Lessons From *SIRIUS* with New Subset Analysis

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9th Angioplasty Summit
2004
Seoul,Korea

Cardiovascular Research Foundation

Lenox Hill Heart and Vascular Institute of New York

Effectivenesss is Broadbased

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SIRIUS - TLR Treatment Effect

Between Control and Sirolimus

Non–Diabetic

Lesion Length

Ref Diam	<12mm	12-15mm	≥15mm
≥3.0mm	77.8%	77.6%	77.0%
2.5-3.0mm	77.0%	76.6%	75.7%
<2.5mm	75.9%	75.3%	74.1%

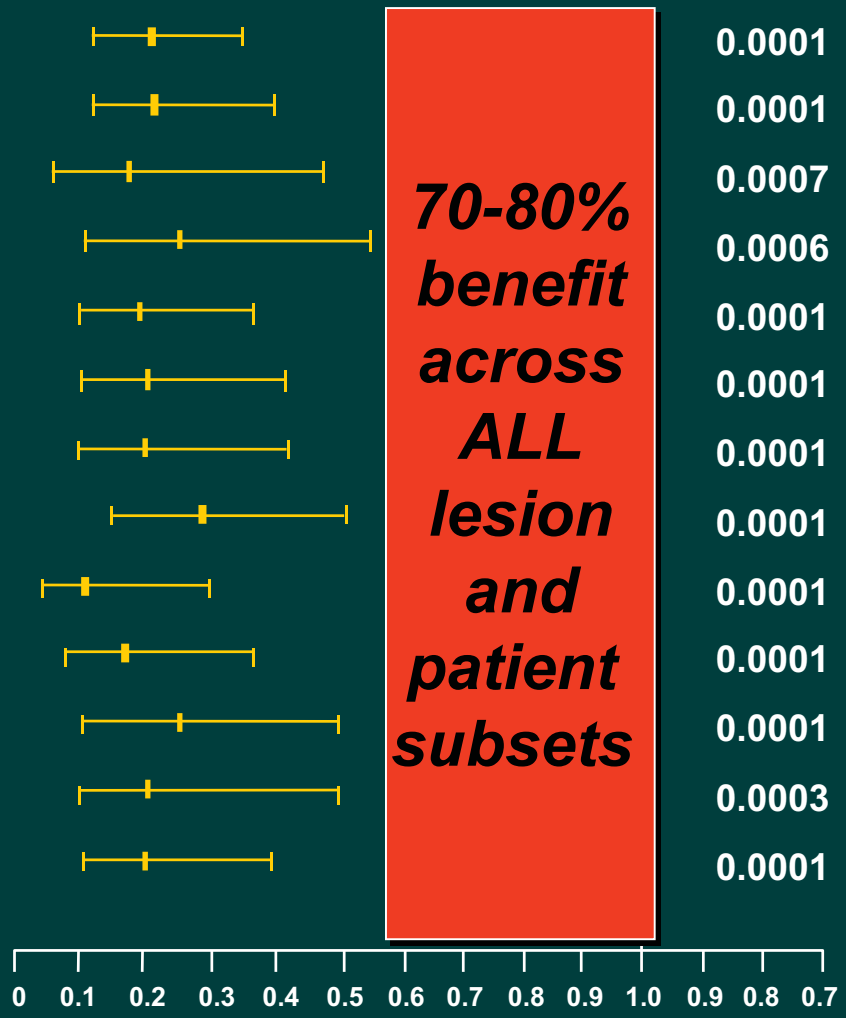
Diabetic

Lesion Length

Ref Diam	<12mm	12-15mm	≥15mm
≥3.0mm	76.9%	76.5%	75.6%
2.5-3.0mm	75.5%	74.8%	73.4%
<2.5mm	73.8%	72.8%	70.8%

SIRIUS – TLR Events

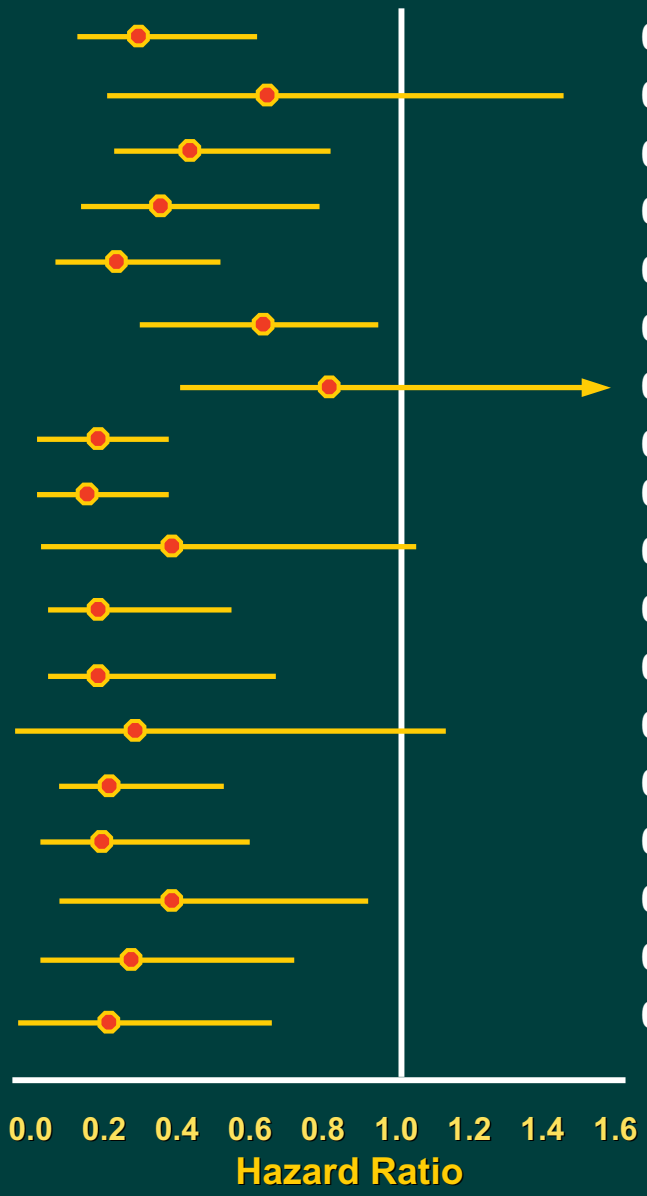
	Sirolimus	Control	P-value	# events prevented per 1,000 patients
Overall	4.1	16.6	0.0001	124
Male	4.4	16.6	0.0001	122
Female	3.4	16.5	0.0007	130
Diabetes	6.9	22.3	0.0006	154
No Diabetes	3.2	14.3	0.0001	111
LAD	5.1	19.8	0.0001	147
Non-LAD	3.4	14.3	0.0001	109
Small Vessel (<2.75)	6.3	18.7	0.0001	125
Large Vessel	1.9	14.8	0.0001	128
Short Lesion	3.2	16.1	0.0001	129
Long Lesion (>13.5)	5.2	17.4	0.0001	122
Overlap	4.5	17.7	0.0003	131
No Overlap	3.9	16.1	0.0001	121



70-80% benefit across ALL lesion and patient subsets

Sirolimus better

RESEARCH Subsets



	HR	95% CI	p-value
Male	0.28	0.15-0.52	<0.001
Female	0.59	0.24-1.45	0.25
Stable angina	0.39	0.21-0.72	0.003
Acute coronary disease	0.30	0.13-0.71	0.006
Single vessel disease	0.21	0.09-0.51	0.001
Multivessel disease	0.47	0.25-0.88	0.02
Diabetes mellitus	0.72	0.30-1.77	0.50
No diabetes mellitus	0.25	0.13-0.47	<0.001
Short lesion (stent length <33 mm)	0.24	0.12-0.48	<0.001
Long lesion (stent length ≥33 mm)	0.41	0.16-1.03	0.06
Large vessel (stent diameter >2.5mm)	0.32	0.16-0.62	0.001
Small vessel (stent diameter ≤2.5mm)	0.33	0.15-0.74	0.007
Bifurcation stenting	0.38	0.13-1.13	0.08
No bifurcation stenting	0.31	0.17-0.56	<0.001
LAD stenting	0.31	0.16-0.59	<0.001
Non-LAD stenting	0.42	0.19-0.92	0.03
No post-dialation	0.35	0.18-0.70	0.003
Post-dialation with 0.5-mm larger balloon	0.13-0.62	0.002	0.28

Lemos et al, *Circulation*, 2004

The Effect is Durable

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SIRIUS – Two Year Follow-up

FU Compliance

	Sirolimus (%) (n=533)	Control (%) (n=525)
@ 270 Days	98.3 (524)	98.3 (516)
@ 360 Days	97.7 (521)	97.5 (512)
@ 720 Days	92.3 (492)	91.6 (481)

SIRIUS – Two Year Clinical Events

All Events to 720 Days

	Sirolimus (%) (n=533)	Control (%) (n=525)	P-value
Death	2.1 (11)	1.3 (7)	0.477
MI – All	3.8 (20)	4.0 (21)	0.874
MI-Non-Q	2.8 (15)	3.4 (18)	0.599
TLR – All	5.8 (31)	21.3 (112)	<0.0001
TLR – CABG	1.1 (6)	2.5 (13)	0.110
TLR – PCI	5.3 (28)	20.6 (108)	<0.0001
TVR (non-TLR)	4.9 (26)	7.2 (38)	0.122
MACE	10.1 (54)	24.4 (128)	<0.0001
TVF	12.0 (64)	26.7 (140)	<0.0001
Stent Thrombosis	0.6 (3)	0.8 (4)	0.854

SIRIUS – Two Year Clinical Events

All Sirolimus Events – 533 Patients

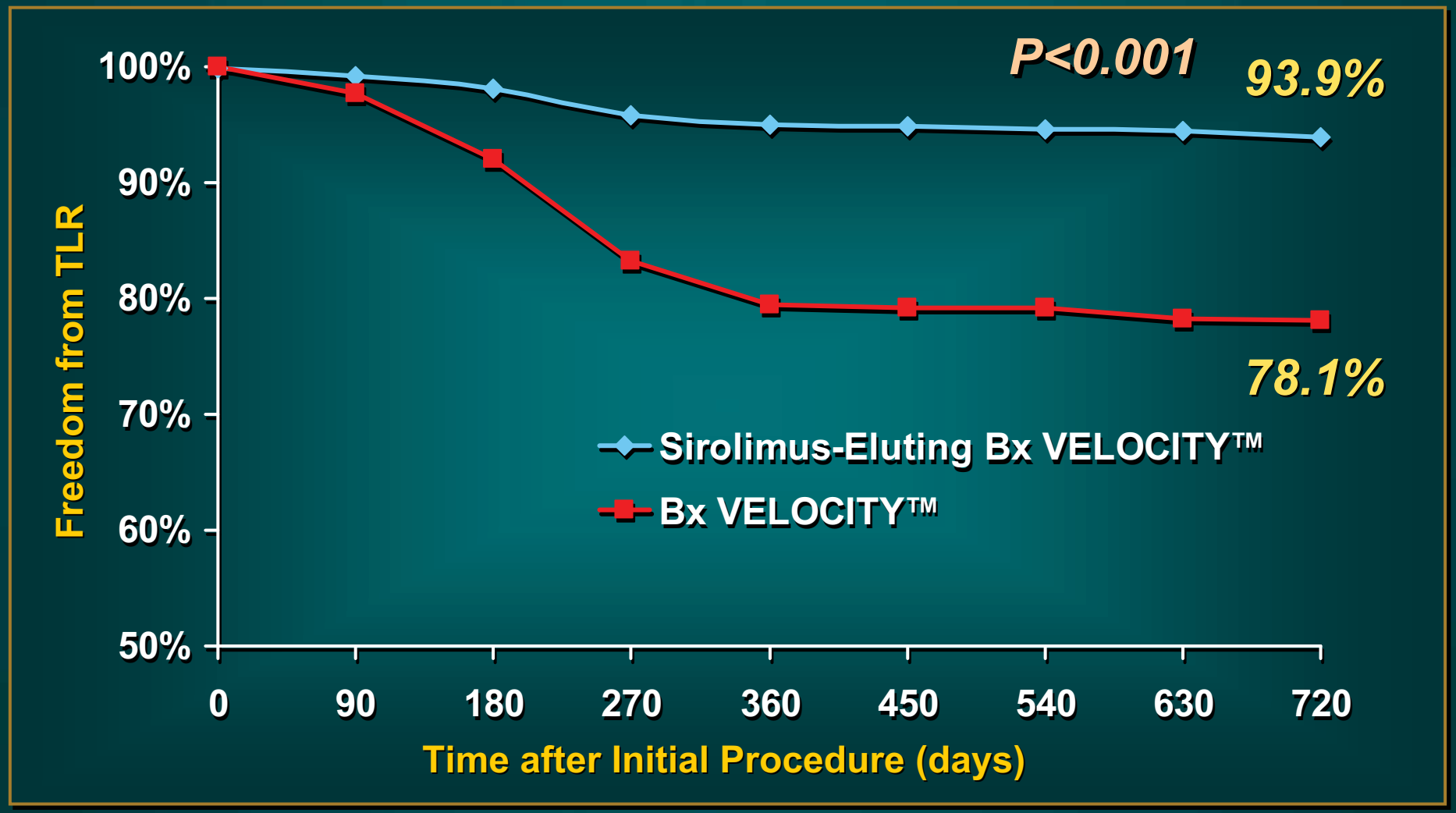
	@ 270 Days % (n)	@ 360 Days % (n)	@ 720 Days % (n)
Death	0.9 (5)	1.3 (7)	2.1 (11)
MI (All)	2.8 (15)	3.0 (16)	3.8 (20)
TLR (All)	4.1 (22)	4.9 (26)	5.8 (31)
TVR (non-TLR)	3.4 (18)	3.6 (19)	4.9 (26)
MACE	7.1 (38)	8.3 (44)	10.1 (54)
TVF	8.8 (47)	9.8 (52)	12.0 (64)
Stent Thrombosis	0.4 (2)	0.4 (2)	0.6 (3)

SIRIUS – Two Year Clinical Events

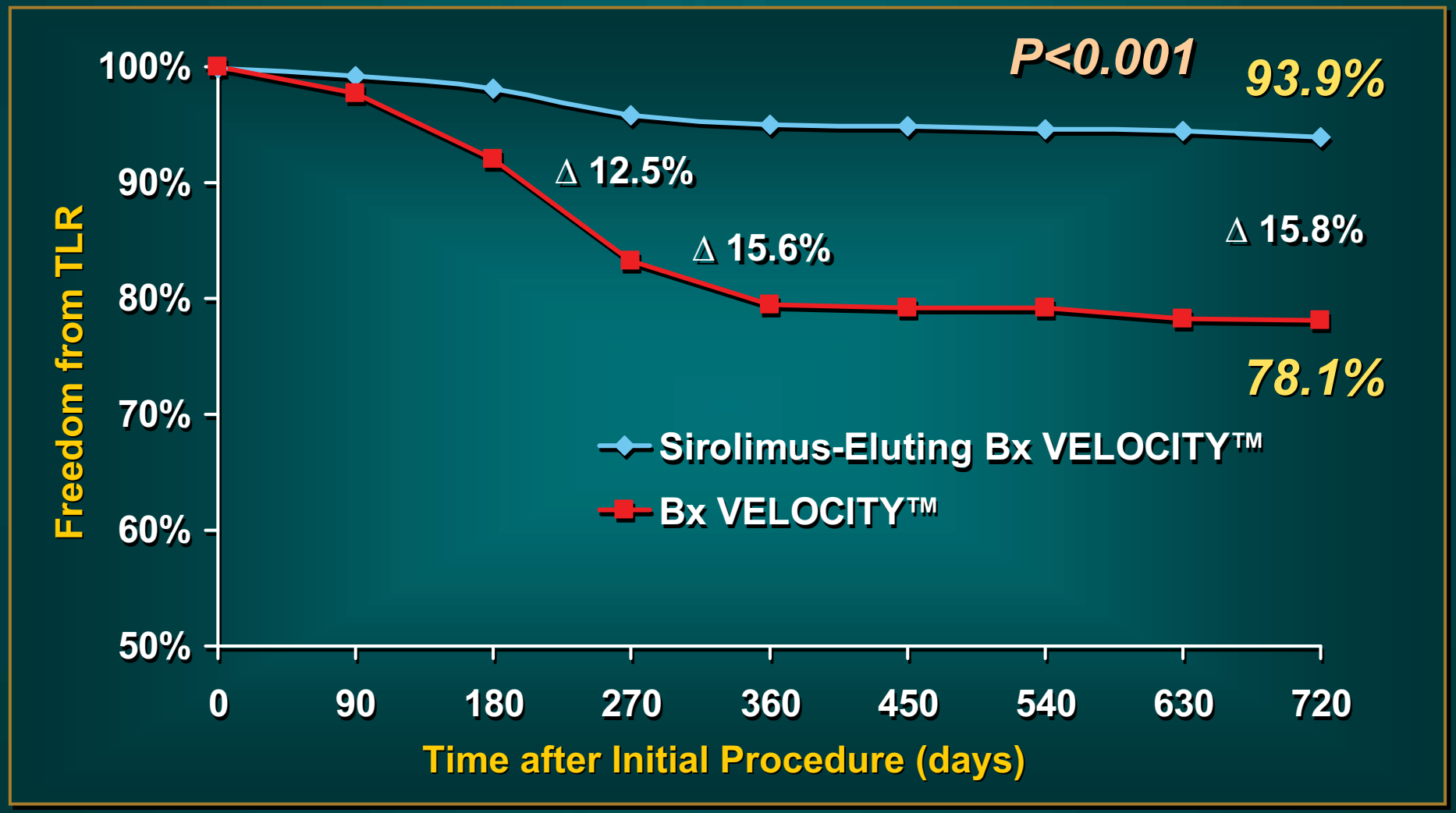
All Control Events – 525 Patients

	@ 270 Days % (n)	@ 360 Days % (n)	@ 720 Days % (n)
Death	0.6 (3)	0.8 (4)	1.3 (7)
MI (All)	3.2 (17)	3.4 (18)	4.0 (21)
TLR (All)	16.6 (87)	20.0 (105)	21.3 (112)
TVR (non-TLR)	4.8 (25)	6.7 (35)	7.2 (38)
MACE	18.9 (99)	22.3 (117)	24.4 (128)
TVF	21.0 (110)	24.8 (130)	26.7 (140)
Stent Thrombosis	0.8 (4)	0.8 (4)	0.8 (4)

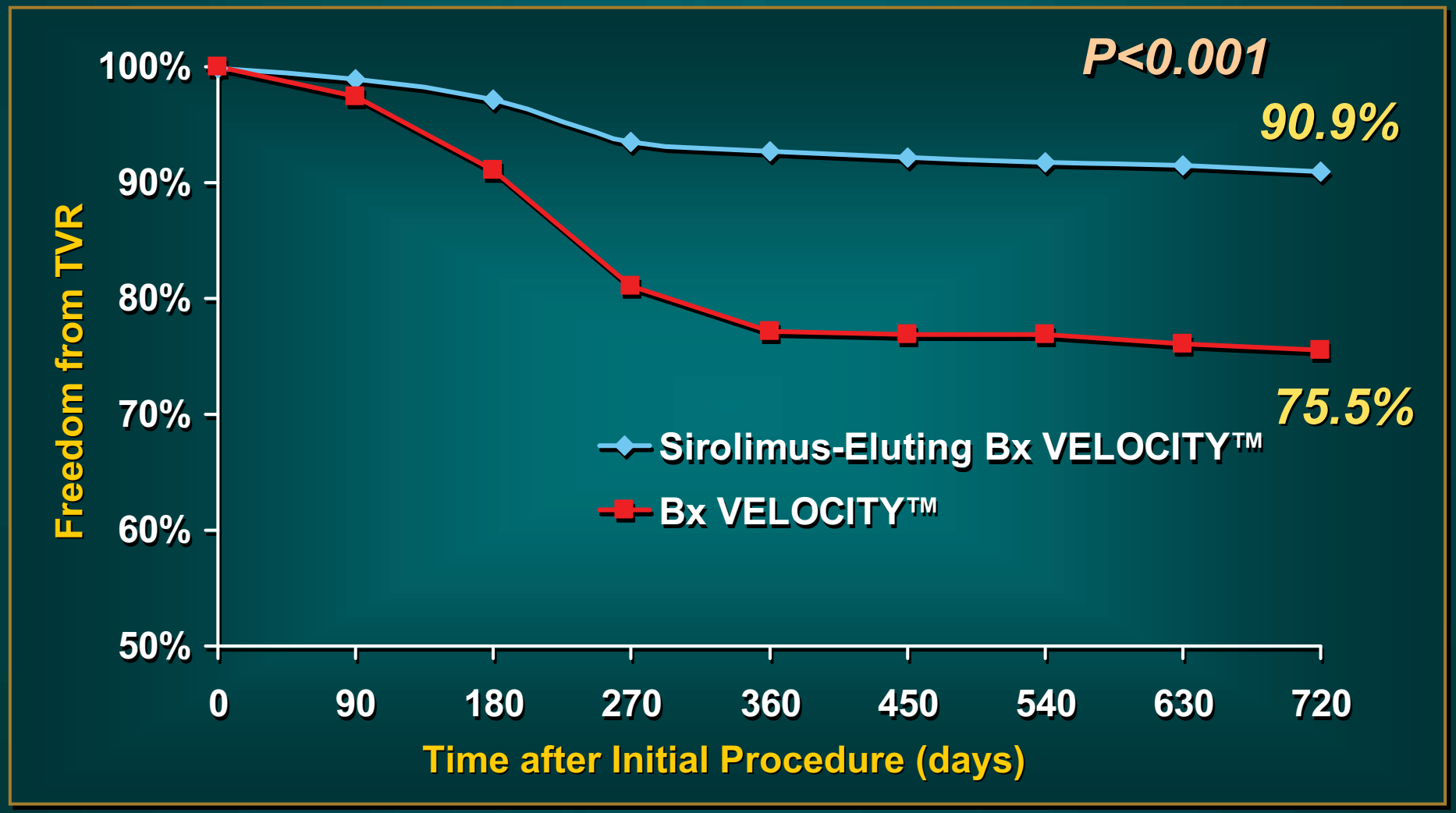
Survival Free from Target Lesion Revascularization – All Patients



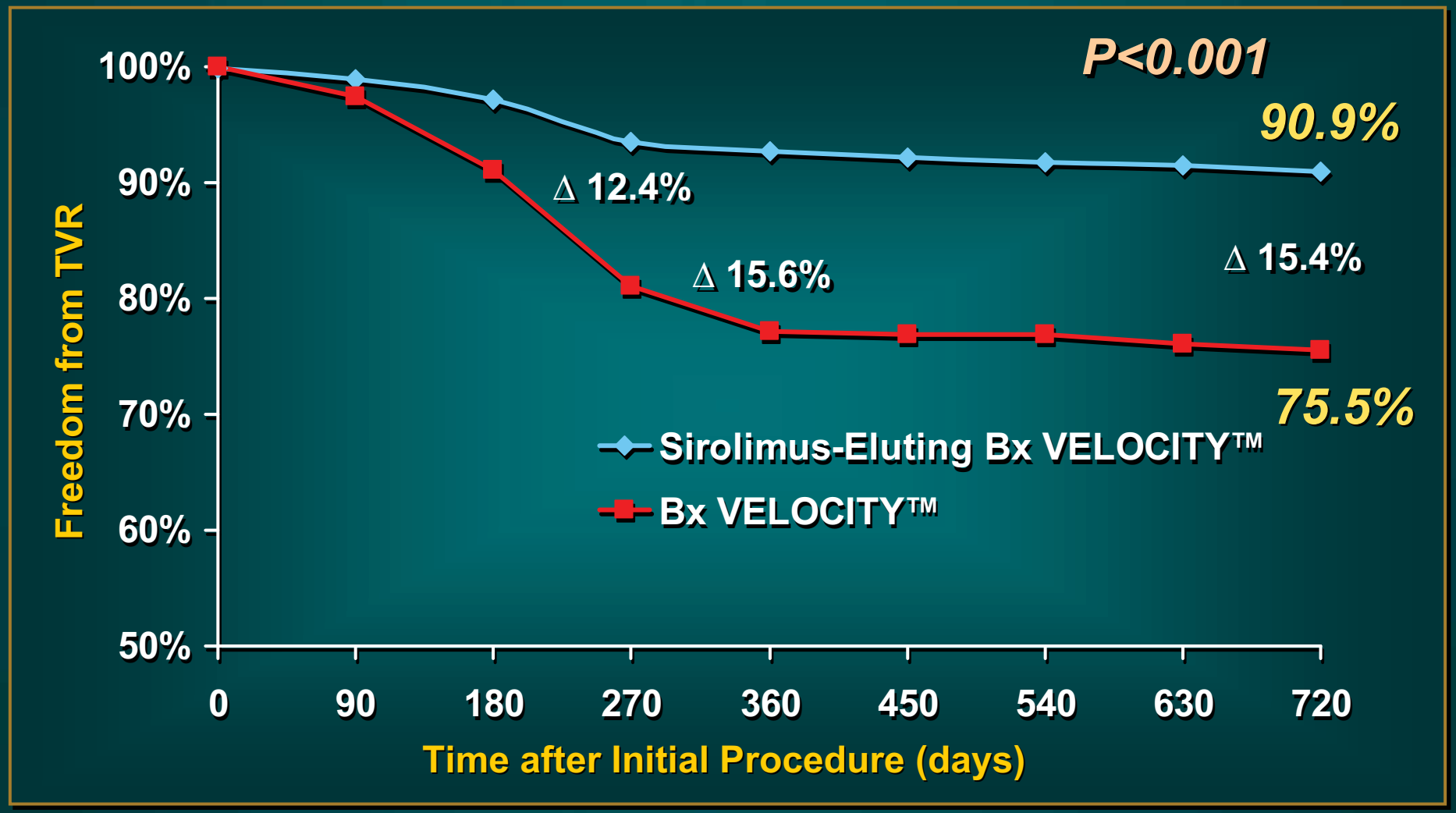
Survival Free from Target Lesion Revascularization – All Patients



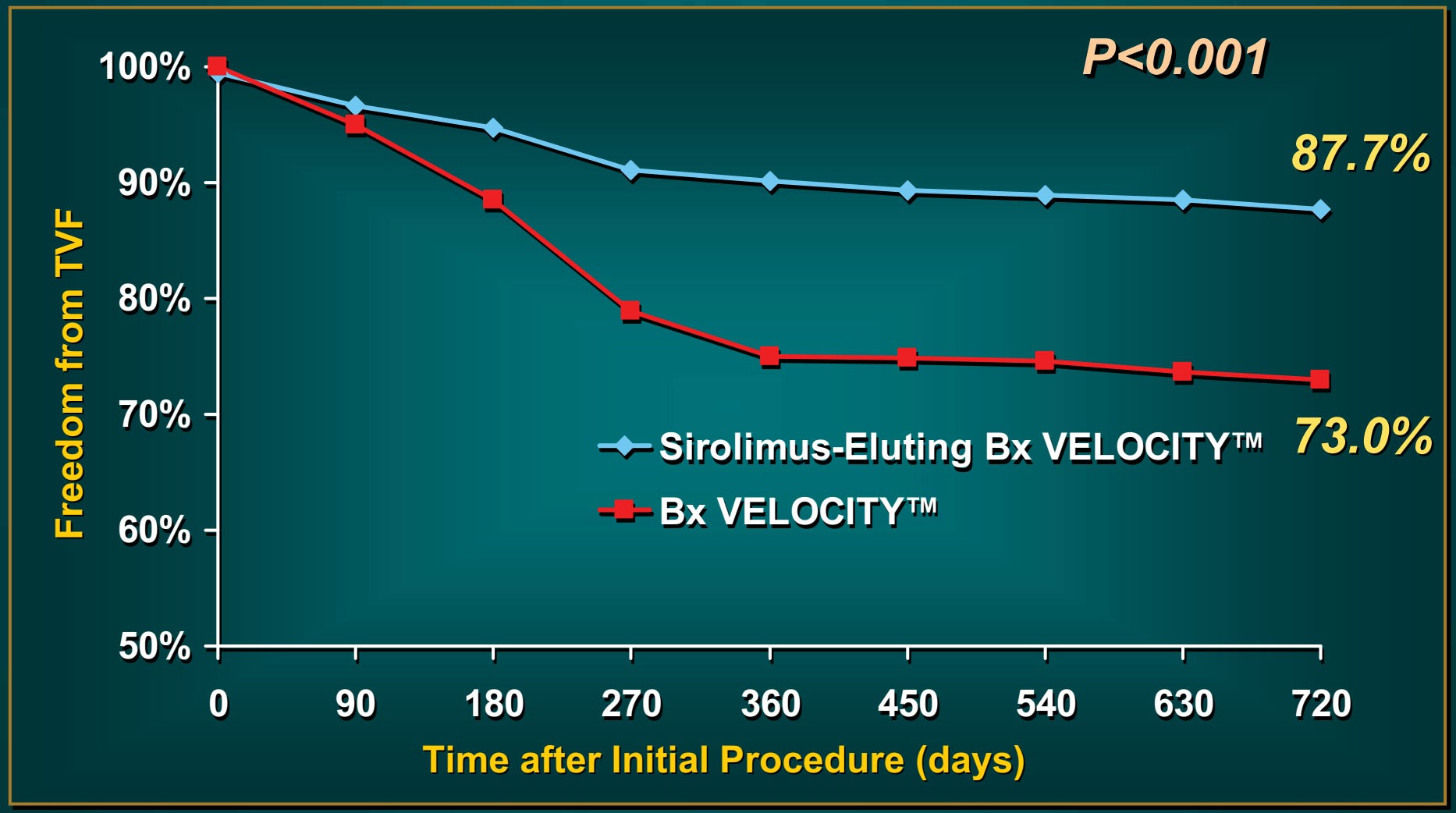
Survival Free from Target Vessel Revascularization – All Patients



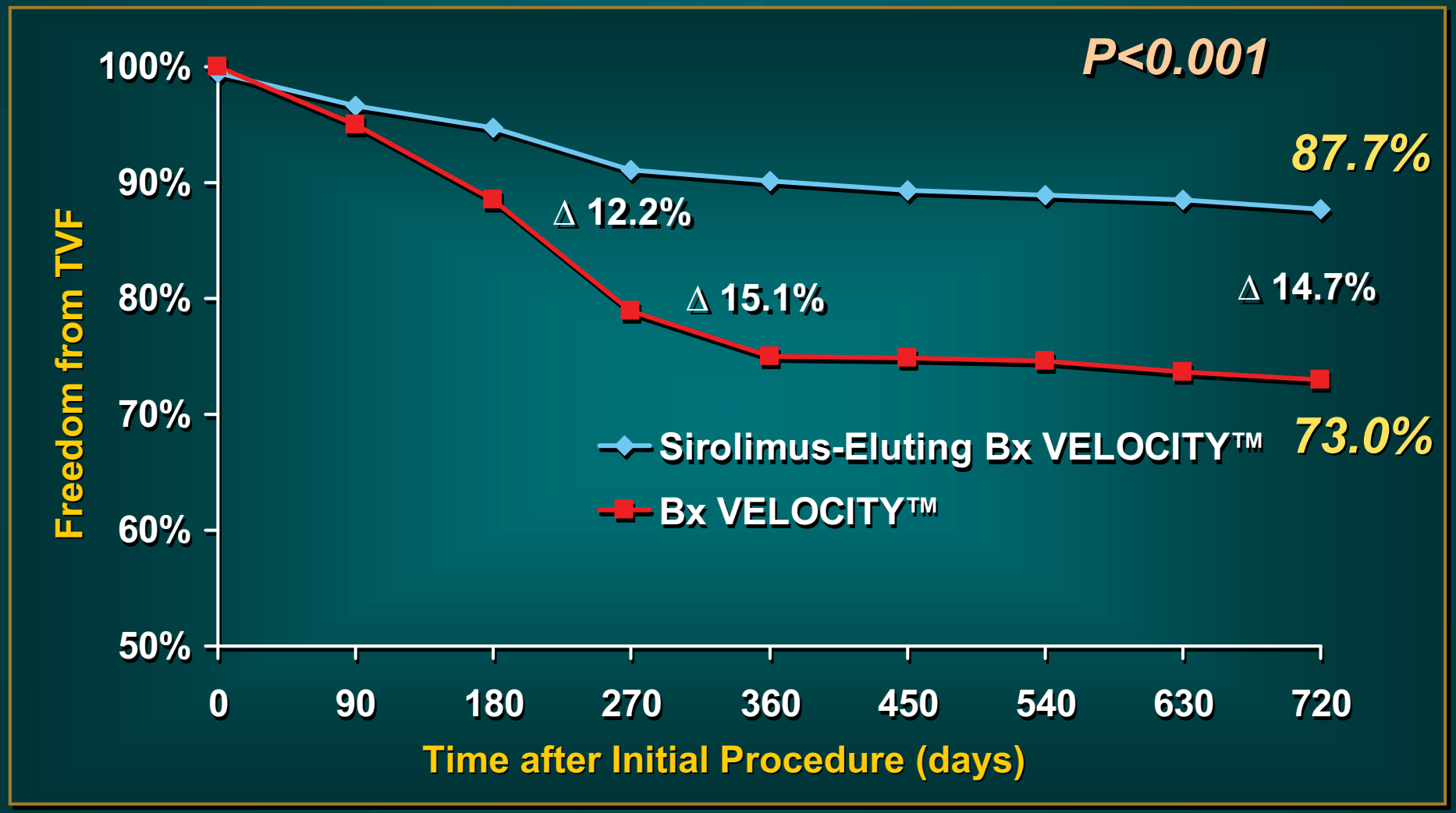
Survival Free from Target Vessel Revascularization – All Patients



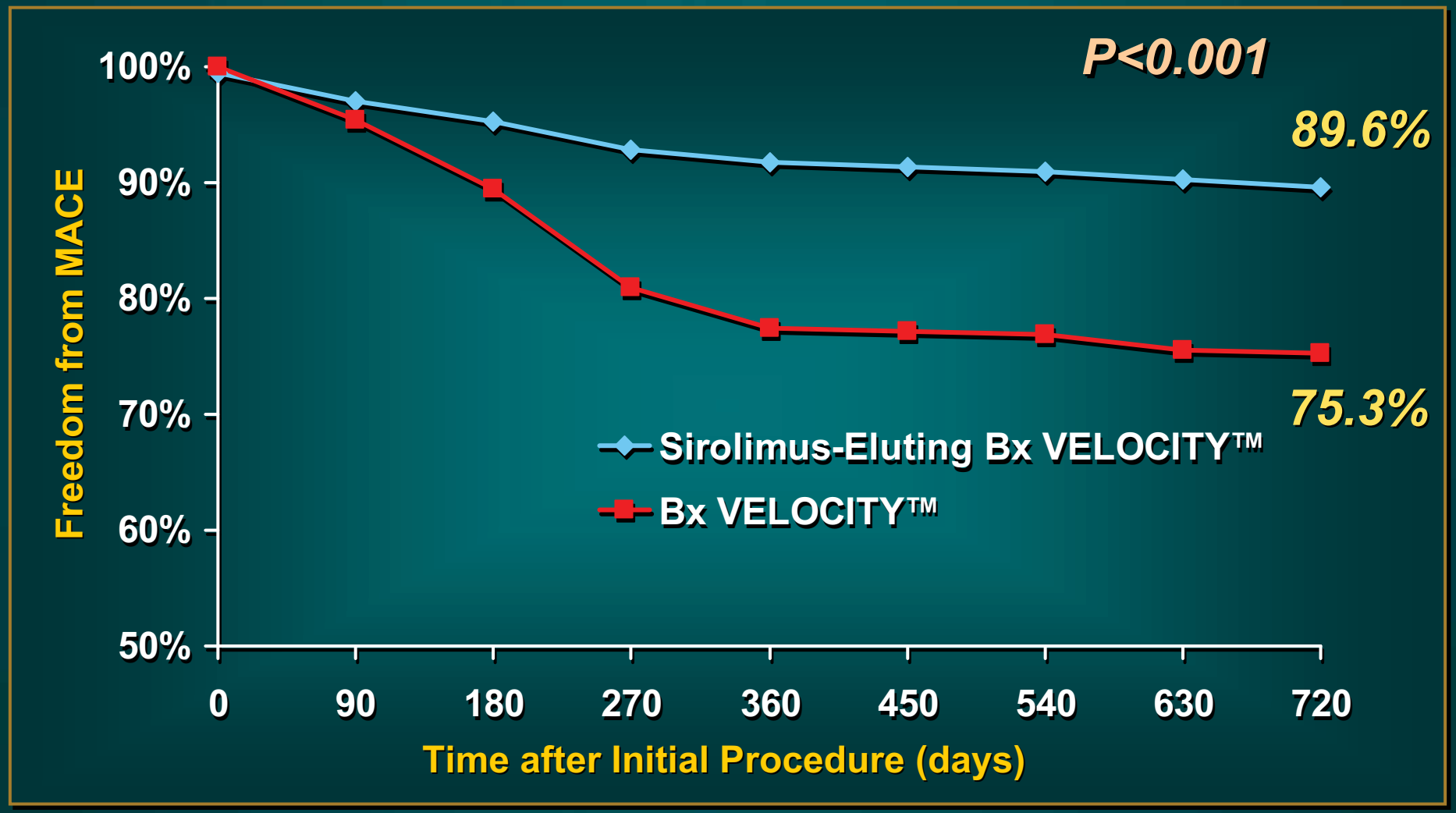
Survival Free from Target Vessel Failure – All Patients



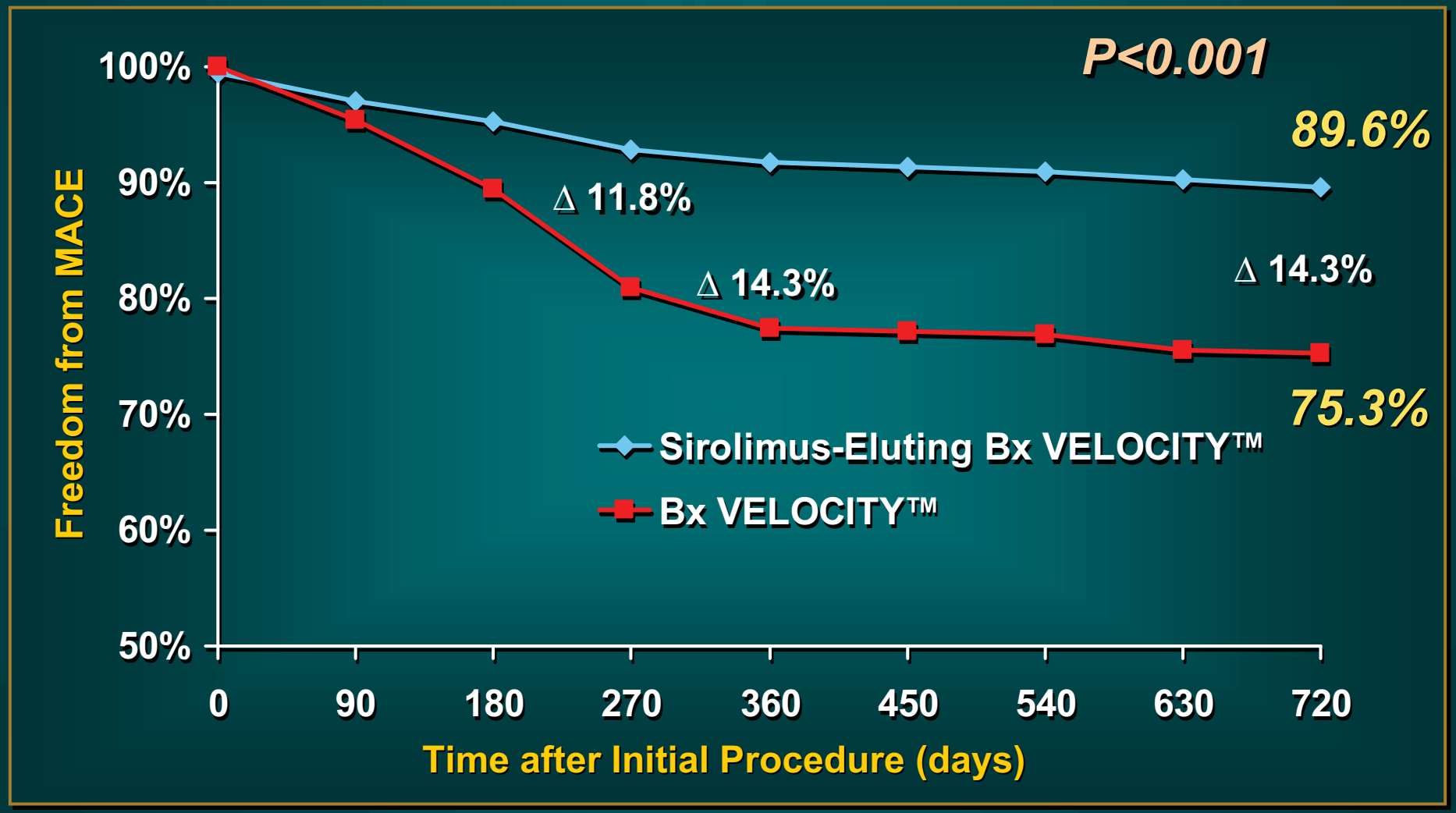
Survival Free from Target Vessel Failure – All Patients



Survival Free from Major Adverse Cardiac Events – All Patients



Survival Free from Major Adverse Cardiac Events – All Patients



There is a Changing Pattern of In-Stent Restenosis

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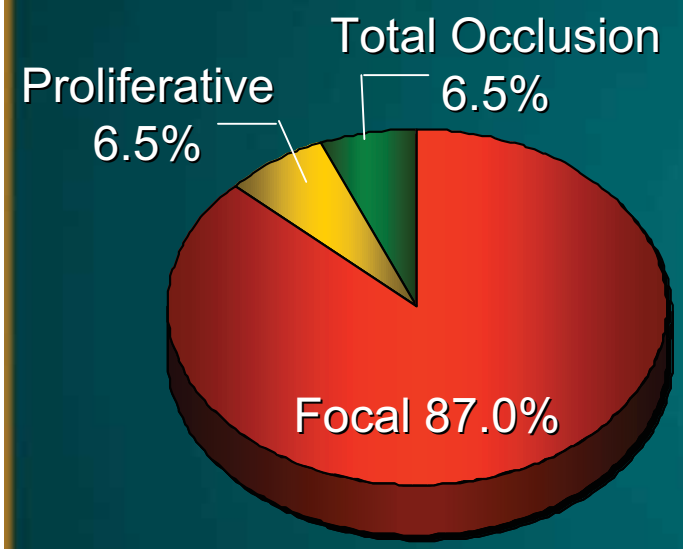
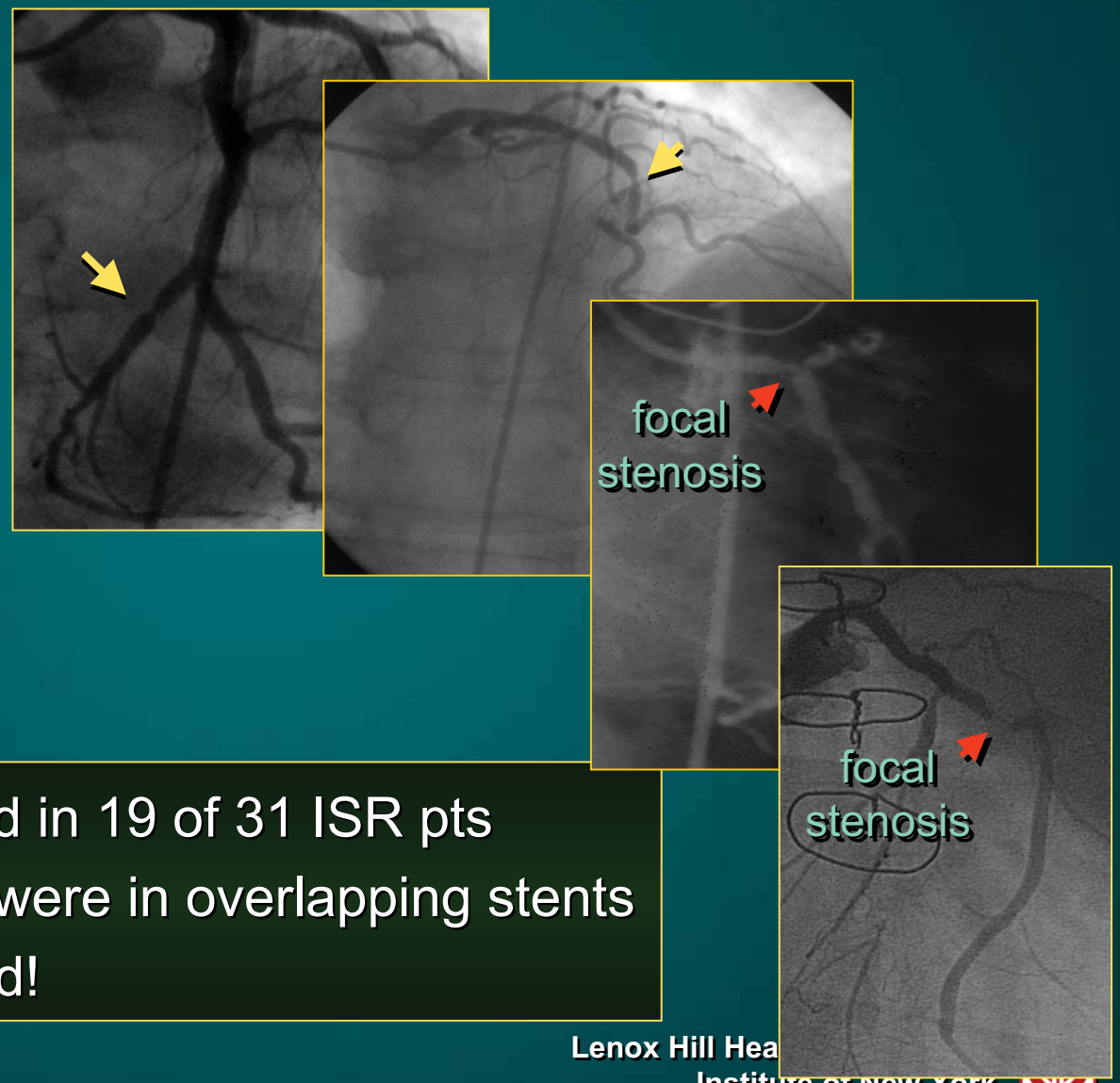
SIRIUS: Mode of Failure

Pattern of Restenosis in SIRIUS (n=31)



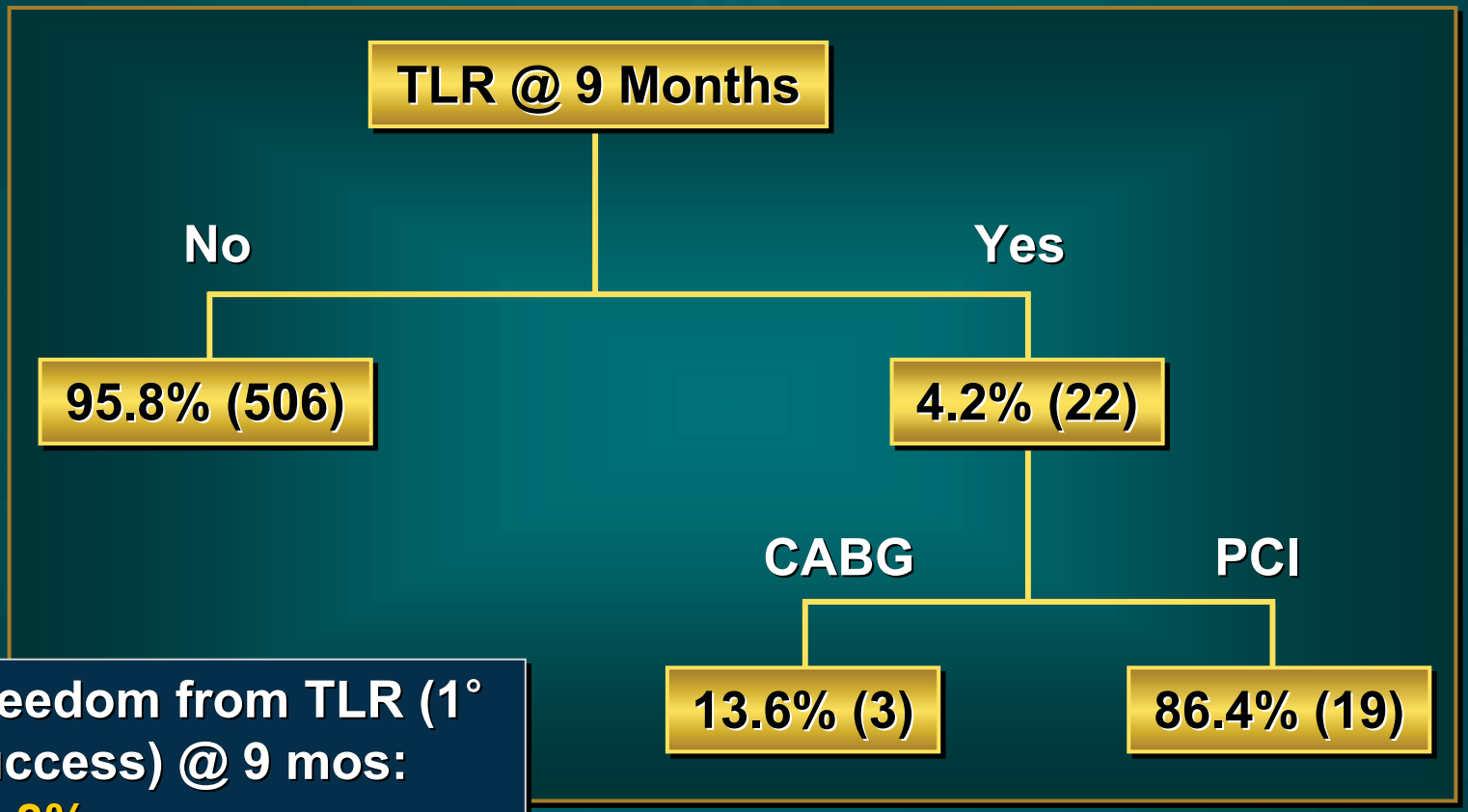


- Margin ISR was noticed in 19 of 31 ISR pts
- 8 of 11 intra-stent ISR were in overlapping stents
- Diffuse ISR is abolished!

What is the Fate of ISR in DES?

SIRIUS – TLR-free at 2 Years

528 Evaluable Sirolimus Patients



Freedom from TLR (1° success) @ 9 mos: 95.8%

SIRIUS

19 Patients with Cypher ISR Treated with PCI
Follow-up to 2 Years

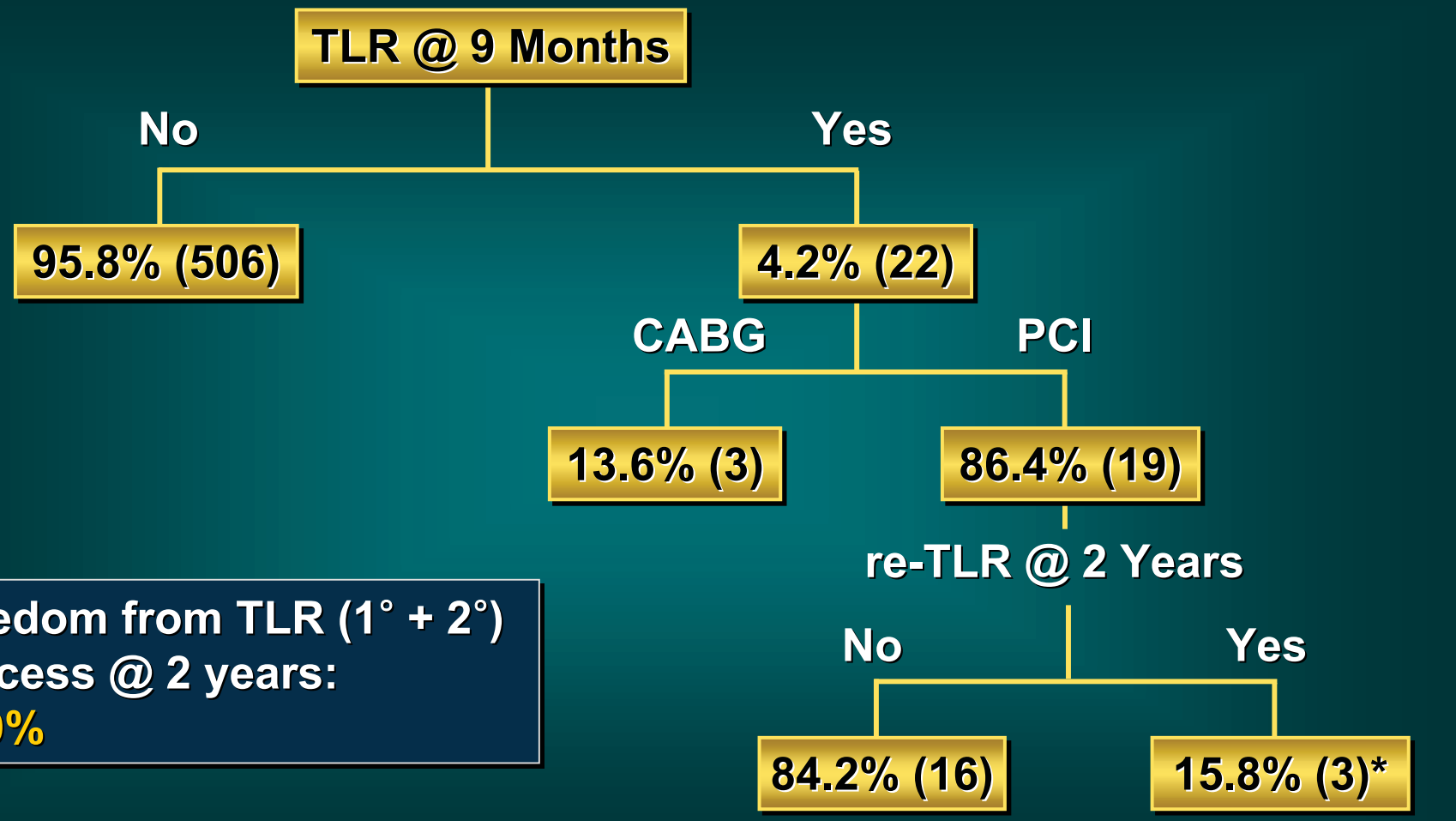
LAD	12
RCA	2
Cx	5
Diabetes	7
Multiple Stents	5
Margin Stenosis	12

Therapy

Bare Stent	15
PTCA (CB)	2
Brachytherapy	2

SIRIUS – TLR-free at 2 Years

528 Evaluable Sirolimus Patients



Freedom from TLR (1° + 2°) success @ 2 years: 98.9%

** Rx = Brachytherapy (2) and CABG (1)*

Outcomes – to 720 Days

No Event	16
PTCA (Brachytherapy)	2 (day 154, 274)
CABG	1

DIRECT :
Direct Stenting Using the Sirolimus-Eluting Bx Velocity™ Stent: Procedural, Clinical, and Angiographic Outcomes Compared to a Predilatation Strategy

J. W. Moses, M.B. Leon, J.J. Popma,
S.A. Cohen, and R.E. Kuntz
(for the DIRECT investigators)

ACC New Orleans
Late Breaking Clinical Trials March 7, 2004

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DIRECT: Background

- Direct stenting (DS) with BMS has modestly reduced procedural time and costs, but not improved long term outcomes
- DS has been discouraged in most DES trials due to fear of possible polymer disruption and reduced drug efficacy
- However, a retrospective analysis of E-SIRIUS suggested possible benefit to DS

DIRECT: Study Follow-up

Direct Stenting n = 225

Clinical FU @ 6 Mo = 92.4%
*Angio FU @ 8 Months =76.4%**

Historic controls from SIRIUS n = 412

Clinical FU @ 6 Mo = 98.0%
Angio FU @ 8 Months =87.1%

* Follow-up ongoing.

DIRECT: Procedural Characteristics

	DIRECT (n=225)	"Controls" (n=412)	P-value
GP 2B 3A	64%	58%	0.15
Max pressure	15.5atm	14.0atm	<0.001
Final balloon (mm)	3.3	3.3	0.4
Stent length (mm)	22.6	21.4	0.04
Stent/Lesion Length	2.1	1.6	0.001
Stent overlap	33.5%	28.2%	0.18

DIRECT: Success Measures

	DIRECT (n=225)	Controls (n=412)	P-value
Device Success (%)	99.6	98.3	0.21
Lesion Success (%)	100.0	99.8	1.00
Procedure Success (%)	99.1	97.3	0.15
Succesful Cypher™ delivery without pre-dilatation (%)*	85.8	-	-
Median Procedure Time (min.)	33	45	<0.01

* 33 out of 34 successful Cypher delivery after pre-dilation with no MACE

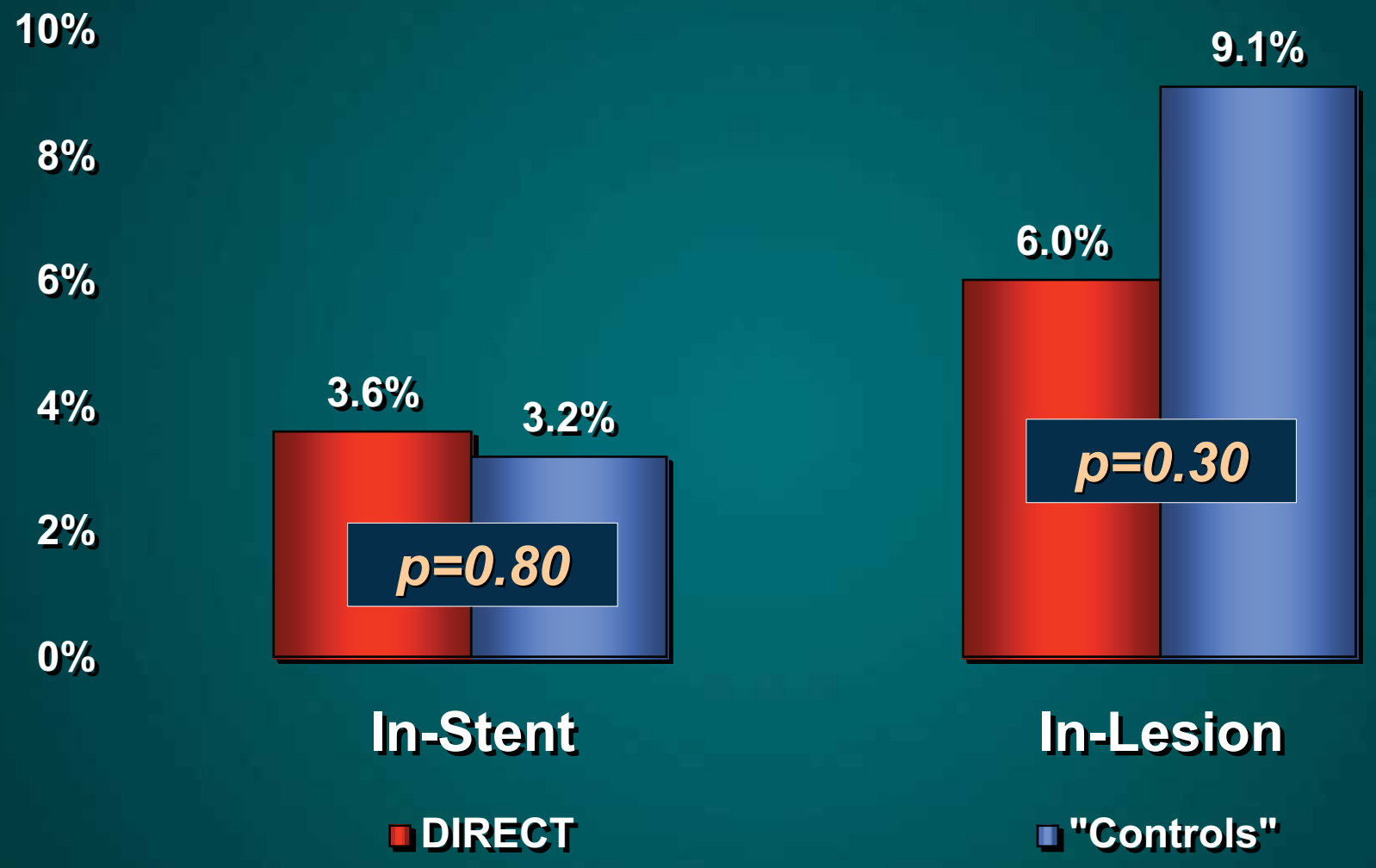
DIRECT: Angiographic Complications

	DIRECT (n=225)	"Controls" (n=412)	P-value
Composite	**1.8%**	**3.7%**	**0.23**
Abrupt Closure	0.0%	0.7%	0.55
Dissection	0.5%	1.5%	0.43
No-reflow	0.0%	0.5%	0.54
Distal emb.	0.0%	0.5%	0.55
Perforation	0.0%	0.0%	-
Thrombus	0.5%	0.2%	1.00
Spasm	0.9%	0.5%	0.62

DIRECT: Clinical Events
All Events (to 6 months)

	DIRECT (n=225)	Controls (n=412)	P-value
30 Day MACE	0.9%	2.4%	0.28
30 MACCE + Angina	20.0%	17.7%	0.38
6 months			
Stent Thrombosis	0.4% (1)	0.2% (1)	0.57
Death	0.4% (1)	0.5% (2)	0.90
MI (all)	0.9% (2)	2.9% (12)	0.18
Q-wave	0.4% (1)	0.7% (3)	0.80
Non Q-wave	0.4% (1)	2.2% (9)	0.16
MACE	2.2% (5)	4.9% (20)	0.21
TLR (all)	1.3% (3)	1.9% (8)	0.70
TVF	3.1% (7)	5.3% (22)	0.38
TVR (non-TLR)	1.3% (3)	1.5% (6)	0.84

DIRECT: 8-mo QCA Binary Restenosis



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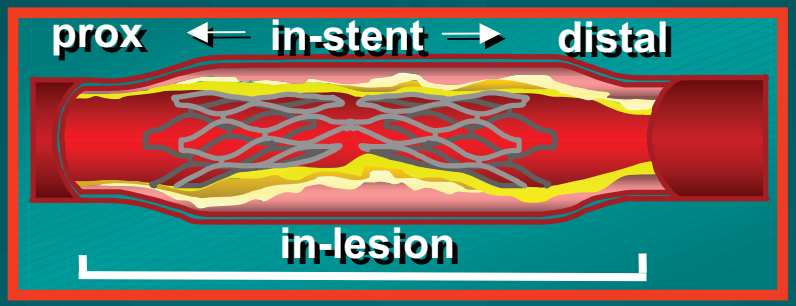
DIRECT: QCA Peri-Stent Analysis

Binary Restenosis (%)

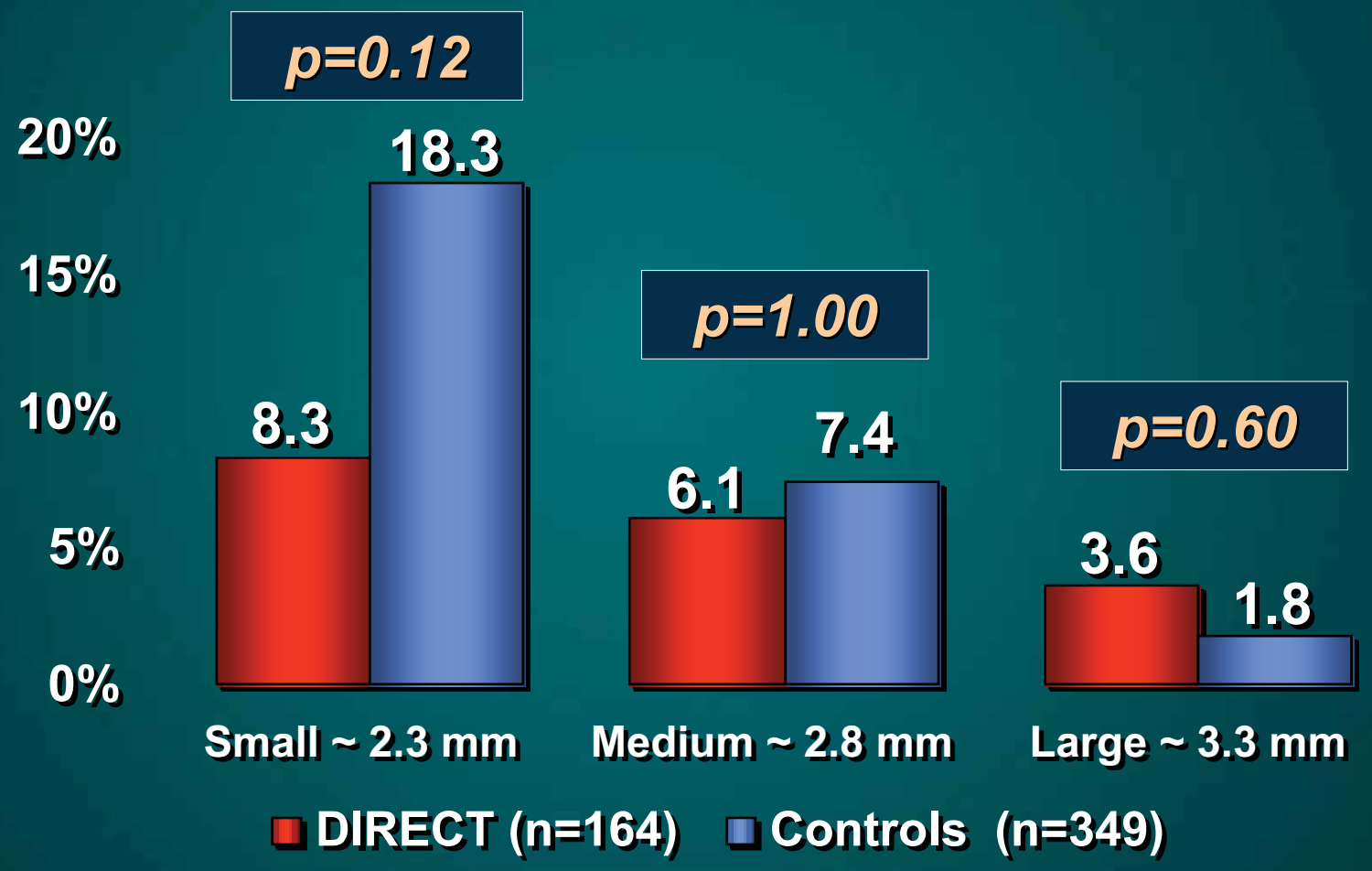


	DIRECT (n=167)	"Controls" (n=412)	P-value
In-stent	3.6	3.2	0.80
Proximal margin	3.1	5.8	0.266
In-lesion	6.0	9.1	0.301
Distal margin	0.0	2.0	0.103

Proximal+distal edge restenosis: 3.1% vs 7.4%, p=0.049

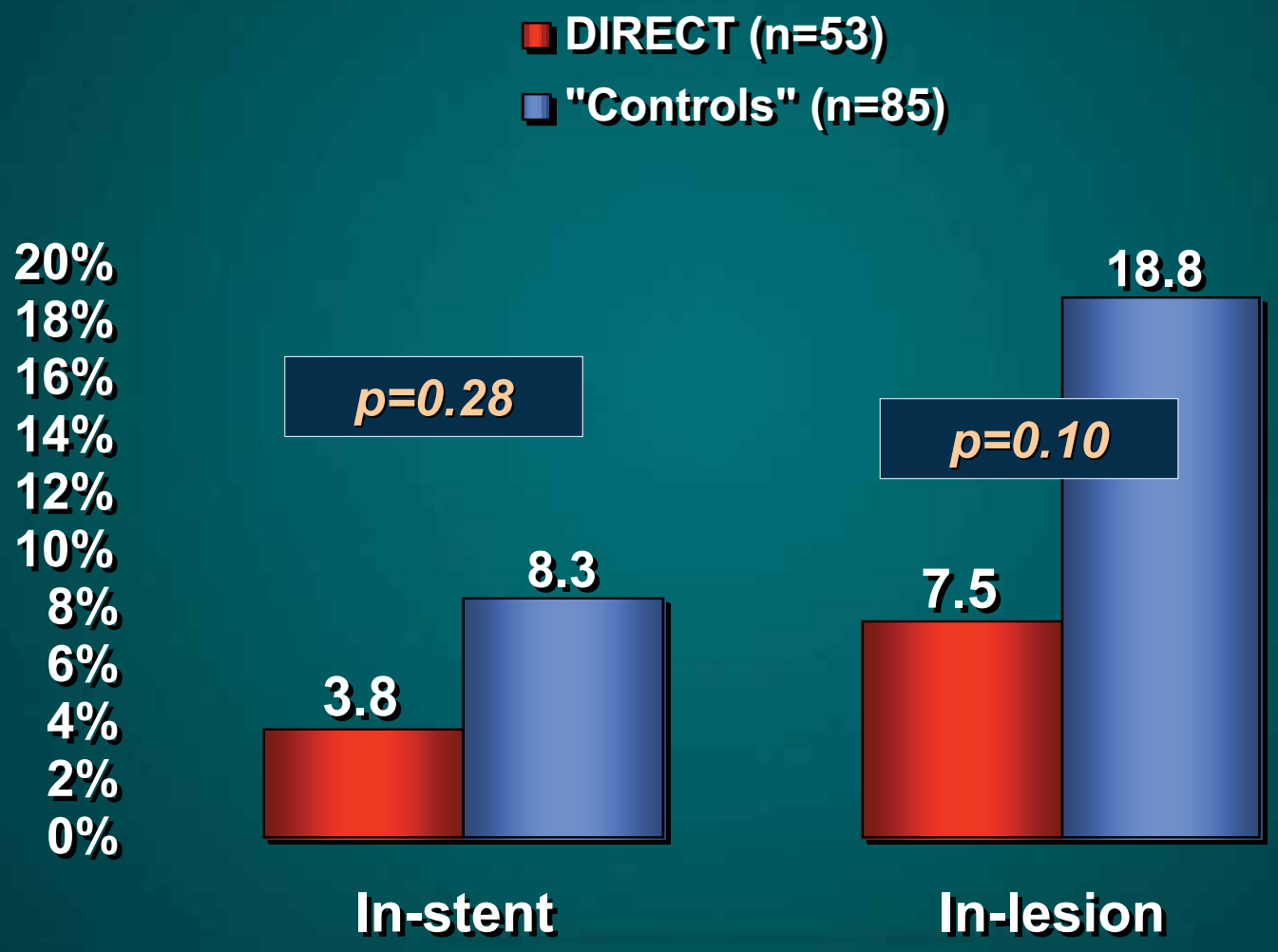
DIRECT: Vessel Size Sub-Analysis

In-Lesion Binary Restenosis



DIRECT: Diabetics

Binary Restenosis



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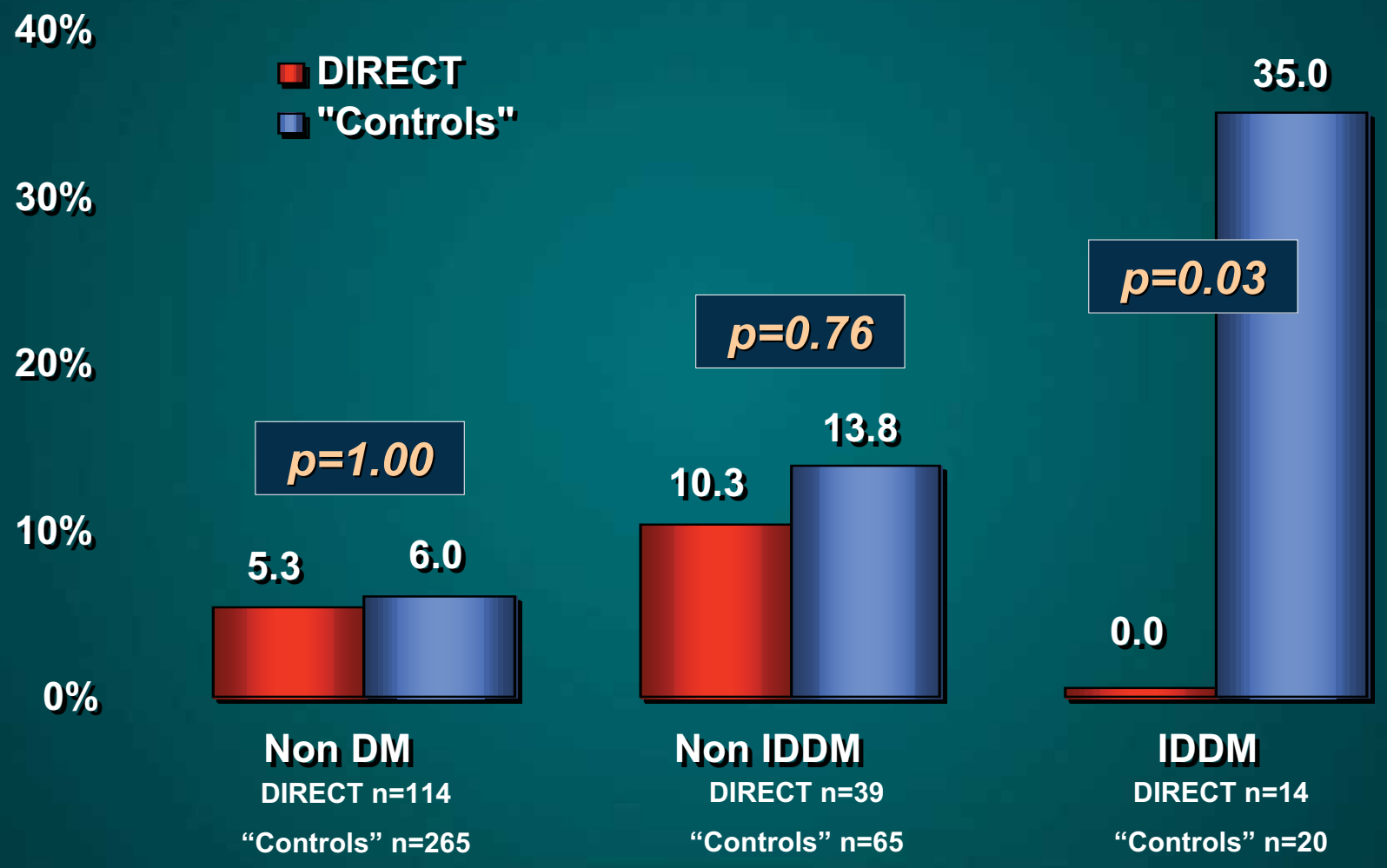
DIRECT: Diabetic Sub Analysis

In-lesion Binary Restenosis



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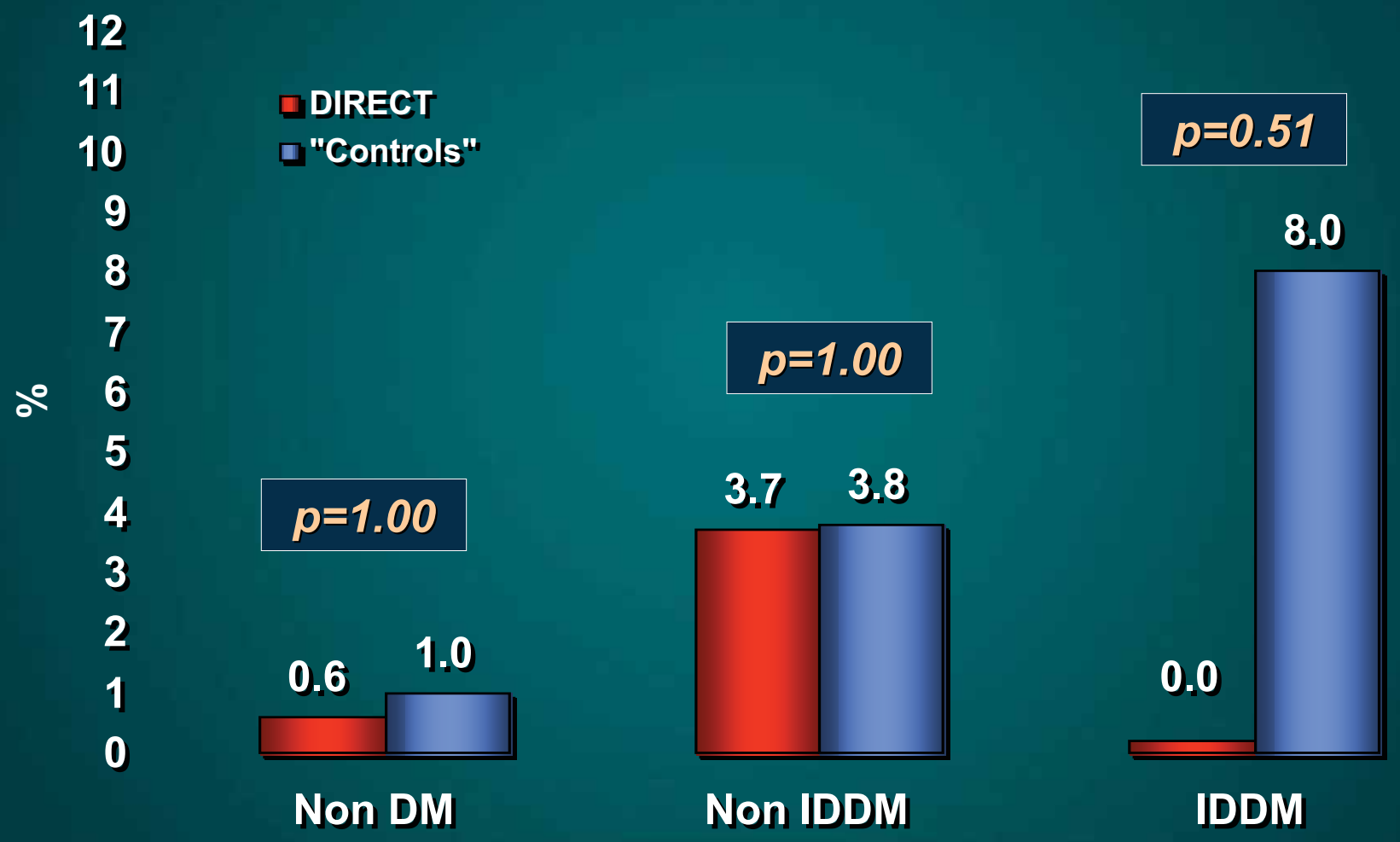
DIRECT: Diabetic Sub Analysis

TLR



Conclusions

1) Cypher is effective across a wide range of lesion subsets
2) The results with Cypher are durable
3) Cypher ISR is generally a benign condition
4) SIRIUS outcomes can be improved upon with technical adjustments