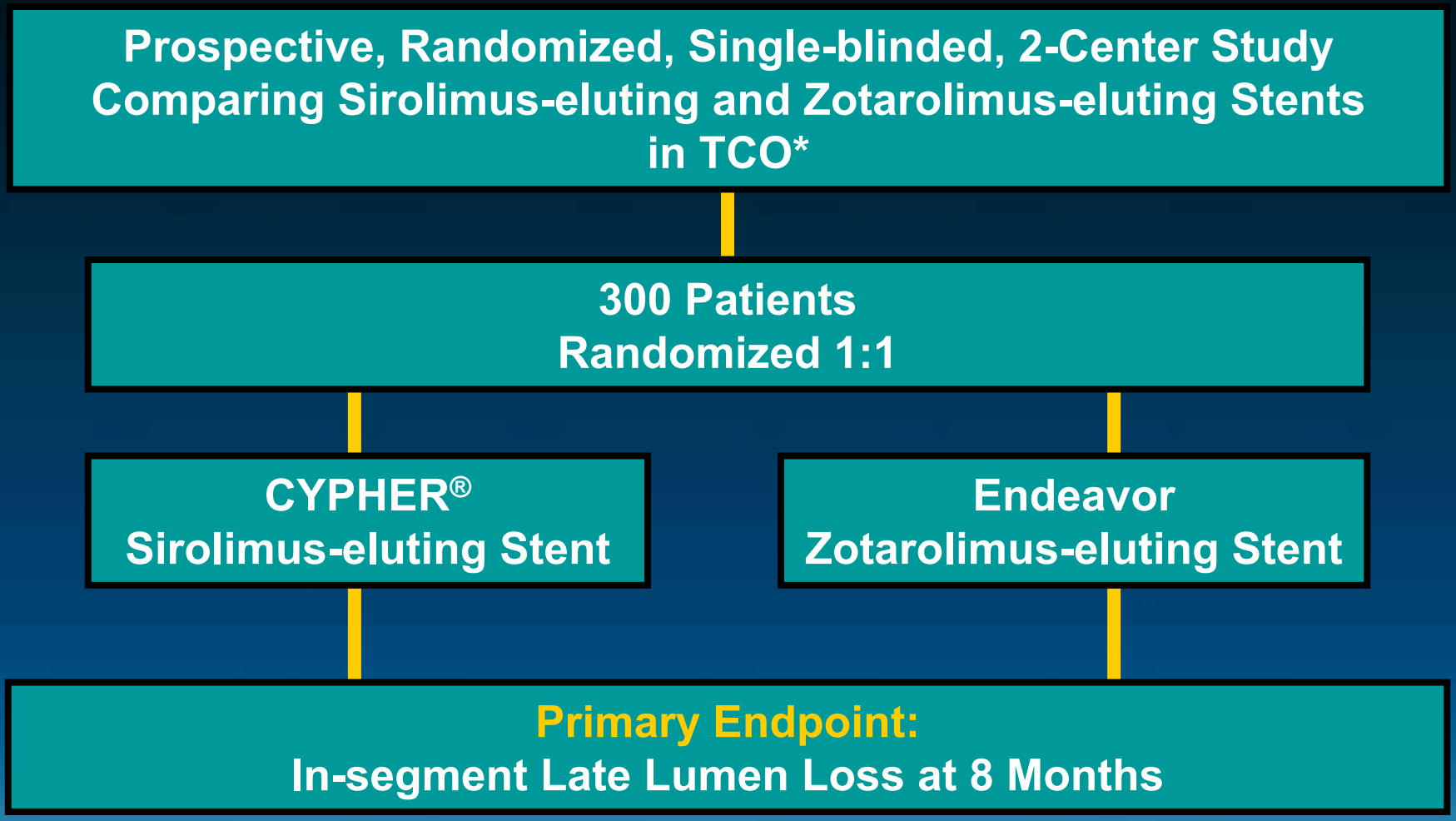
Evaluation of Stent Fracture at 6 Months

	Patients with Stent Fracture N = 32	Patients w/o Stent Fracture N = 168	p-value
Mean Stent Length (mm)	69.7 ± 24.6	45.0 ± 22.2	<0.001
Overlapping Stents	100.0% (30/30)	89.9% (107/119)	0.06
Binary Restenosis			
In-segment	21.9% (7/32)	11.7% (16/137)	0.07
In-stent	15.6% (5/32)*	7.4% (10/136)	0.09
Stent Thrombosis	3.1% (1/32)	0.0% (0/165)	0.16

* Of the 5/32 fracture patients with in-stent restenosis, 2 patients had restenosis at the site of fracture (1 patient had restenosis at 2 separate fracture sites).

PRISON III Study Design



**Total chronic occlusion (TCO) defined as ≥2 weeks with TIMI 0 or 1 flow*

Evidence-based Rationale for DES in CTO Revascularization

Summary

- Despite greater lesion complexity than in prior CTO trials, percutaneous revascularization with DES results in substantial reductions in angiographic restenosis and the need for repeat revascularization
  - In *ACROSS/TOSCA 4*, when restenosis following SES treatment of CTOs occurs, it most commonly occurs beyond the stent margins but within the treated segment

Evidence-based Rationale for DES in CTO Revascularization

Summary

- Treatment of CTOs with DES has introduced new benefits, new dilemmas
  - Aside from ↓ABR, long term patency with DES may be associated with preservation of improved LV function
  - Strut fracture and LSM may be more common; clinical implications uncertain
  - Duration of dual antiplatelet therapy uncertain
- Planned 5-year follow-up in *ACROSS/TOSCA 4* should further qualify the long-term clinical outcomes in this complex patient population