Why Even Favorable 1 year Data from HORIZON Shouldn't Compel DES Usage in AMI

TCT Asia Pacific, 22nd April, 2009

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Should DES be Implanted in patients presenting with AMI?

- Plaque rupture with an underlying necrotic core is the main cause of AMI (75%). *(Arubustini E, et al. Heart 2000)*
- Pathologic studies have shown delayed healing following DES implantation vs. BMS. *(Joner M, et al. J Am Coll Cardiol 2006)*
- Clinical studies are ambiguous but the larger, with long-term follow-up suggest that AMI patients are at greater risk of LST. *(Sianos G, JACC 2006, Daemen J, ESC congress 2007, Steg PG. Euro Heart J 2009)*

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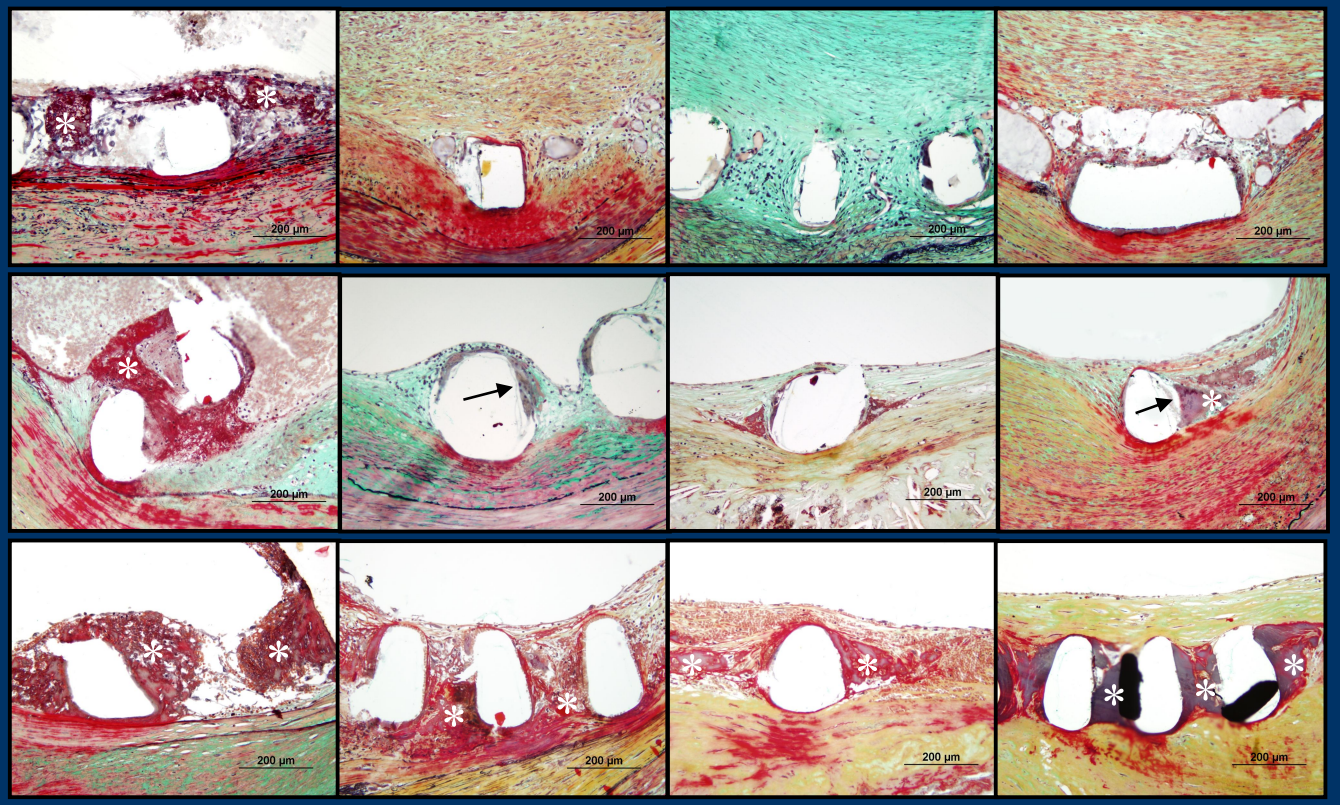
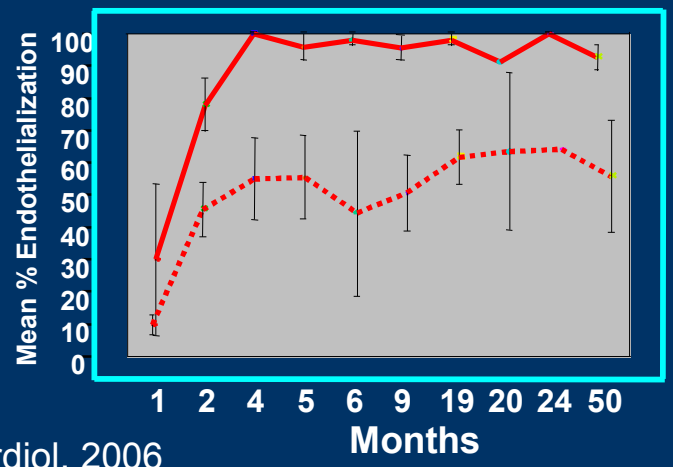
Healing of DES (Cypher and Taxus) vs. BMS in Man



Finn, AV et al. ATVB 2007



* = Fibrin

BMS

DES

Joner M & Finn AV. J Am Coll Cardiol. 2006

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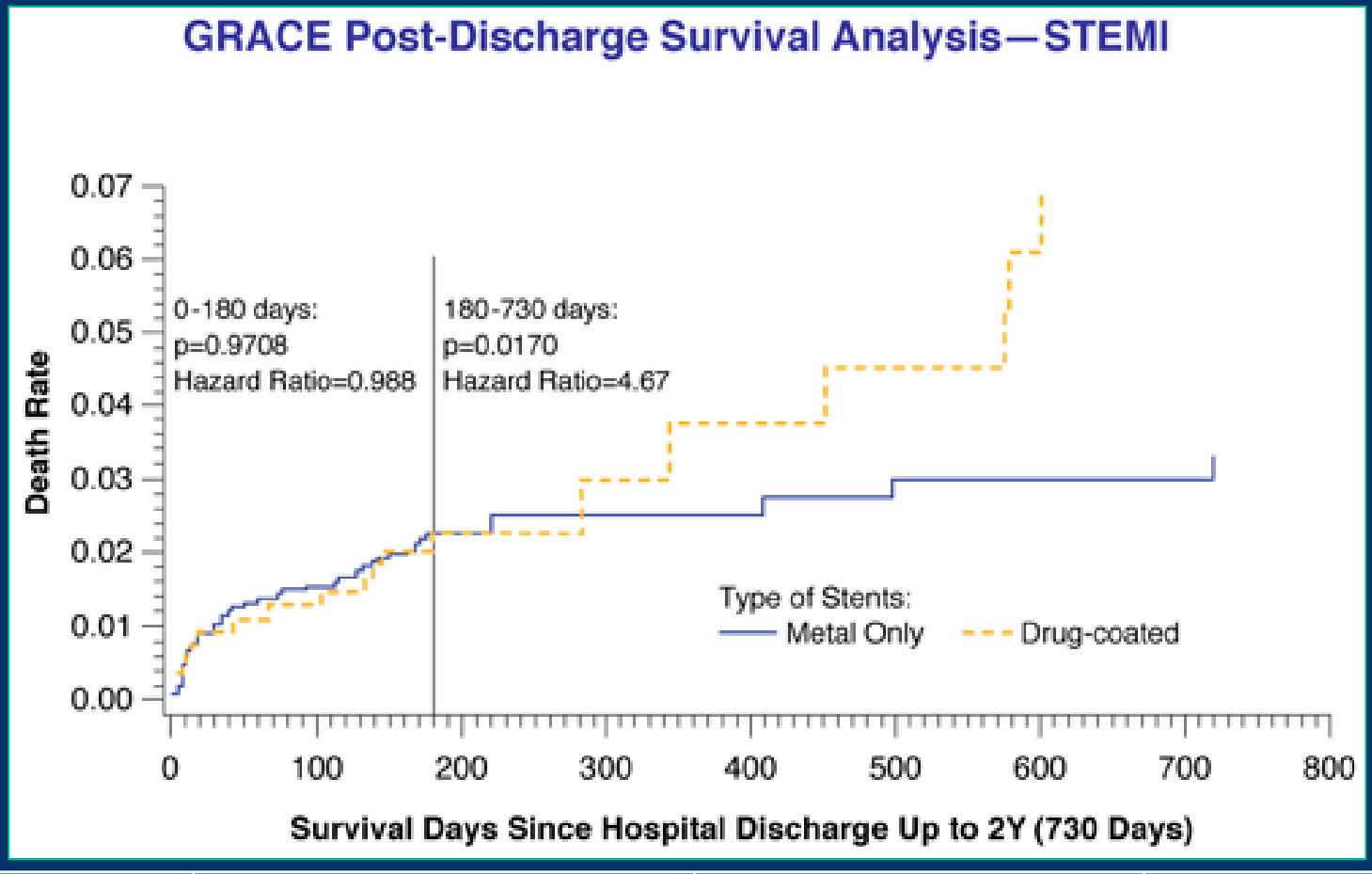
Increased death rate in STEMI patients with DES as compare to BMS



	Discharge to 6 months	6 months – 2 years	1 to 2 years
Hazard ratio (p value)	0.72 (p=0.32)	5.55 (p<0.01)	8.01 (p=0.01)

5093 patients with STEMI

Steg, PG, From GRACE registry, ESC2007

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Conflicting Data... DES is better in AMI?

Table 3. Two-Year Adjusted Clinical Outcomes.

Initial Presentation	2-Year Outcome	Drug-Eluting Stent	Bare-Metal Stent	Absolute Risk Difference	P Value*
		no./total no. (%)		*% (95% CI)*	
Any myocardial infarction					
	Death	276/2570 (10.7)	330/2570 (12.8)	–2.1 (–3.8 to –0.4)	0.02
	Recurrent myocardial infarction	227/2570 (8.8)	263/2570 (10.2)	–1.4 (–3.0 to 0.2)	0.09
	Repeat target-vessel revascularization	247/2570 (9.6)	373/2570 (14.5)	–4.9 (–6.7 to –3.1)	<0.001
Myocardial infarction with ST-segment elevation					
	Death	110/1298 (8.5)	150/1298 (11.6)	–3.1 (–5.4 to –0.8)	0.008
	Recurrent myocardial infarction	91/1298 (7.0)	104/1298 (8.0)	–1.0 (–3.0 to 1.0)	0.34
	Repeat target-vessel revascularization	132/1298 (10.2)	181/1298 (13.9)	–3.8 (–6.2 to –1.3)	0.003

Mauri L et al. N Engl J Med 2008;359:1330-1342

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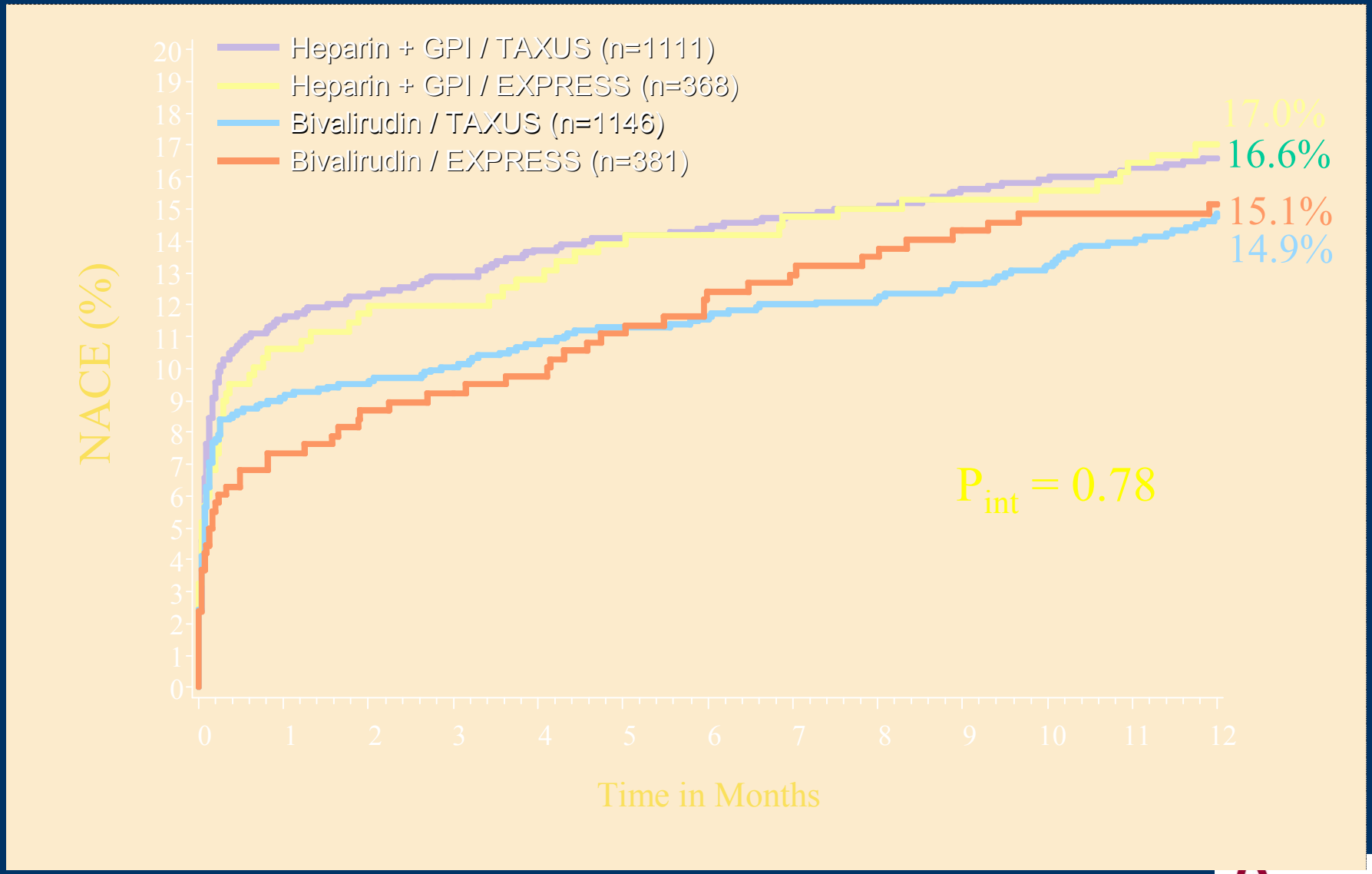
1-Year Net Adverse Clinical Events*



* MACE (death, reinfarction, ischemic TVR or stroke) or major bleeding (non CABG)

HORIZION Trial

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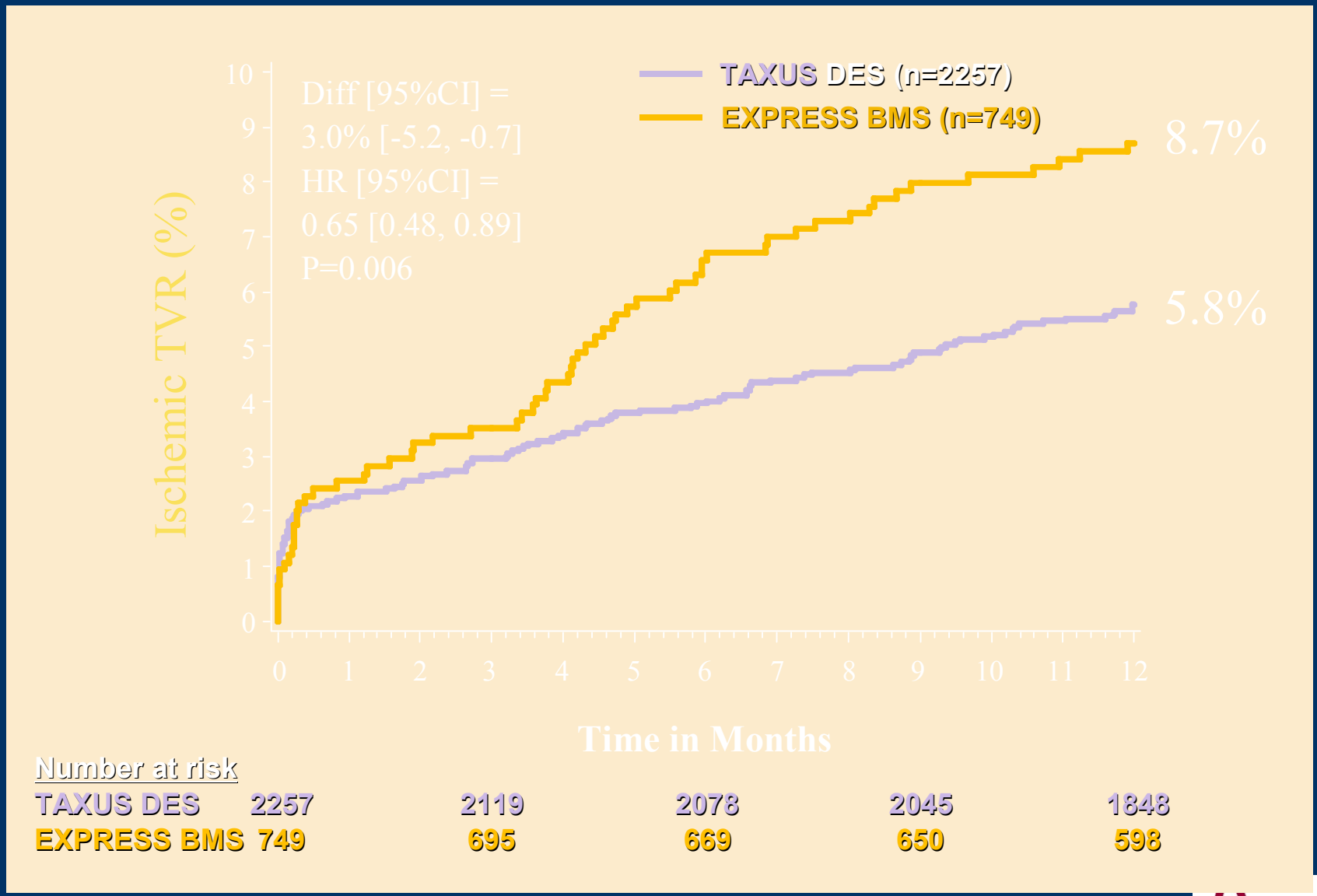
Secondary Efficacy Endpoint: Ischemic TVR



HORIZION Trial

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Should we be using DES in all lesions "on label" and "off label"?

What has been accomplished by use of DES …

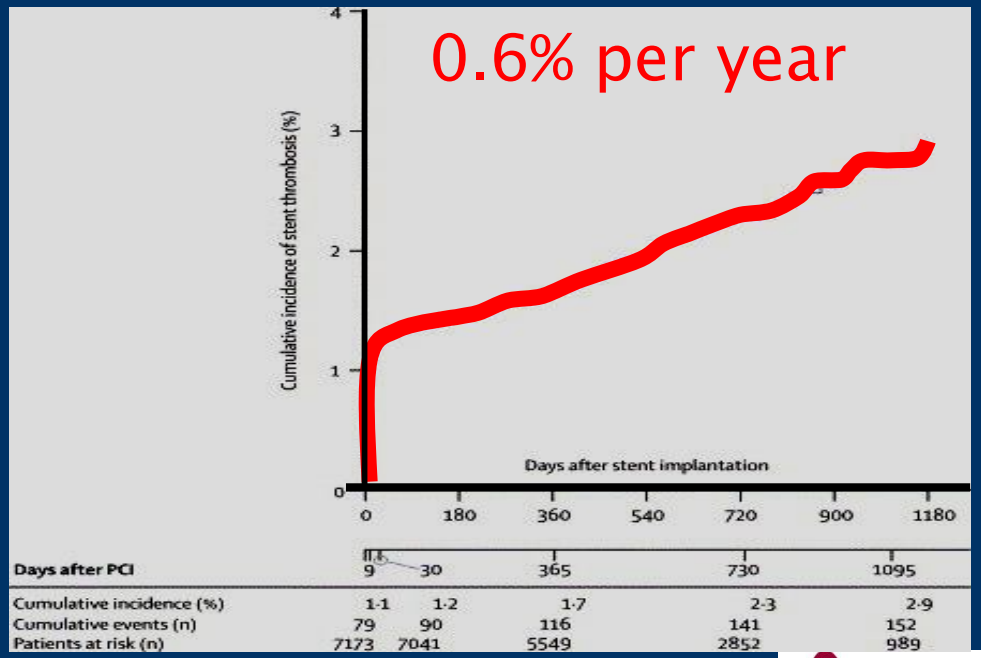
Dramatic reduction in restenosis rates as compared to BMS

But the problem is…

Late thrombosis has emerged as a safety concern

"Off Label"

- AMI
- Bifurcation
- LM
- Long lesions
- Saphenous vein grafts



Daemen J et al. Lancet 2007; 369: 667

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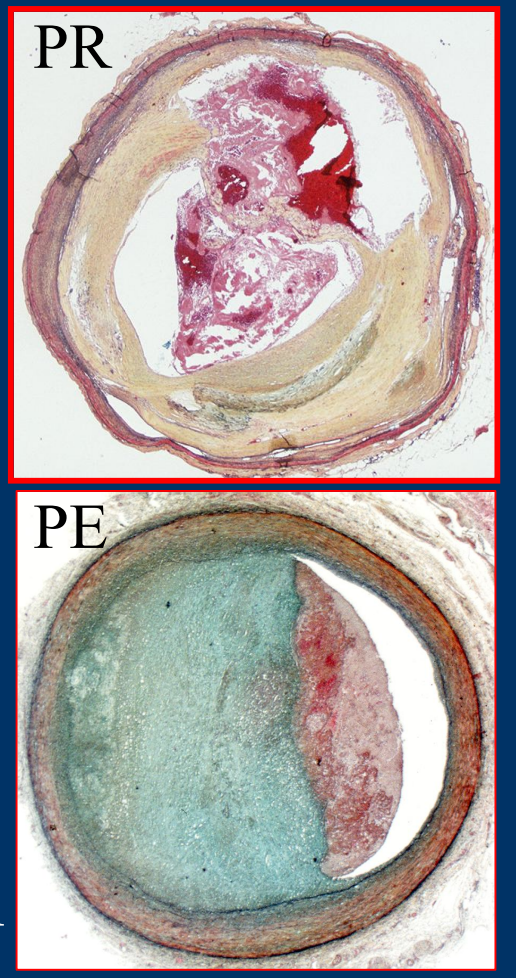
What have we learnt from Pathology Studies?

- The main cause of Acute Myocardial Infarction is Plaque Rupture (PR) (75-80%)
- The second most frequent is plaque erosion (PE)
- Clinical and autopsy studies have shown that the underlying luminal narrowing in patients presenting with AMI is at least in ~50% of cases - <50% diameter stenosis



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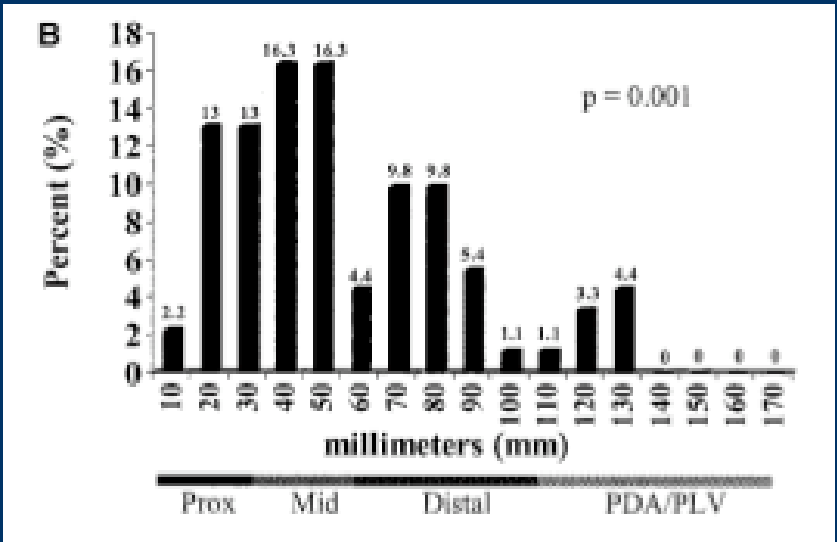
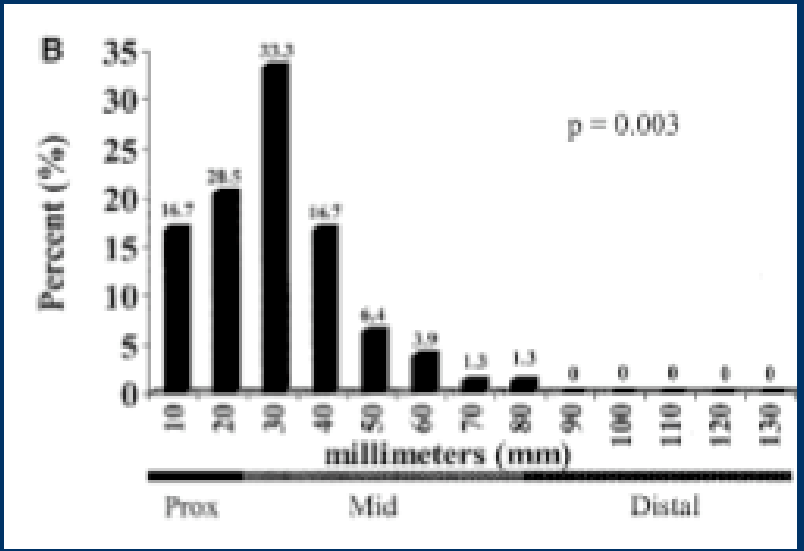
Location of Thrombus in STEMI

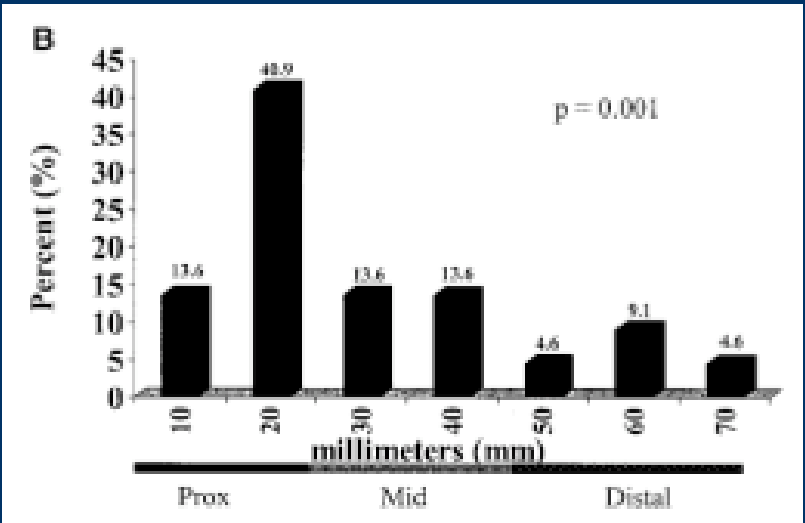
RCA



LAD



LCX



CA vessel diameter
3.15 ± 0.37 mm

Antoniucci D, et al. Catheter Cardiovasc Interv. 2000

Wang JC, et al. Circulation 2004

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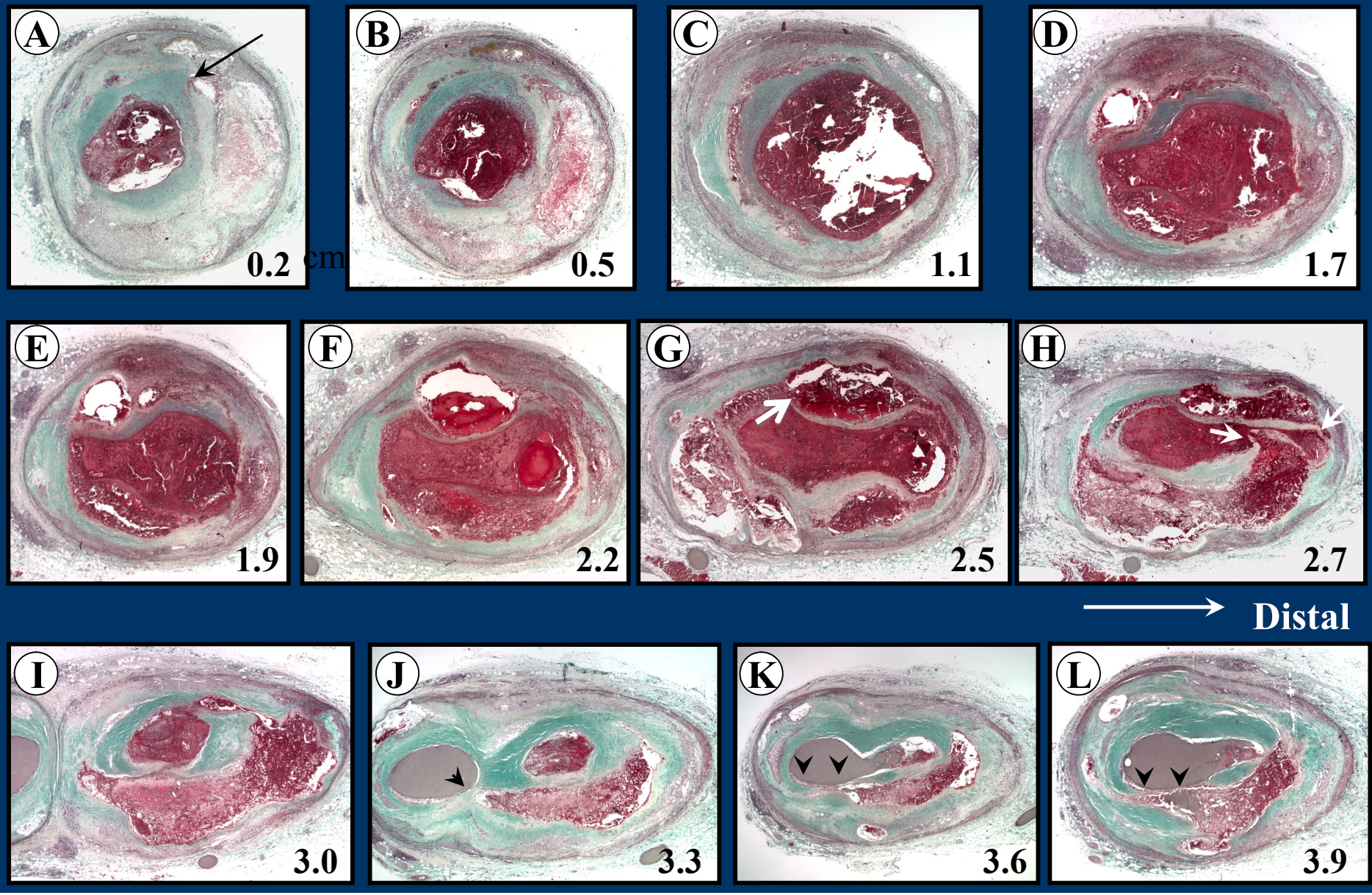
Serial Coronary Sections (cm) Demonstrating Extent of Thrombus With Propagation Proximal and Distal to Rupture Site

Proximal LCx



Frequency Distribution of % X-sectional Area Stenosis by Plaque in Coronary Thrombosis

% stenosis	Age (years)	Plaque Erosion	Plaque Rupture	All cases
50-59	42±5	3 (14%)	1 (4%)	4 (8%)
60-69	46=7	5 (23%)	4(14%)	9 (18%)
70-79	49±21	10 (45%)	11 (39%)	21 (42%)
80-89	50±50	3 (14%)	5 (18%)	8 (16%)
90-99	52±16	1 (5%)	7 (25%)	8 (16%)
Total	49±10	22 (100%)	28 (100%)	50 (100%)

68%: not severely narrowed

Farb A, et al. Circulation 1996

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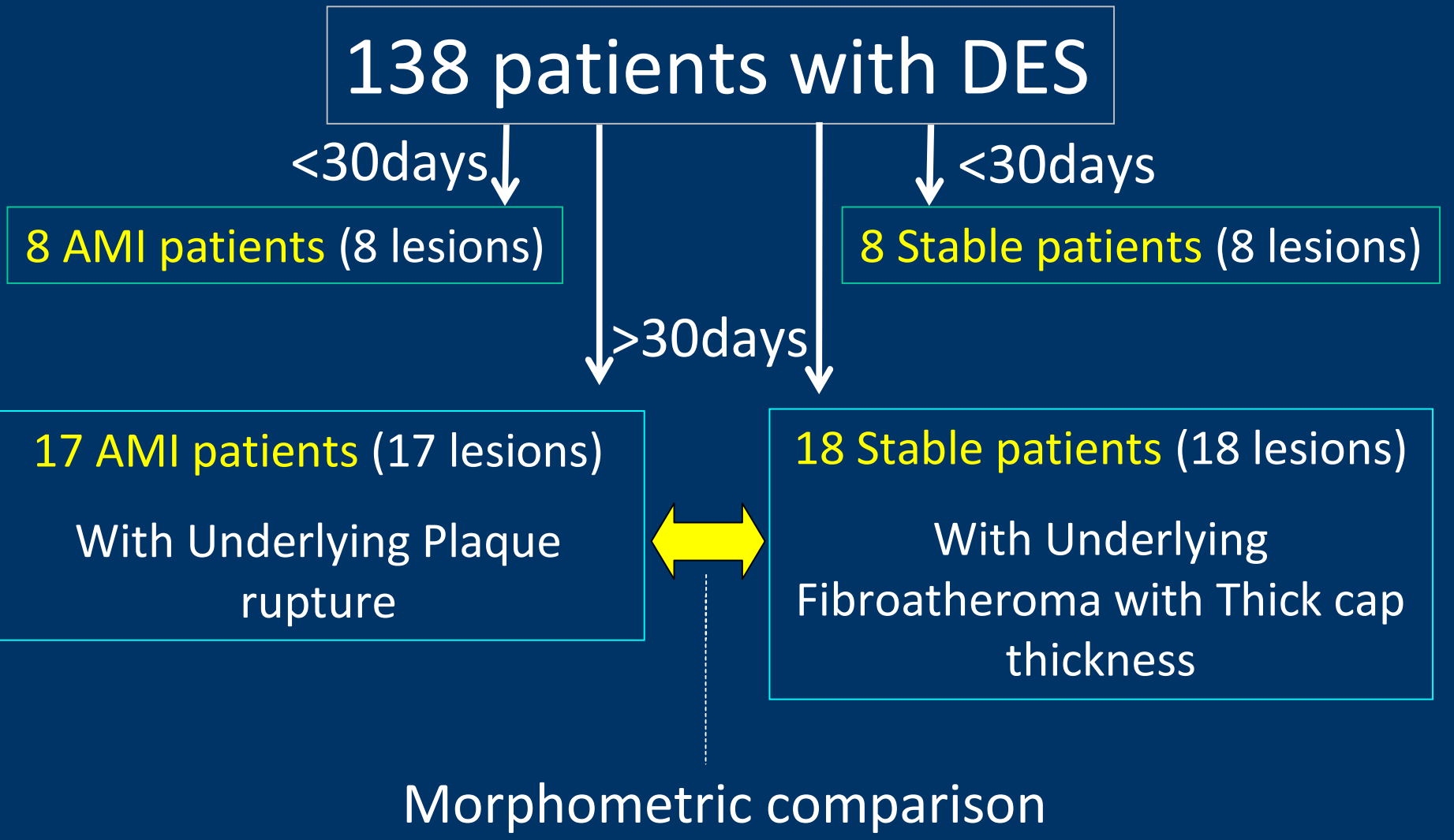
Study design



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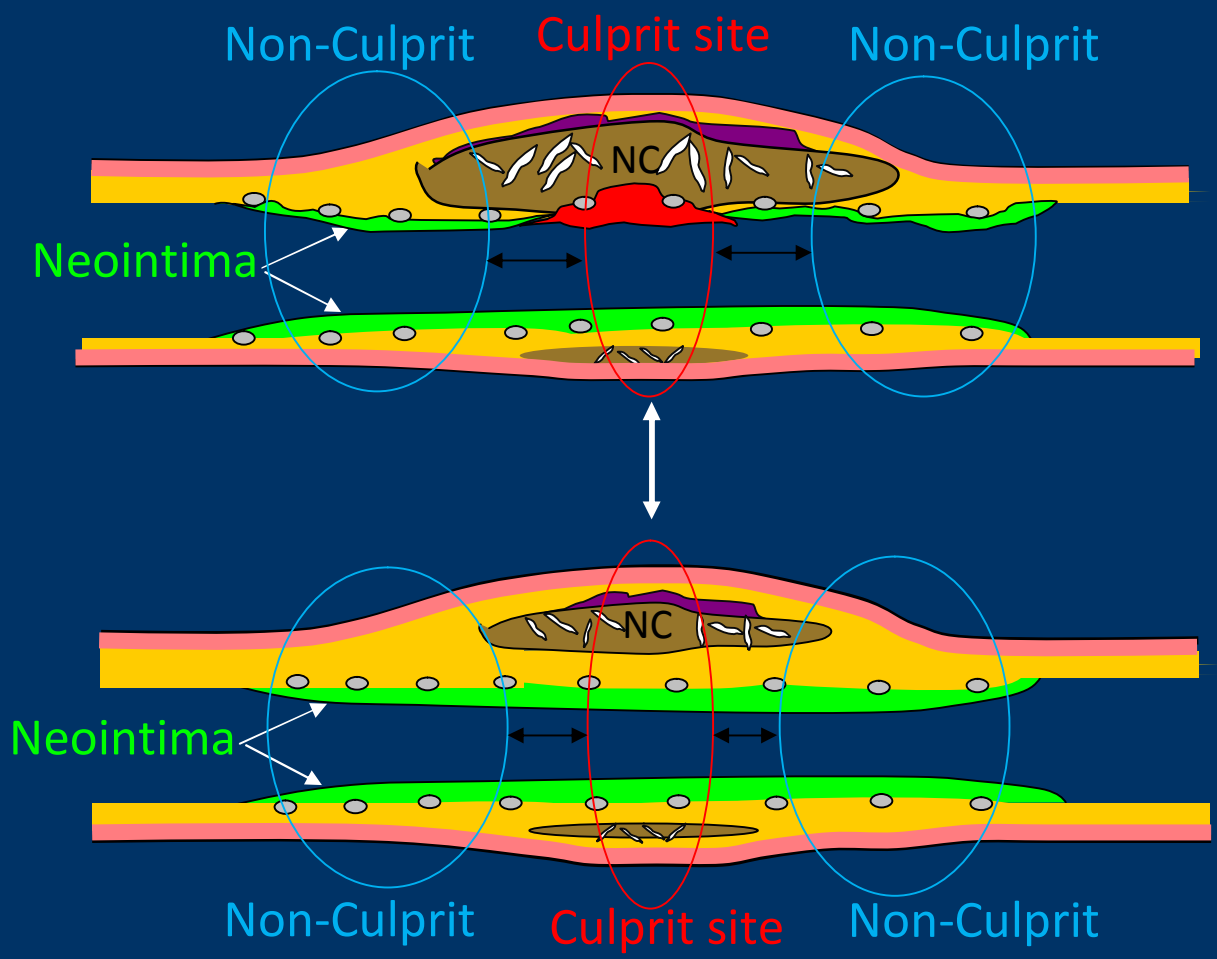
Morphometric comparison



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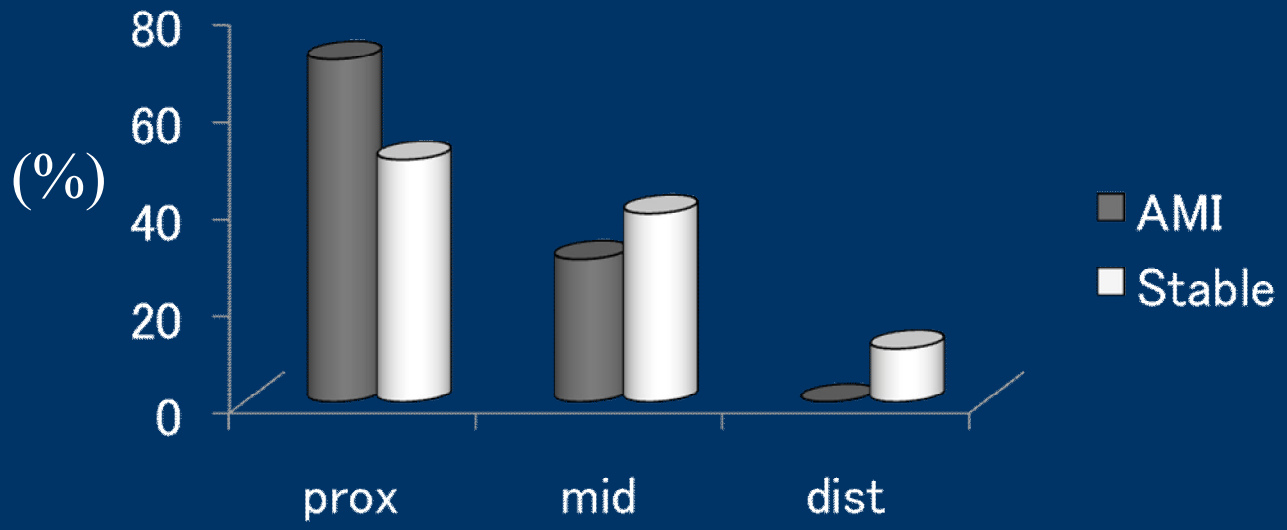
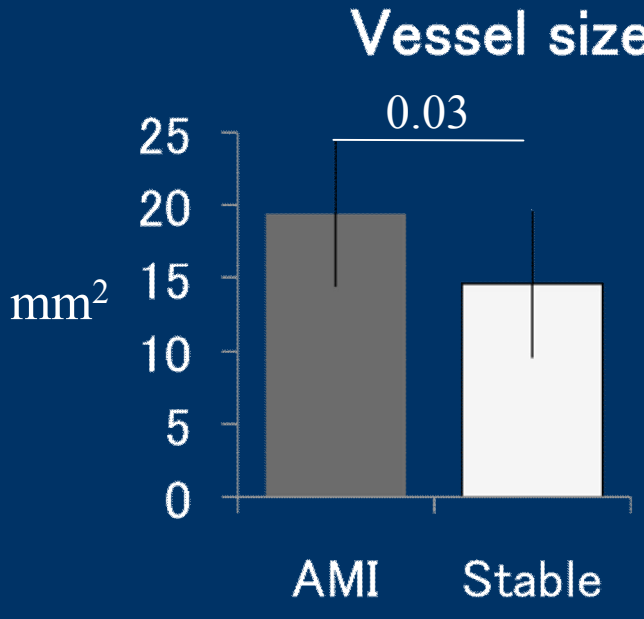
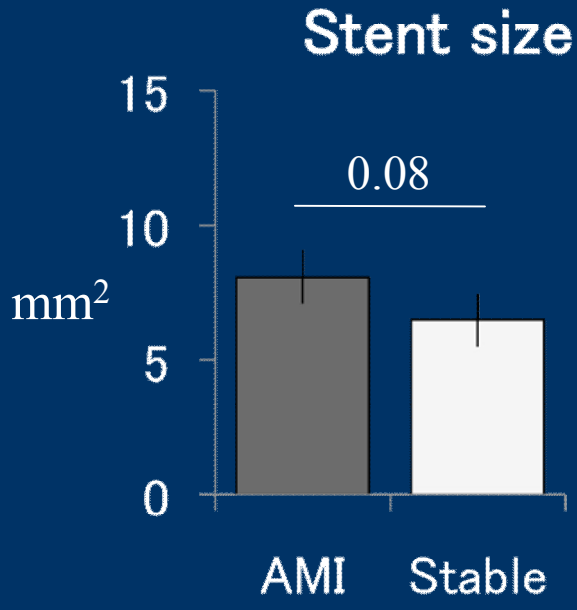
AMI lesions are located more in the proximal Segments







Data from Nakazawa et al. Circulation 2008

Patient / Lesion Characteristics >30days

	AMI Patients N=17	Stable Patients N=18	p value
Age, yrs	58 ± 15	57 ± 11	0.80
Male gender, %	82	89	0.33
Stent duration, day	270 (65, 465)	315 (113, 570)	0.36
Cypher / Taxus	7 / 10	9 / 9	0.34
Number of stents	1.5 ± 1.0	1.2 ± 0.4	0.26
Stent length, mm	22.0 (20.0, 44.0)	22.0 (15.3, 32.3)	0.16
Late Thrombosis, %	41	11	0.04
Very Late	12	0	0.13
Restenosis, %	0	6	0.32

Nakazawa, G et al. Circulation 2008

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Underlying Plaque Morphology (AMI vs. Stable >30 days)

	AMI lesions (n=17)	Stable lesions (n=18)	p value
EEL, mm^2	19.4 ± 7.1	14.6±4.8	0.03
Stent Area, mm^2	7.3 (5.7, 9.3)	5.7 (5.1, 8.0)	0.08
Plaque Area, mm^2	11.2 ± 4.5	8.1±3.6	0.03
Necrotic Core Area, mm^2	2.6 (1.8, 4.4)	1.0 (0.6, 1.4)	<0.0001
% NC area	31 ± 11	16 ± 9	<0.0001
NC Arc, º	180 (180, 270)	90 (90, 180)	<0.0001
Fibrous cap thickness, µm	55 ± 24*	286 ±118	<0.0001
Longitudinal NC length, mm	16.2 ± 8.3	10.0 ± 4.9	0.01
Rupture site length, mm	6.3 (2.9, 8.6)	0	<0.0001
% Struts penetrating NC	30 (15, 39)	0	0

* = remnants of fibrous cap

Nakazawa, G et al. Circulatio

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Morphometry and Pathologic Assessment at Culprit Site (AMI vs. stable patients)

	AMI with rupture (n=17)	Stable with FA (n=18)	p value AMI vs. Stable
Neointimal thickness, mm	0.04 (0.02, 0.09)	0.11 (0.07, 0.21)	**0.008**
Strut with fibrin deposition, %	63 ± 28	36 ± 27	**0.008**
Strut with inflammation, %	35 (27, 49)	17 (7, 25)	**0.003**
Uncovered strut, %	49 (16, 96)	9 (0, 39)	**0.01**

Nakazawa, G et al. Circulatio

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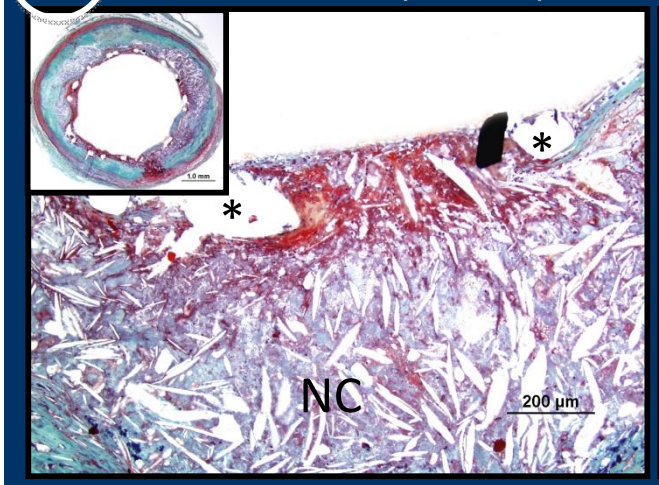
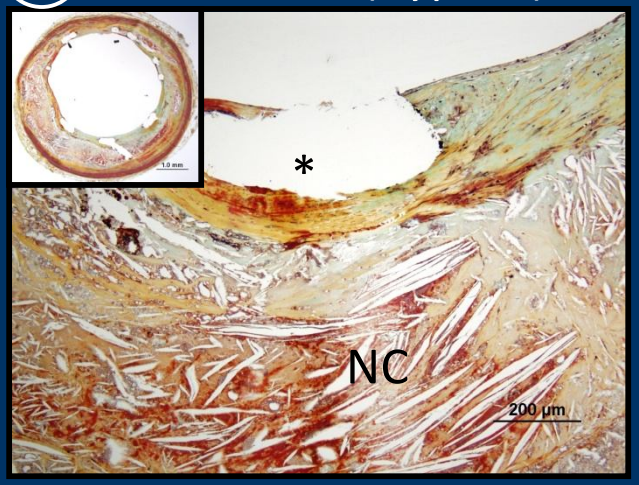
AMI lesions (with Plaque Rupture)

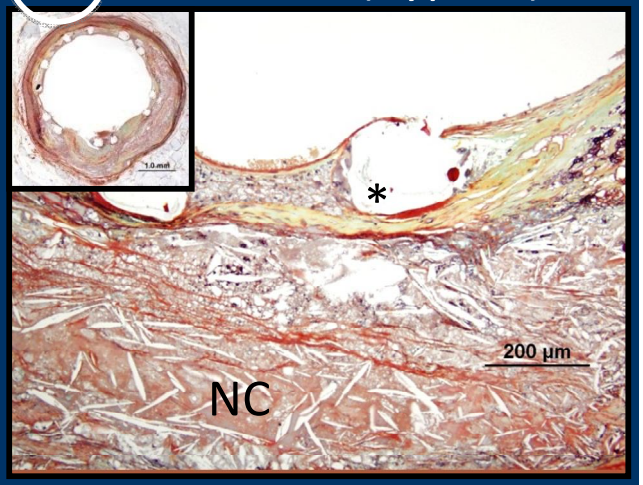
A 9 months (Taxus)



B 13 months (Cypher)

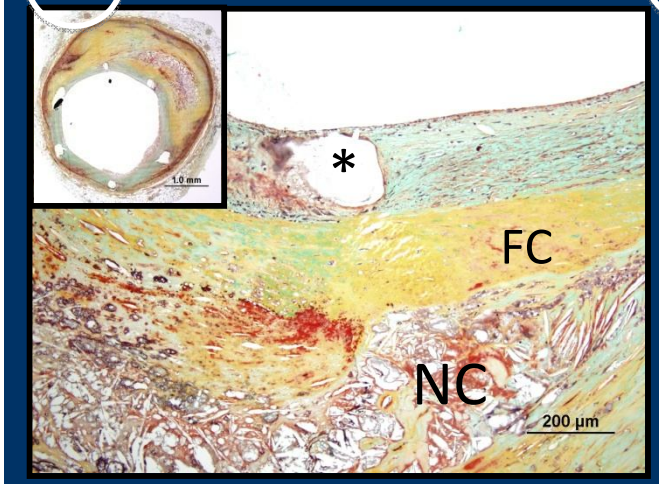


C 24 months (Cypher)

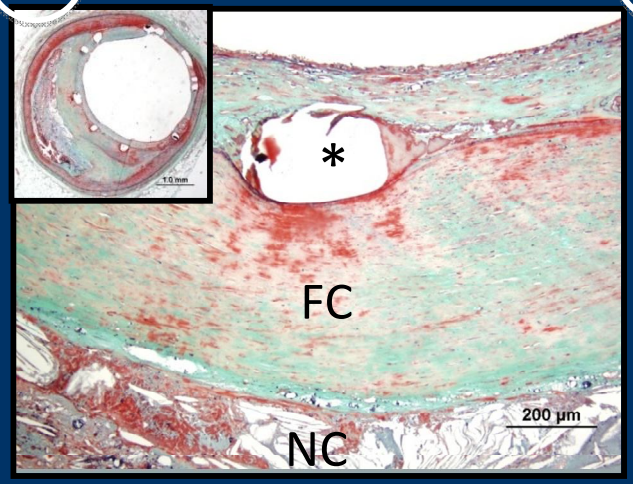


Stable Lesions (with Fibroatheroma and thick cap)

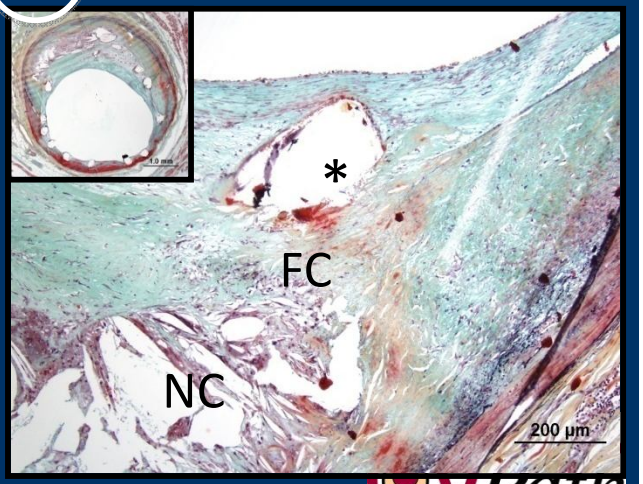
D 7 months (Cypher)



E 18 months (Taxus)



F 19 months (Cypher)



Nakazawa, G et al. Circulatio

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Morphometry and Pathologic Assessment (Culprit vs. Non-Culprit in AMI)

	AMI Patients with rupture		p value Culprit vs Non-Culprit
	Culprit	Non-Culprit	
Neointimal thickness, mm	0.04 (0.02, 0.09)	0.07 (0.04, 0.20)	**0.008**
Strut with fibrin deposition, %	63±28	52±27	**0.04**
Strut with inflammation, %	35 (27, 49)	30 (13, 38)	**0.04**
Uncovered strut, %	49 (16, 96)	19 (3, 34)	**0.02**

Nakazawa, G et al. Circulation 2008

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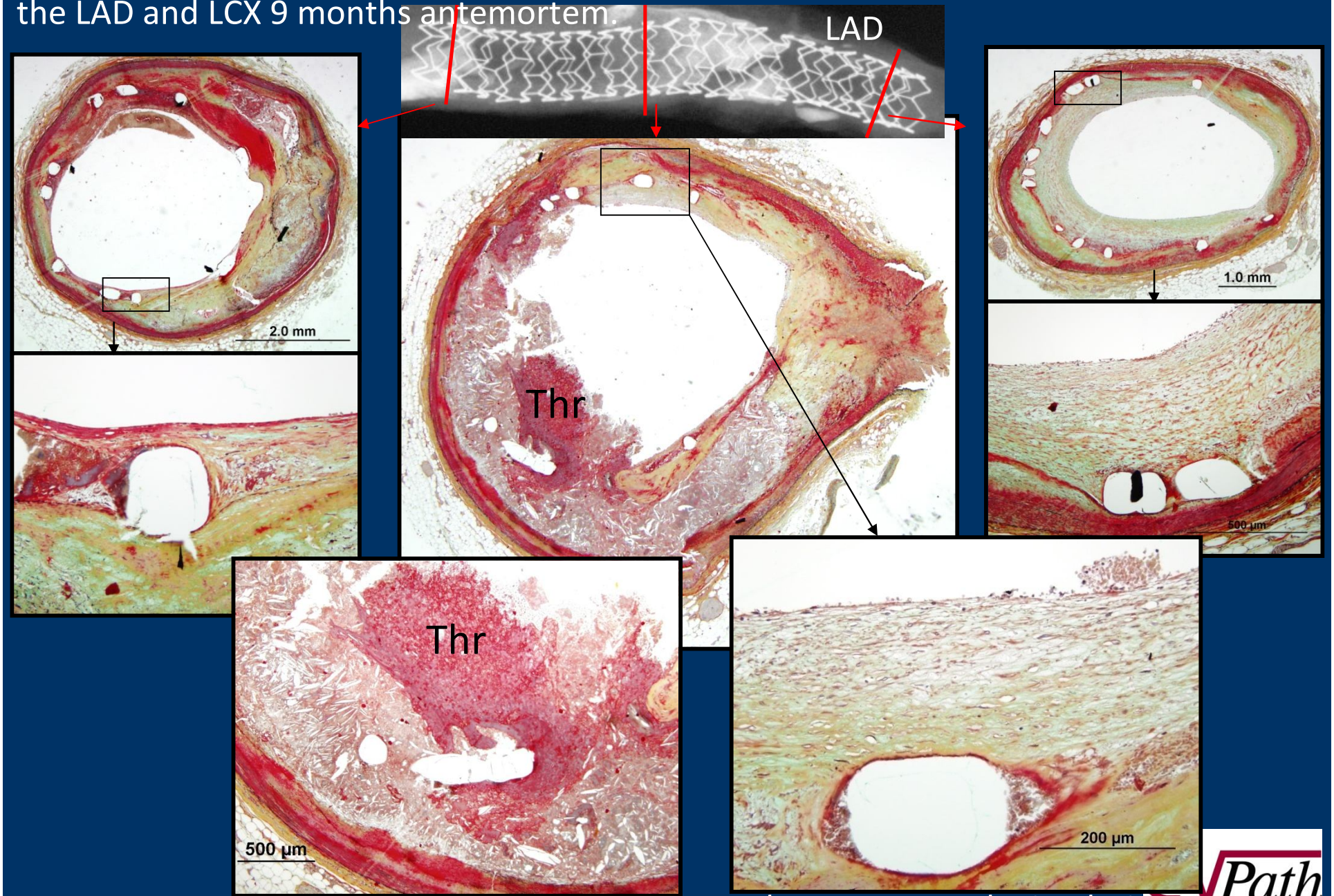
65 yrs old male, presenting acute coronary syndrome, stent (Taxus) implantation in the LAD and LCX 9 months antemortem.



Nakazawa, G et al. Circulatio

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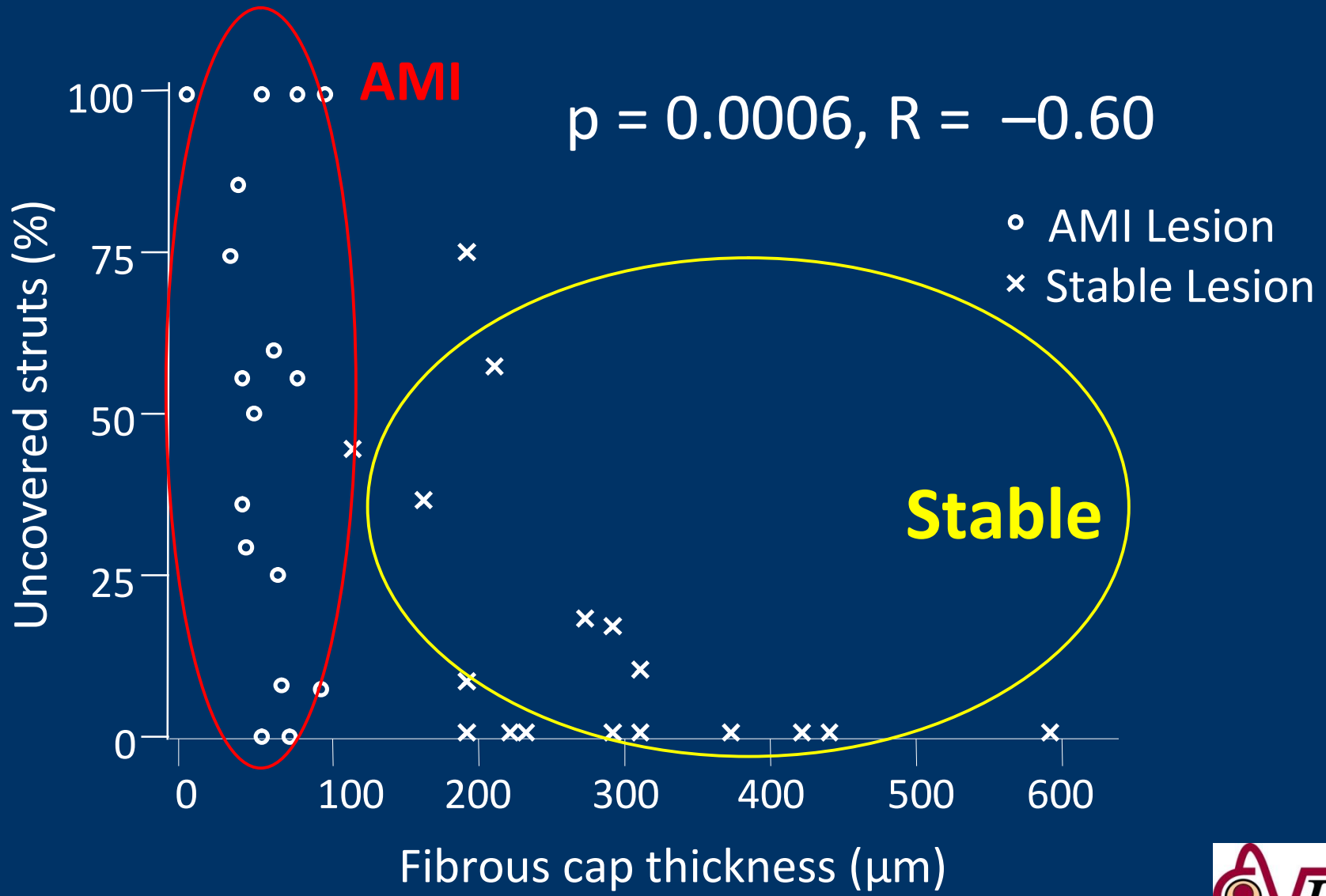
Influence of underlying "Fibrous Cap thickness" on the percentage of "Uncovered struts"



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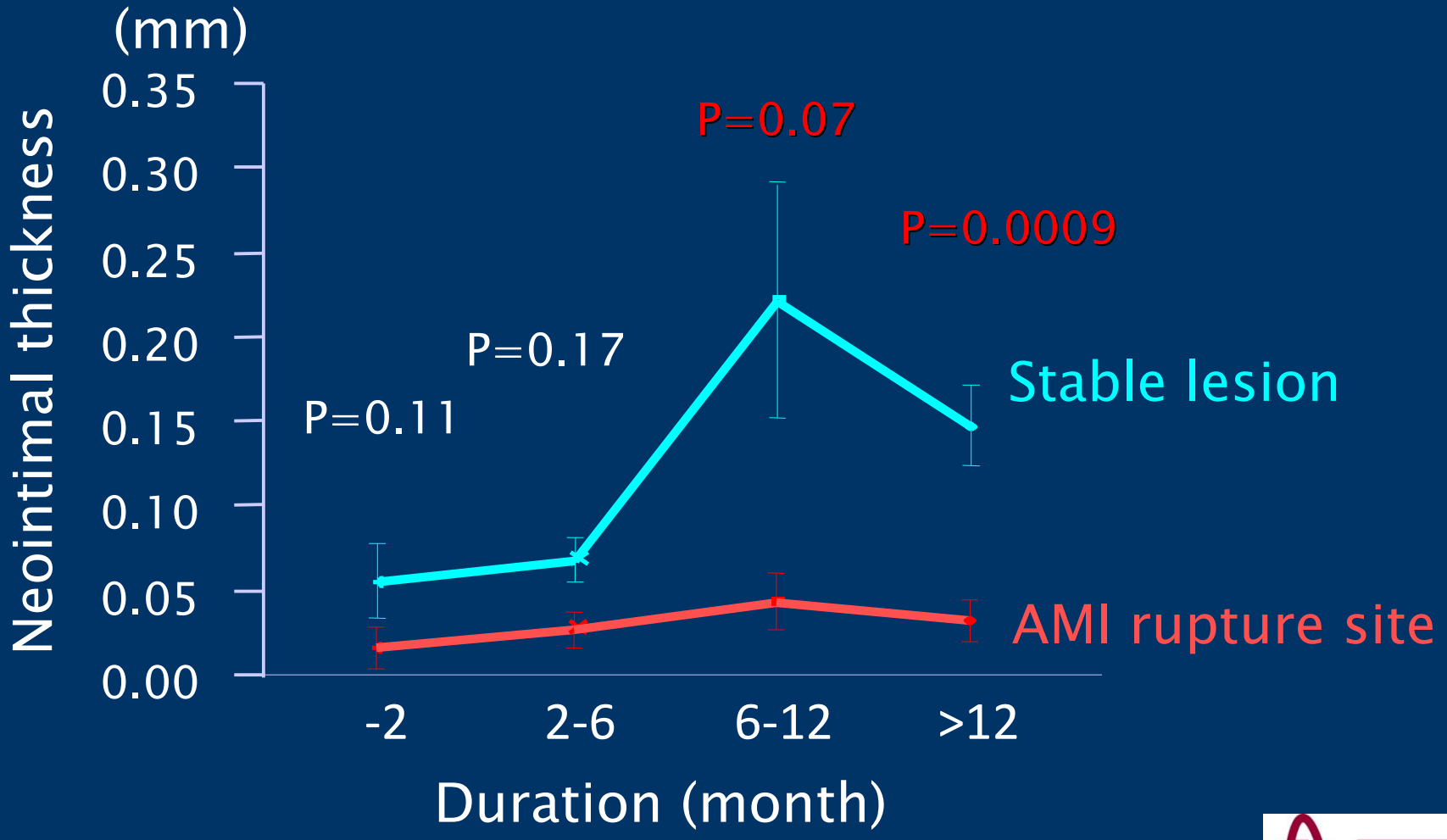
Which group of patients will need Long-term (>12 months) Plavix??



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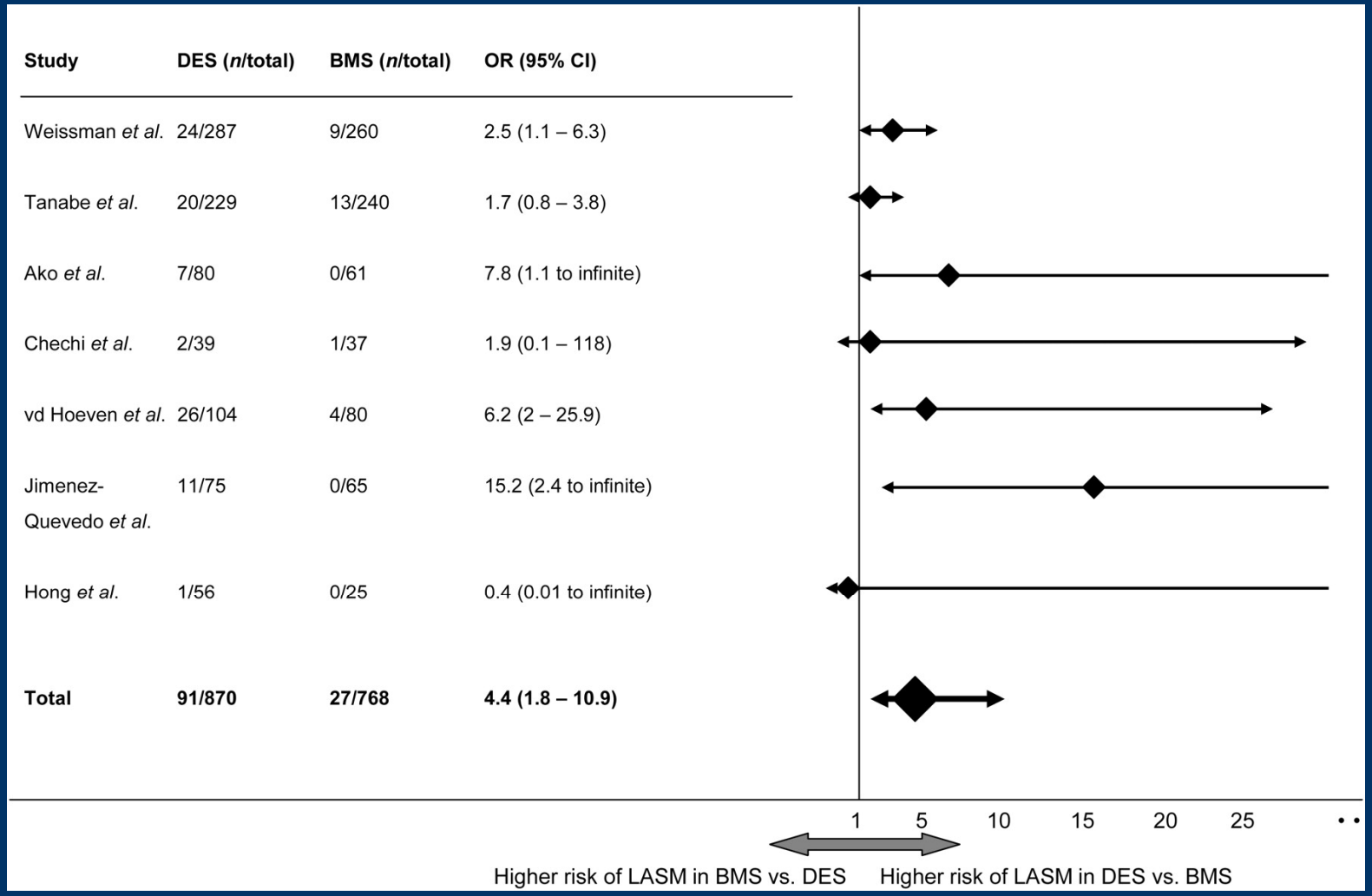
DES have higher incidence of late stent malapposition

Study	DES (*n*/total)	BMS (*n*/total)	OR (95% CI)
Weissman *et al.*	24/287	9/260	2.5 (1.1 – 6.3)
Tanabe *et al.*	20/229	13/240	1.7 (0.8 – 3.8)
Ako *et al.*	7/80	0/61	7.8 (1.1 to infinite)
Chechi *et al.*	2/39	1/37	1.9 (0.1 – 118)
vd Hoeven *et al.*	26/104	4/80	6.2 (2 – 25.9)
Jimenez-Quevedo *et al.*	11/75	0/65	15.2 (2.4 to infinite)
Hong *et al.*	1/56	0/25	0.4 (0.01 to infinite)
Total	**91/870**	**27/768**	**4.4 (1.8 – 10.9)**



Hassan, A. K.M. et al. Eur Heart J 2009

Very late thrombosis with late stent malapposition (LSM) is higher compared with those without LSM (OR=6.51, CI 95% 1.34-34.91, p=0.02)

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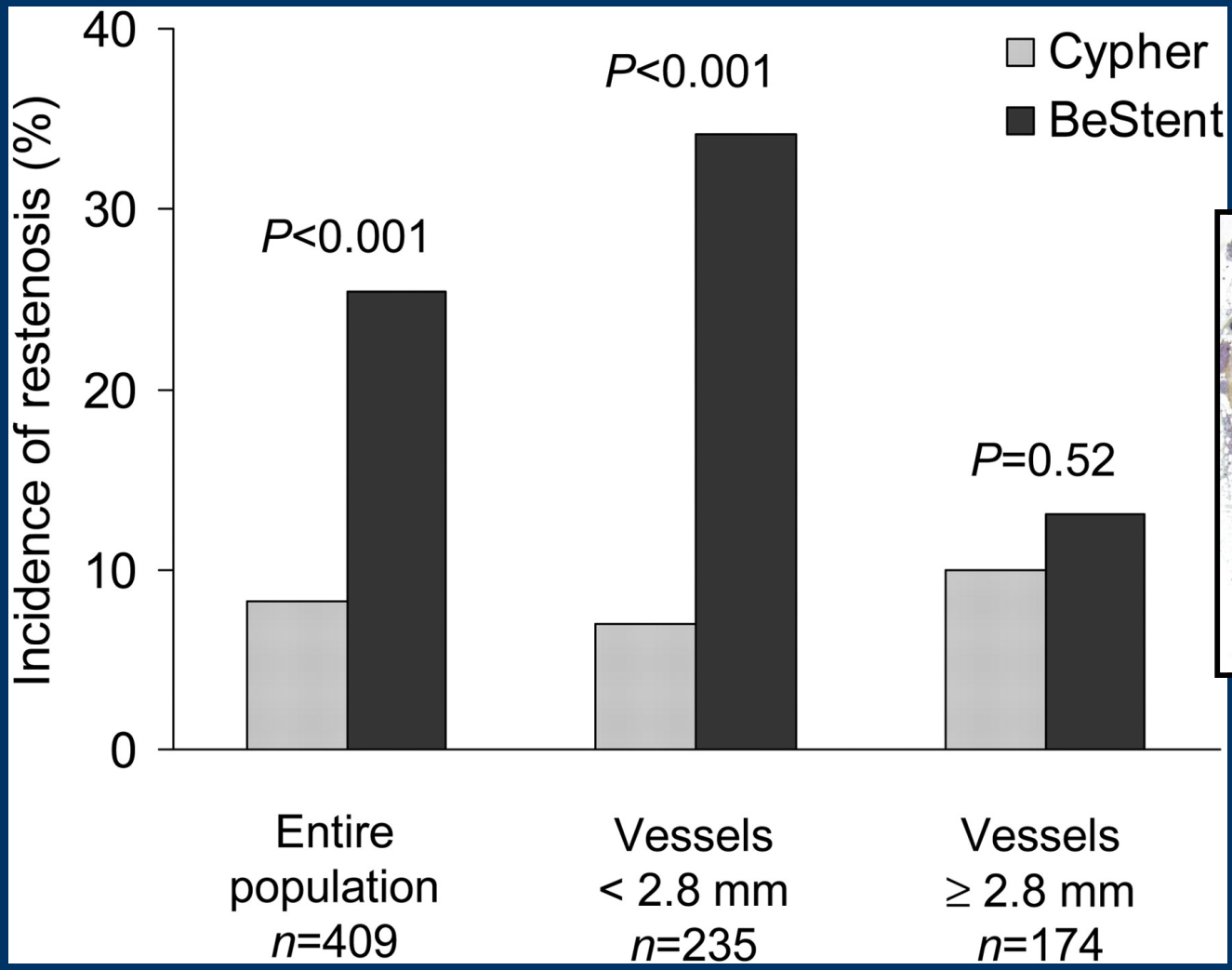
Angiographic restenosis rates with Cypher stent and BeStent, in the entire population, and in the subgroups of patients with vessel size <2.8 mm and >=2.8 mm



Pache, J. et al. Eur Heart J 2005 26:1262-1268; doi:10.1093/eurheartj/ehi098

European Heart Journal

Conclusions: BMS all the way

- From Pathophysiologic studies it is absolutely clear that DES should not be used in AMI patients since vessel wall remains unhealed even beyond 1 year, they are for the most part proximal lesions and LST will result in fatalities,
- A good BMS is the safest way to treat AMI

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