

# *Impact of Chronic Coronary Arterial Response to Drug-Eluting Stent Implantation*

*- Serial Integrated Backscatter Intravascular Ultrasound analysis -*



Shinjo Sonoda, Yoshitaka Muraoka, Yuki Tsuda

Seiya Tanaka, Masahiro Okazaki, Yutaka Otsuji

Department of Cardiovascular medicine,  
University of Occupational and Environmental Health,  
Kitakyushu, Japan

# *Background*

- ◆ Pathological studies have suggested that vasculotoxic effect of drug-eluting stents (DES) is a part of the subsequent restenosis and stent thrombosis.
- ◆ However, little is known regarding tissue characteristics of plaque outside the stent struts (peristent) and instent neointimal tissue components in-vivo.
- ◆ Recently integrated backscatter intravascular ultrasound (IB-IVUS) has enabled in-vivo tissue characterization of coronary plaque. This can be applicable to evaluate peristent plaque and neointima.

# Healing of DES vs. BMS in Man

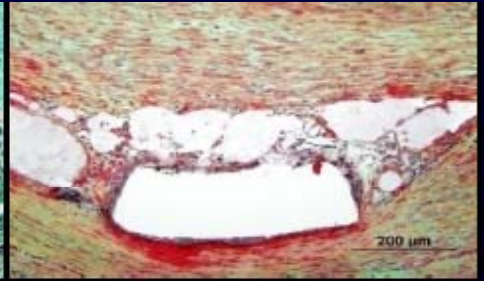
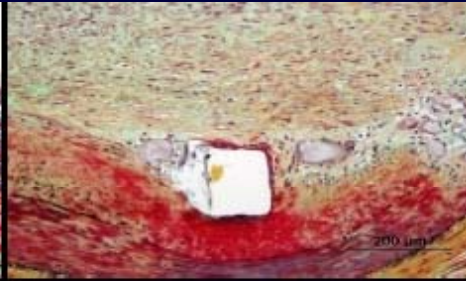
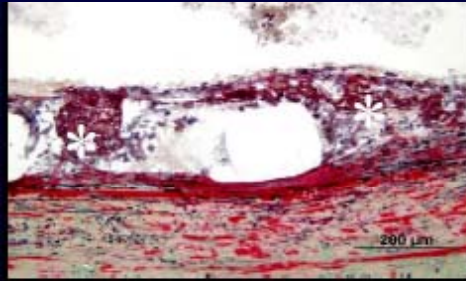
2 weeks

3 months

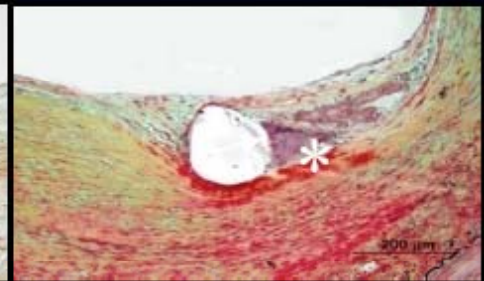
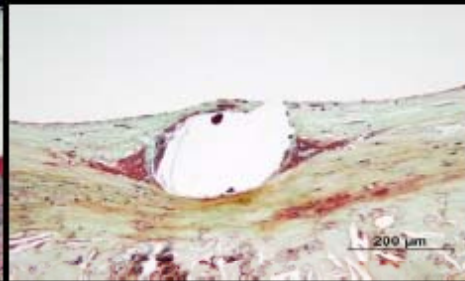
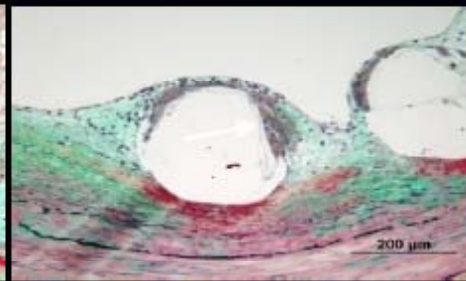
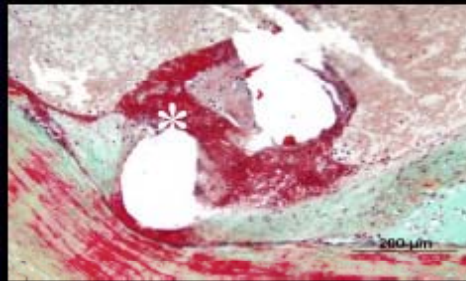
9-12 months

15-18 months

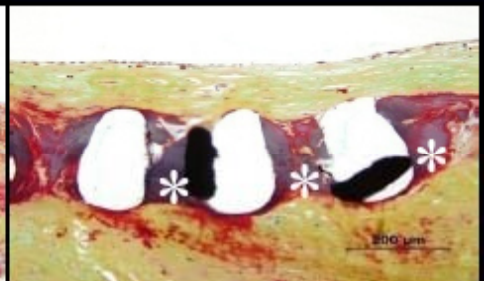
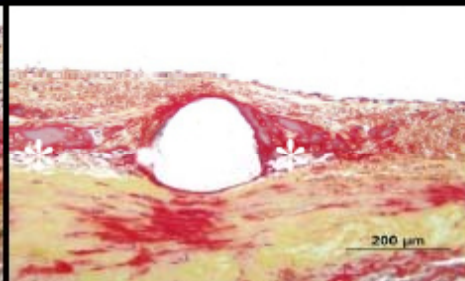
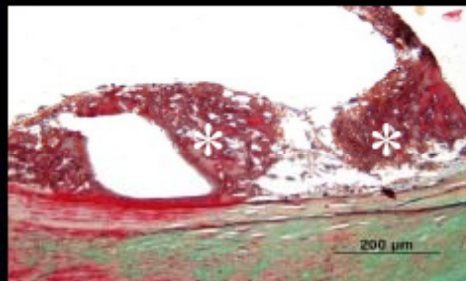
BMS



SES



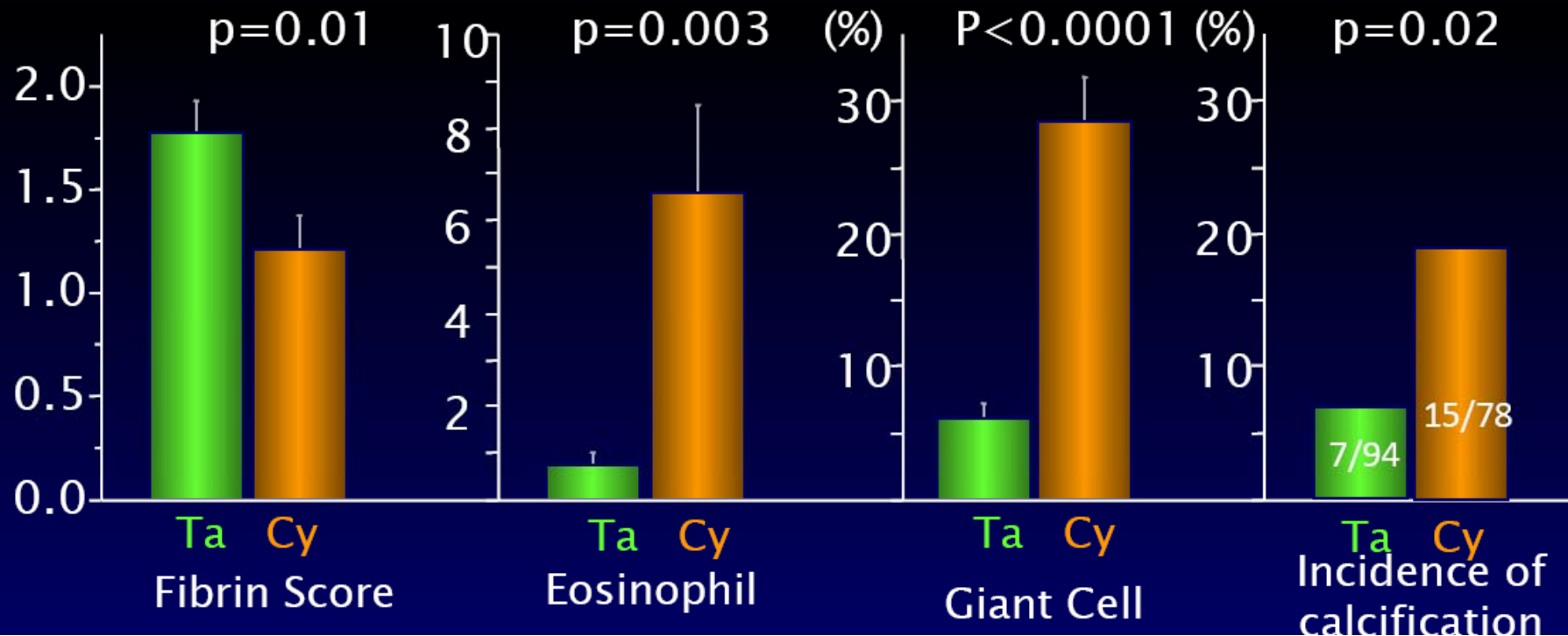
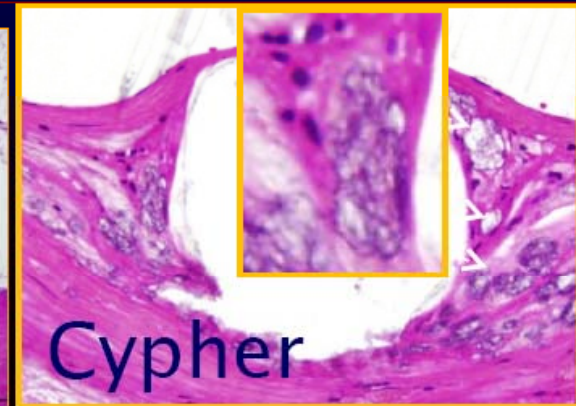
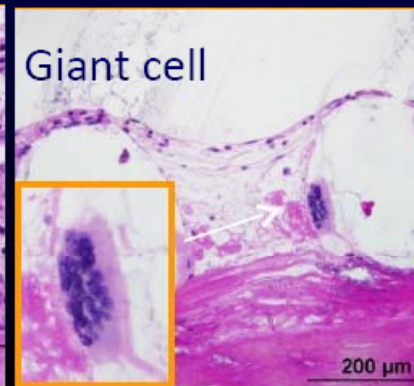
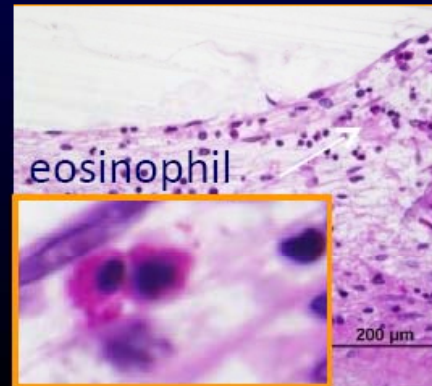
PES



\* fibrin

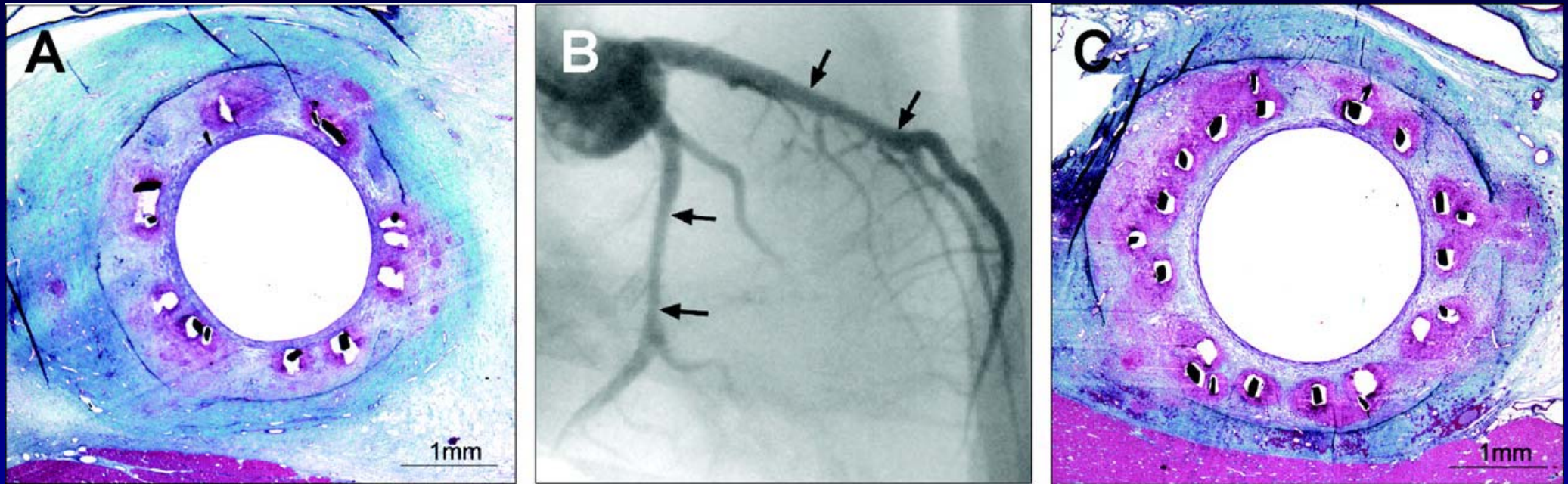


# Different Neointimal Response Between Cypher vs. Taxus in Man



# Angiography vs. Histology

swine model (post DES implantation)

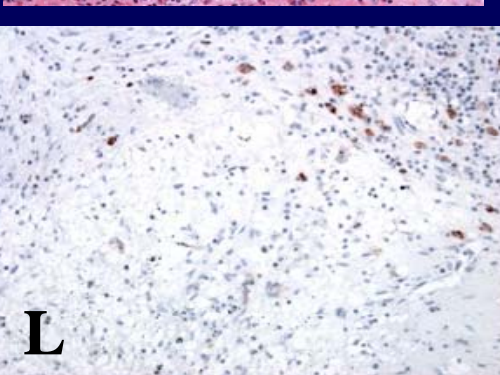
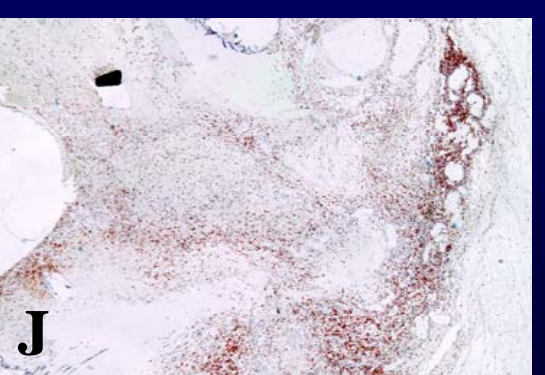
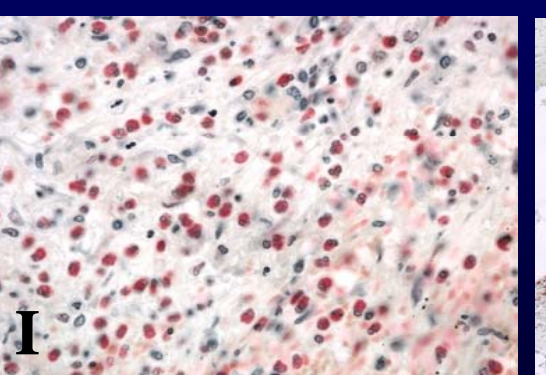
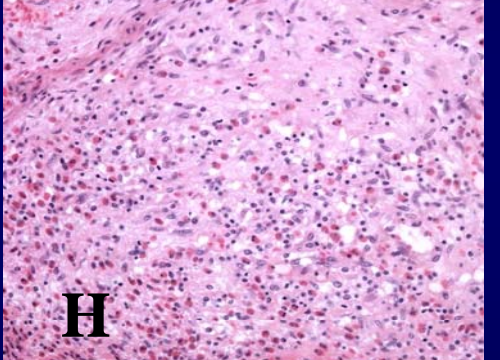
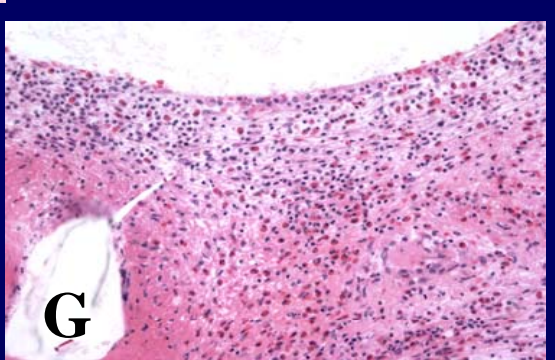
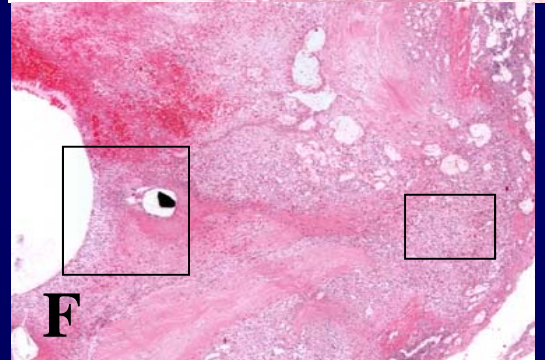
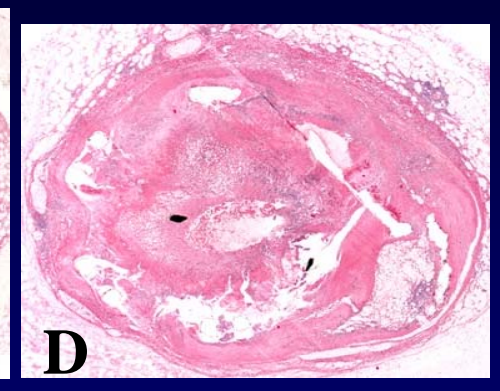
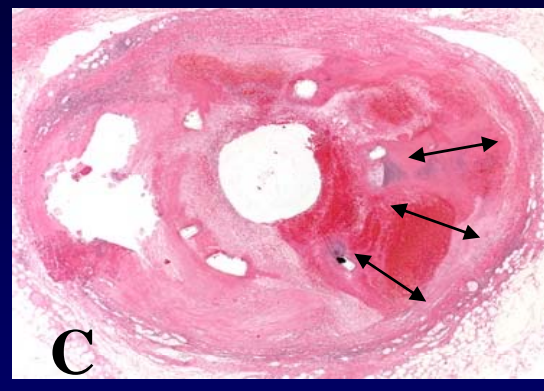
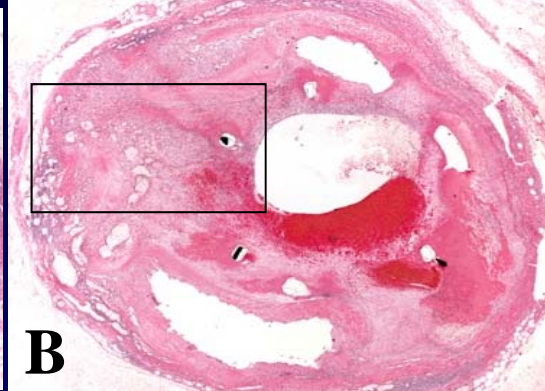
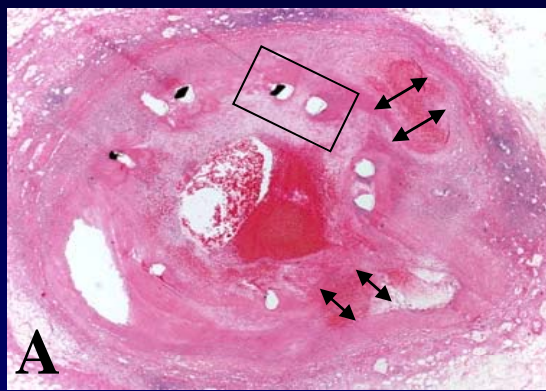


Wilson, G. J. et al. *Circulation* 2009;120:141-149



# Case of Late stent thrombosis

Cypher stent in LCx for UAP 18-months prior to onset of CP.



Luna stain

T-lymphocytes

B-lymphocytes

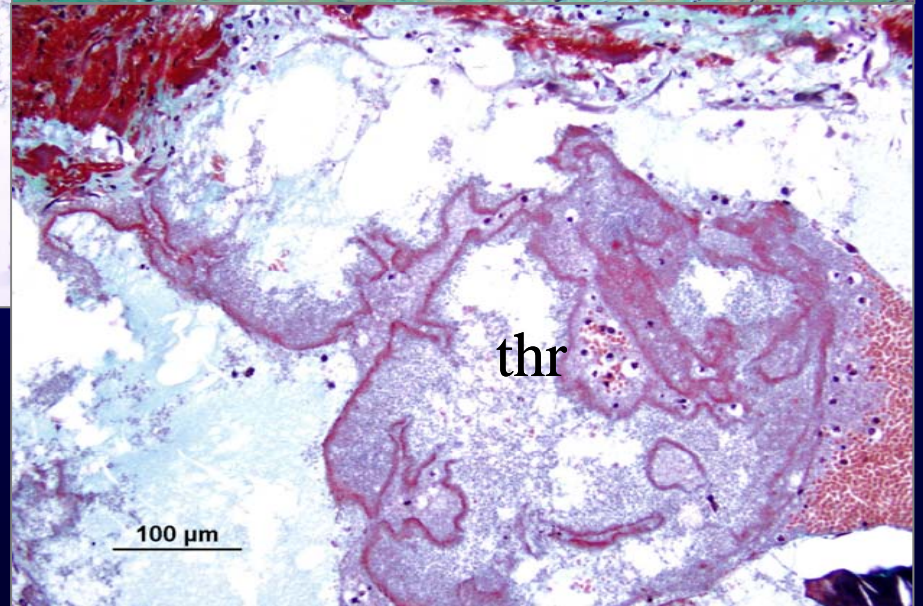
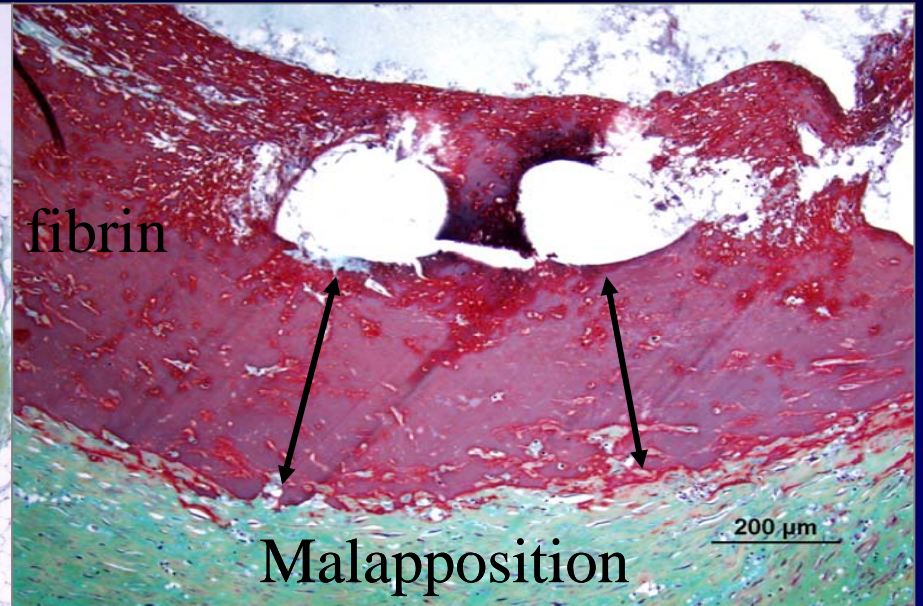
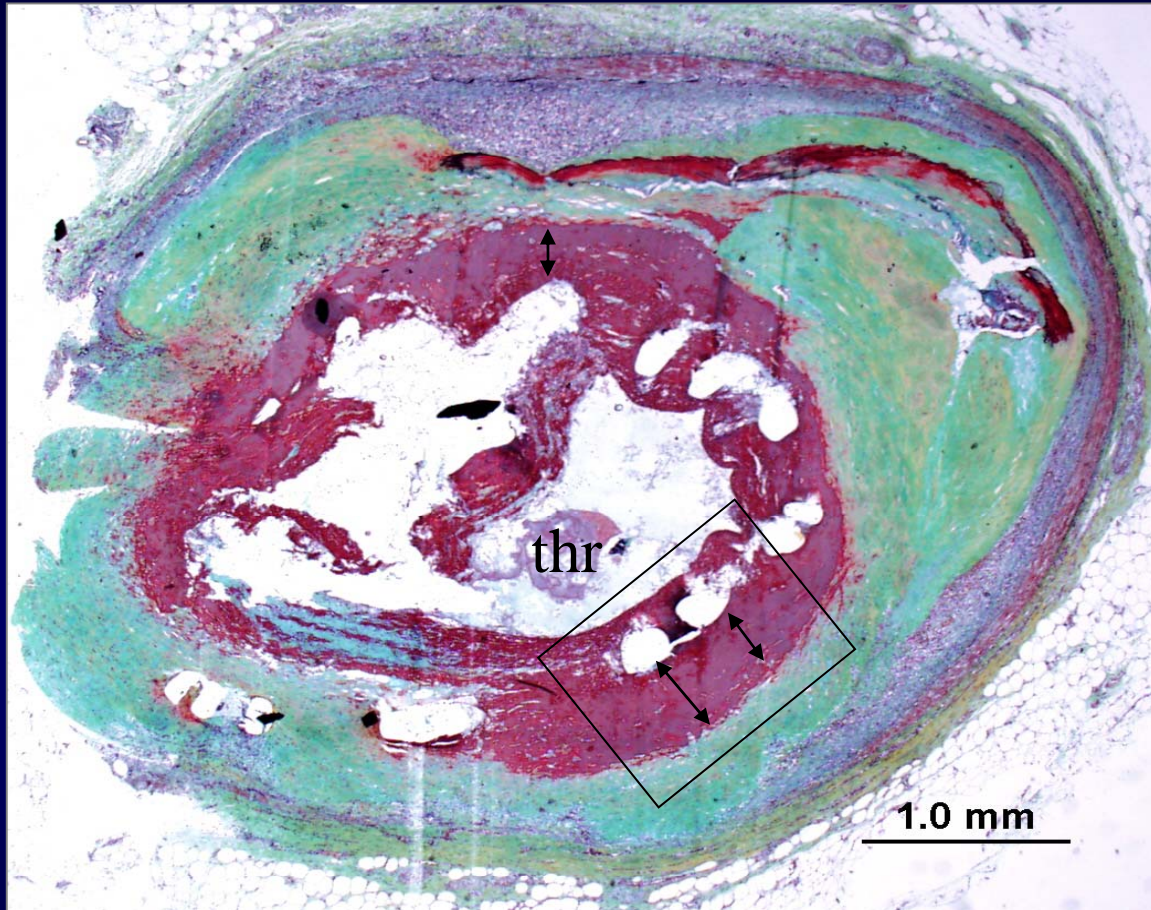
Macrophage

Courtesy of Dr. Nakazawa



# Stent Malapposition with extensive fibrin deposition

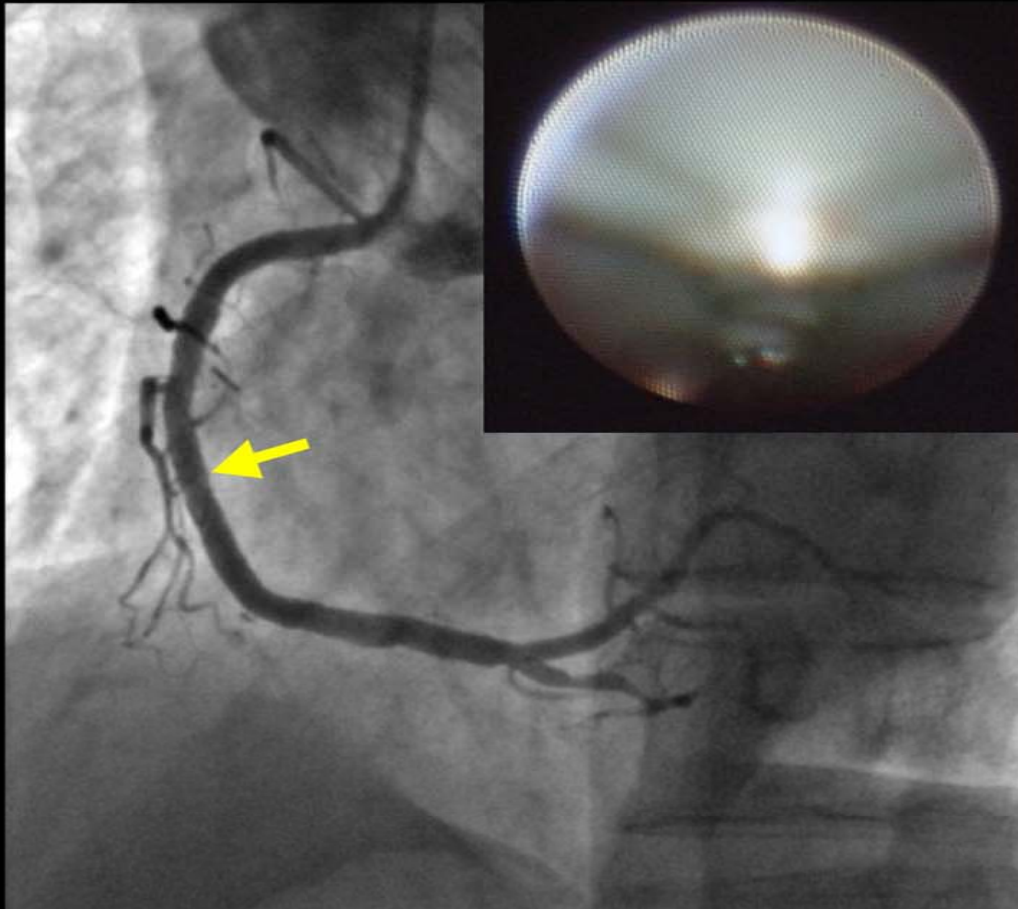
*9 months following Taxus stents implantation*



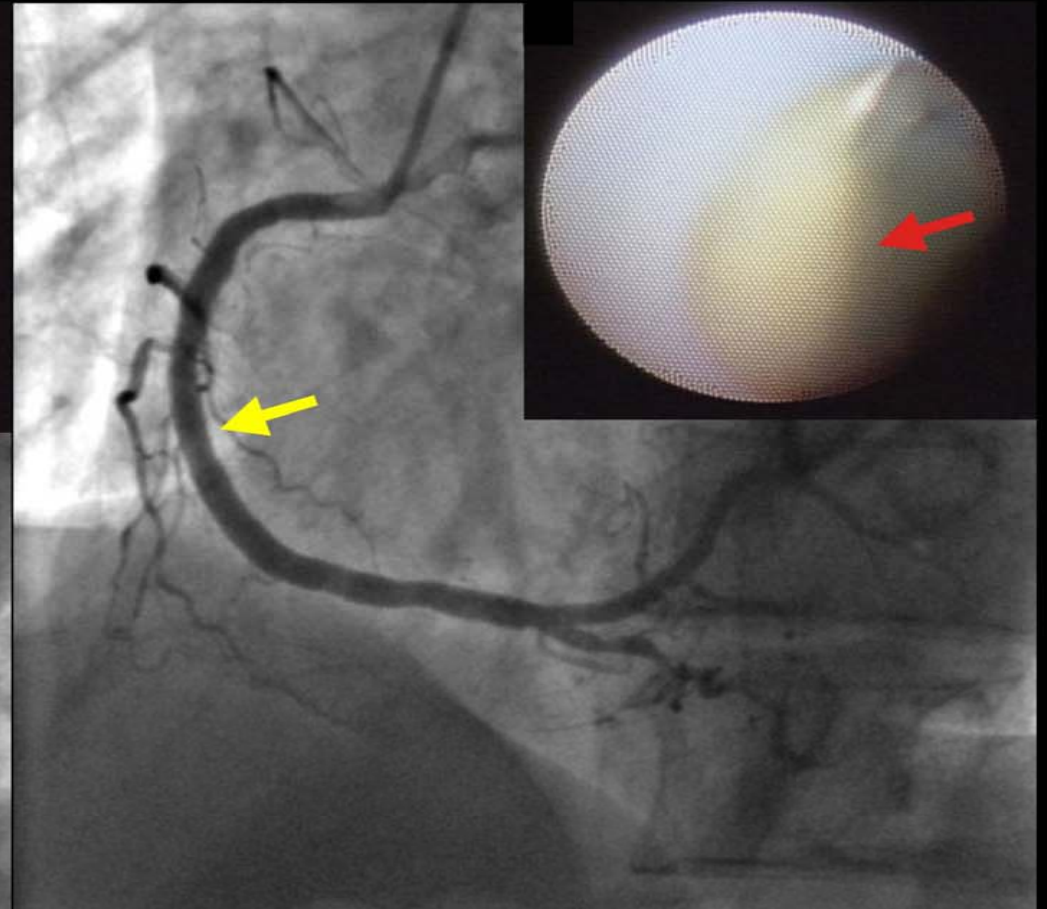


# Newly formed “Yellow Neointima” in SES

A

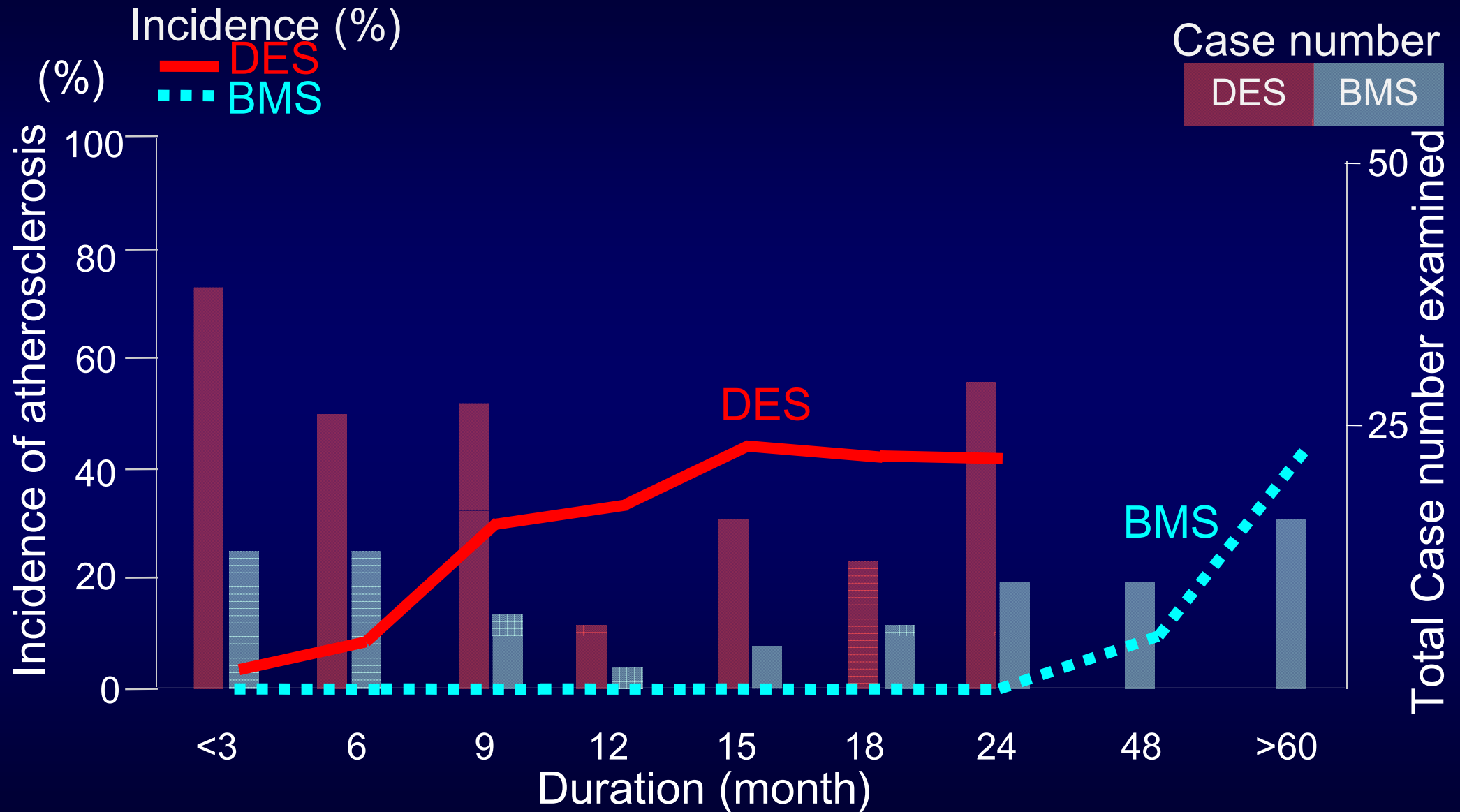


B





# Incidence and Timing of Atherosclerotic Change



# Background

- ◆ Pathological studies have suggested that vasculotoxic effect of drug-eluting stents (DES) is a part of the subsequent restenosis and stent thrombosis.
- ◆ However, little is known regarding tissue characteristics of plaque outside the stent struts (persistent plaque) and instent neointimal tissue components in-vivo.
- ◆ Recently integrated backscatter intravascular ultrasound (IB-IVUS) has enabled in-vivo tissue characterization of coronary plaque, which can be applicable to evaluate persistent plaque and neointima.



# *Objective 1*

*To Evaluate In-stent Neointimal Tissue Component  
Using Integrated Backscatter Intravascular Ultrasound*

## *Authors' Disclosure*

<i>Shinjo Sonoda</i>	<i>Nothing to disclose</i>
<i>Yoshitaka Muraoka</i>	<i>Nothing to disclose</i>
<i>Yuki Tsuda</i>	<i>Nothing to disclose</i>
<i>Seiya Tanaka</i>	<i>Nothing to disclose</i>
<i>Masahiro Okazaki</i>	<i>Nothing to disclose</i>
<i>Yutaka Otsuji</i>	<i>Nothing to disclose</i>



# *Background 1*

- ◆ Previous histopathological study revealed that the major cause of in-stent restenosis (ISR) after bare-metal stents (BMS) implantation was neointimal hyperplasia. It is believed that neointimal hyperplasia consists of smooth muscle cell proliferation.
- ◆ Although ISR occurred after drug-eluting stents (DES) implantation, tissue characteristics of neointima has not been fully investigated.

# *Background 2*

- ◆ Recent pathological studies have suggested that neointima of DES shared many characteristics with that of BMS.
- ◆ Integrated backscatter intravascular ultrasound (IB-IVUS) has enabled in-vivo tissue characterization of coronary plaque.
- ◆ It is possible to use IB-IVUS system to compare neointimal tissue components in both stents.



# *Objective*

To compare neointimal tissue components between DES and BMS restenosis using IB-IVUS.

# Methods

2007.11-2009.10

6-8 M follow-up CAG: 207 cases, 290 lesions



TLR (target lesion revascularization): 41 cases, 43 lesions

BMS: 25 cases, 26 lesions

SES: 11 cases, 12 lesions

PES: 5 cases, 5 lesions

**Pre re-PCI: IVUS and IB-IVUS analysis**

DES restenosis

12 cases, 13 lesions

compare



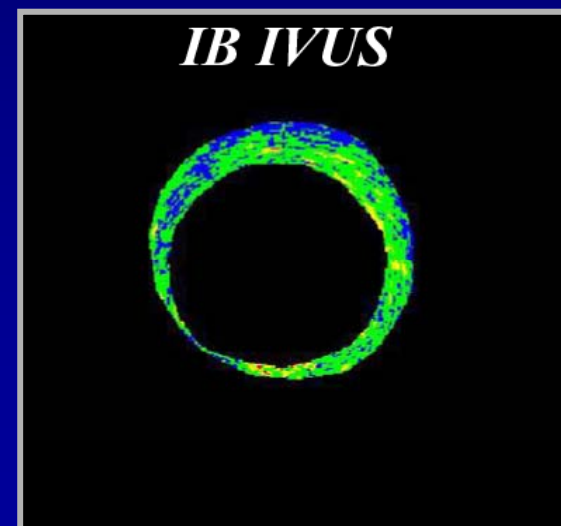
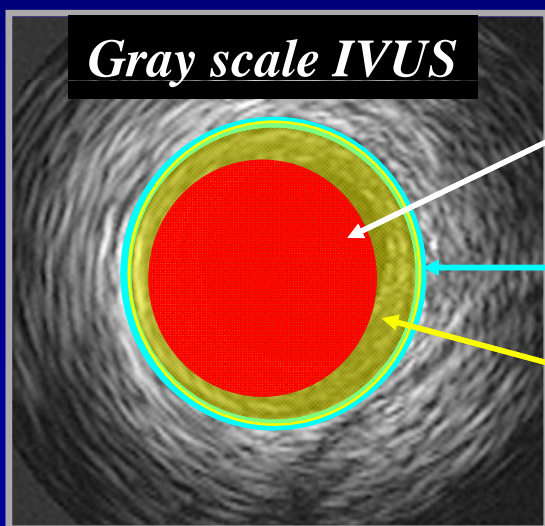
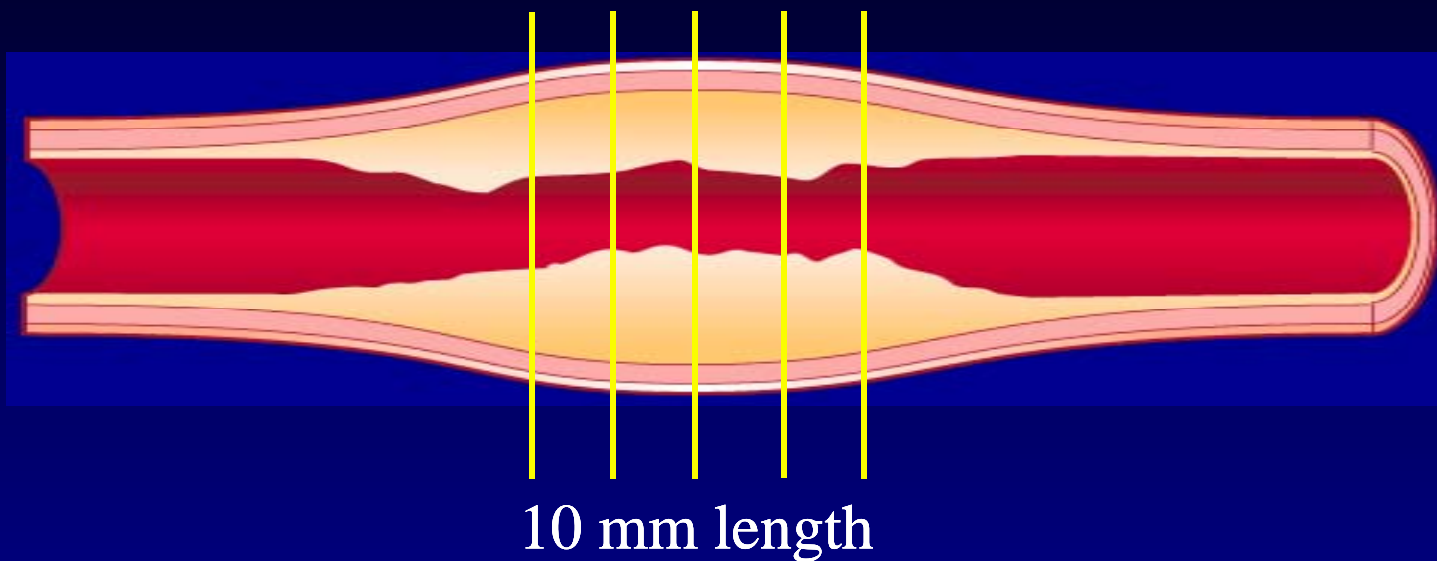
BMS restenosis

16 cases, 18 lesions

\* Inadequate images were excluded.

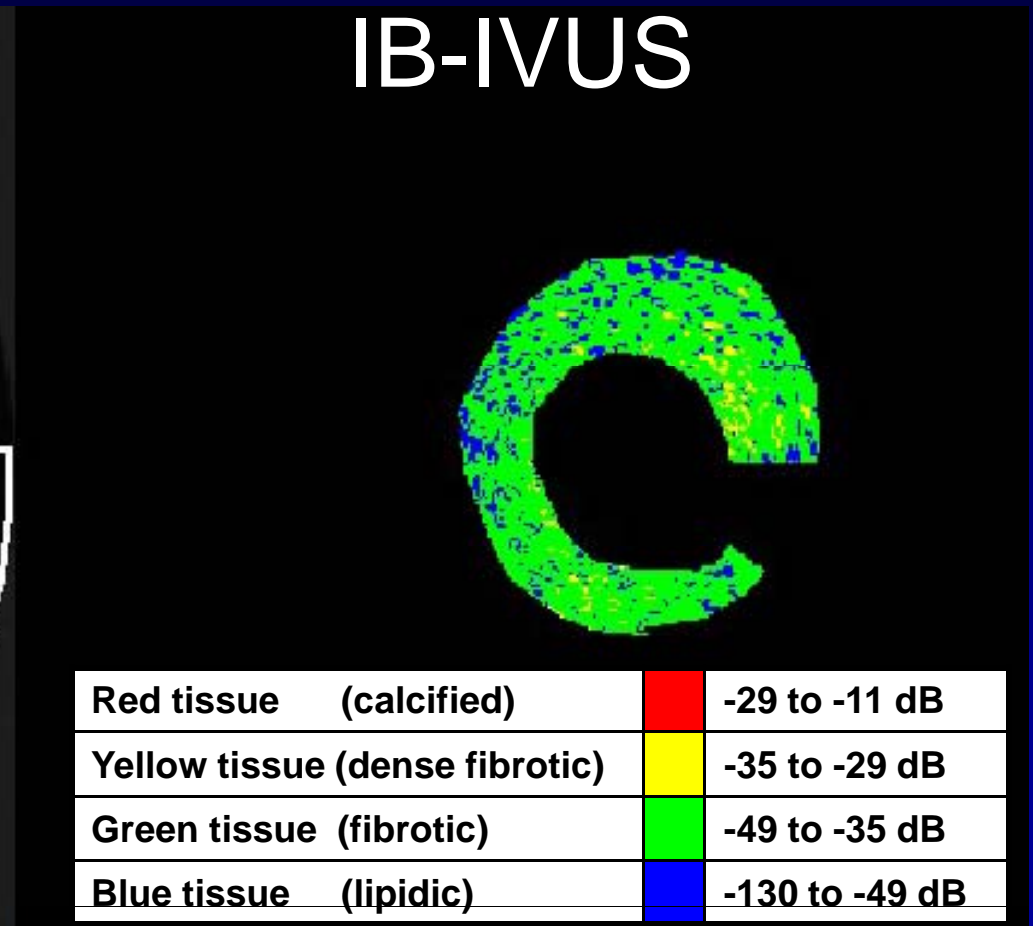
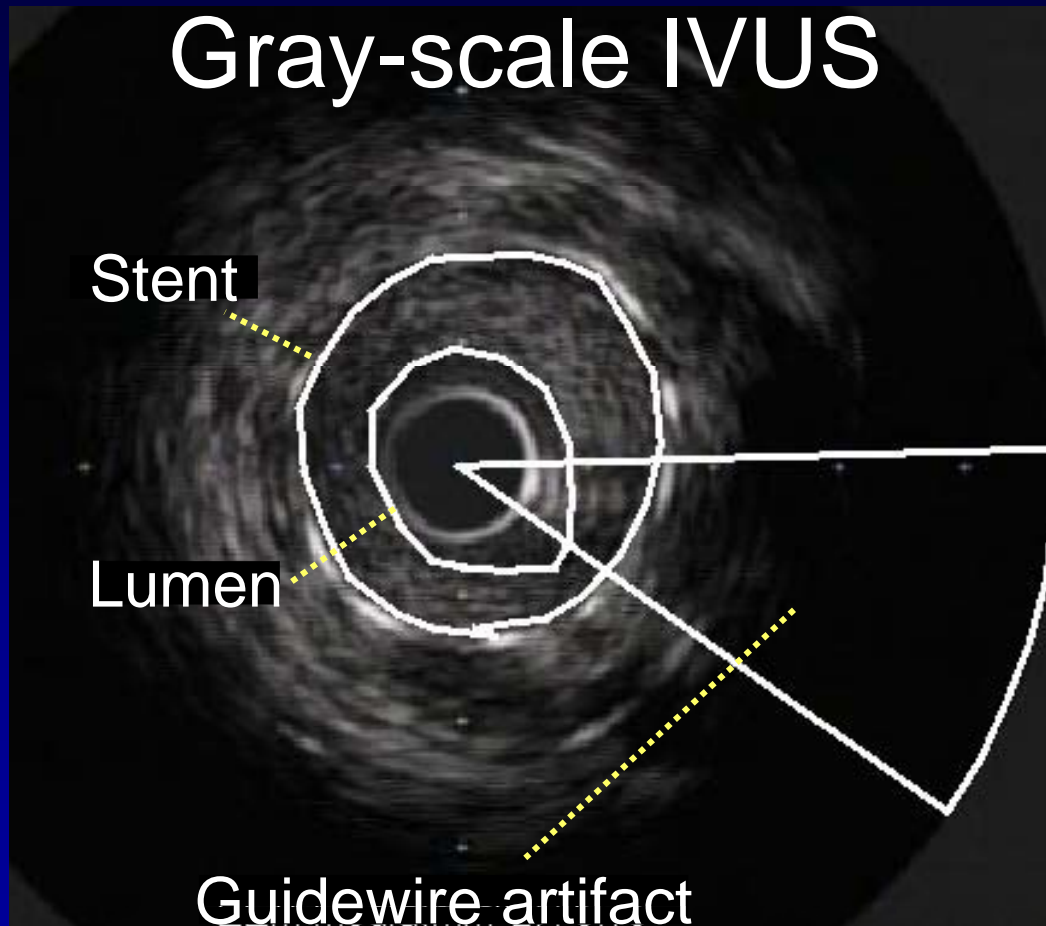


# IB-IVUS Analysis (coronary plaque)



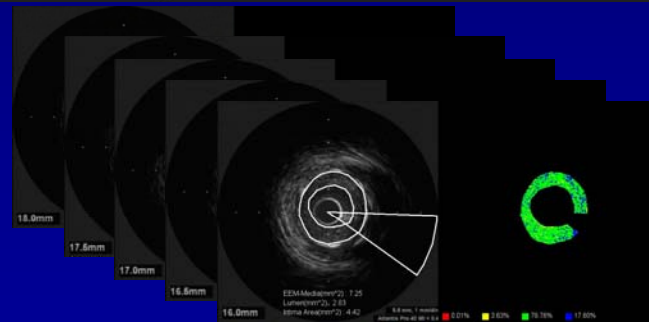
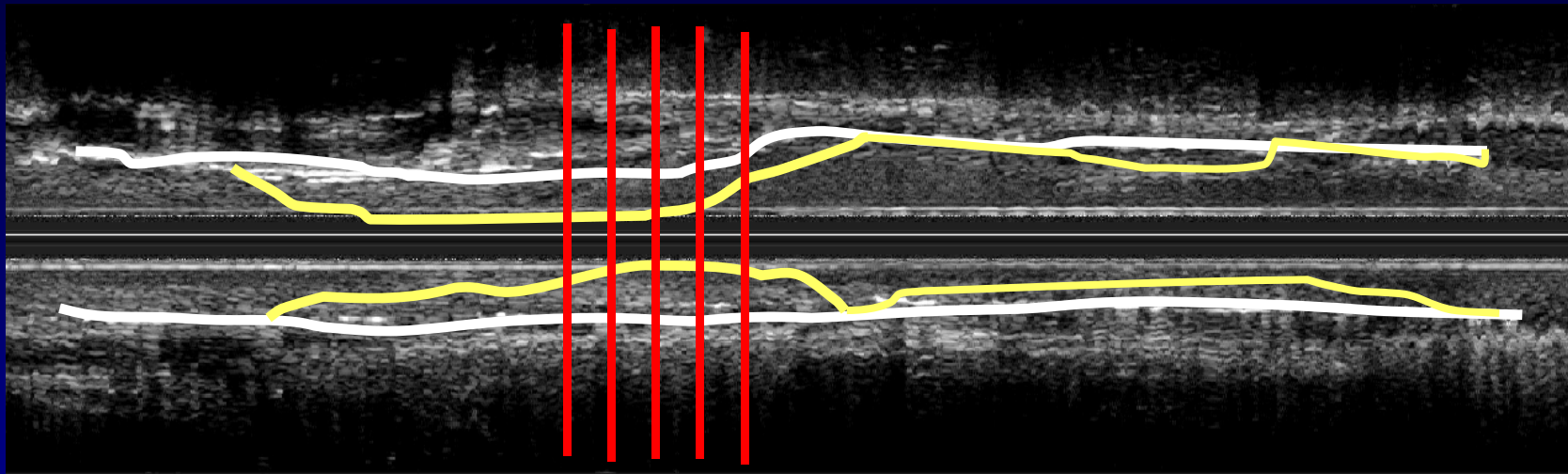
■ Calcified   ■ Dense fibrous   ■ Fibrous   ■ Lipid

# Neointimal Tissue Characterization using IB-IVUS



# Neointimal Tissue Characterization using IB-IVUS

TLR site

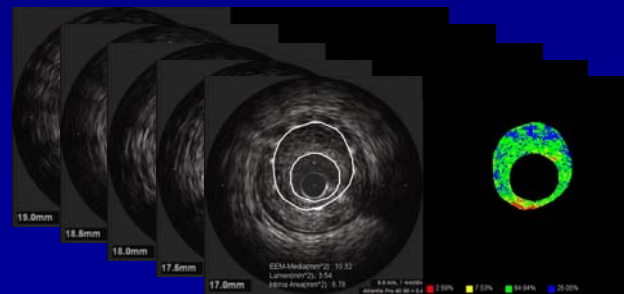
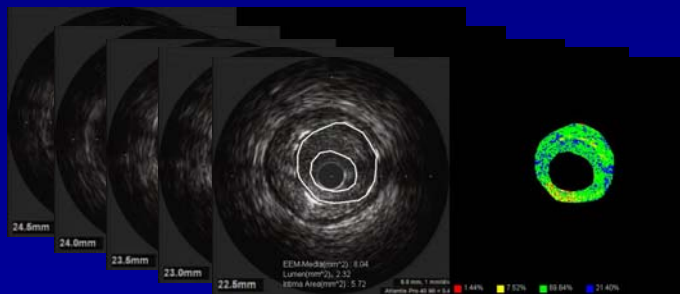
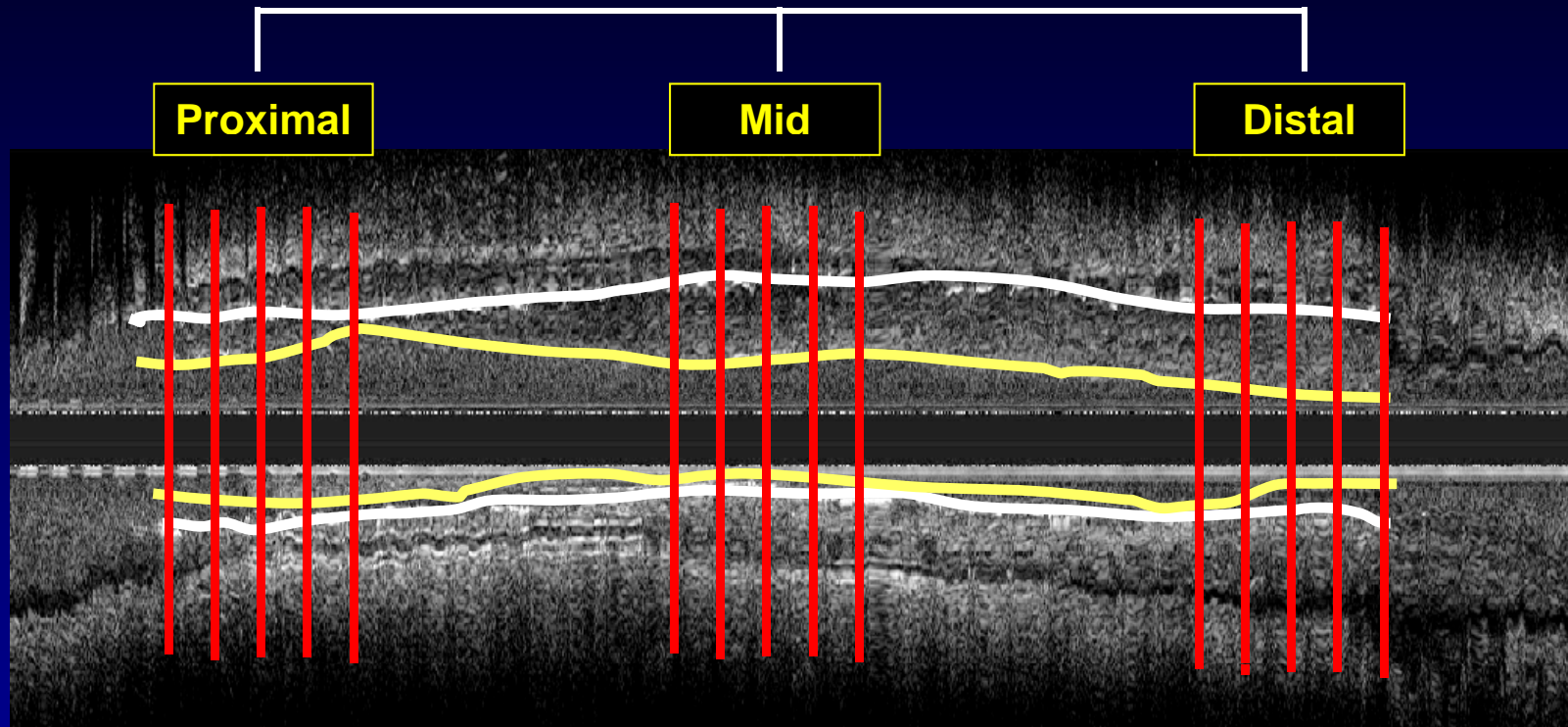


\* Pullback speed: 0.5 mm/sec

Tissue contents: Average of 5 frames  
(10mm)

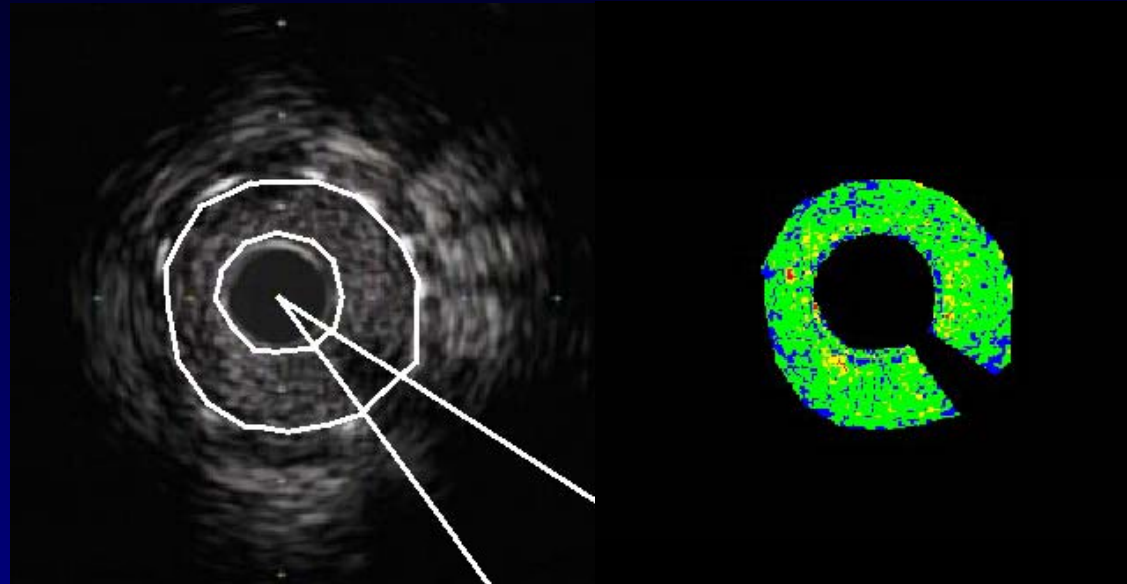


# Evaluation of neointimal tissue heterogeneity



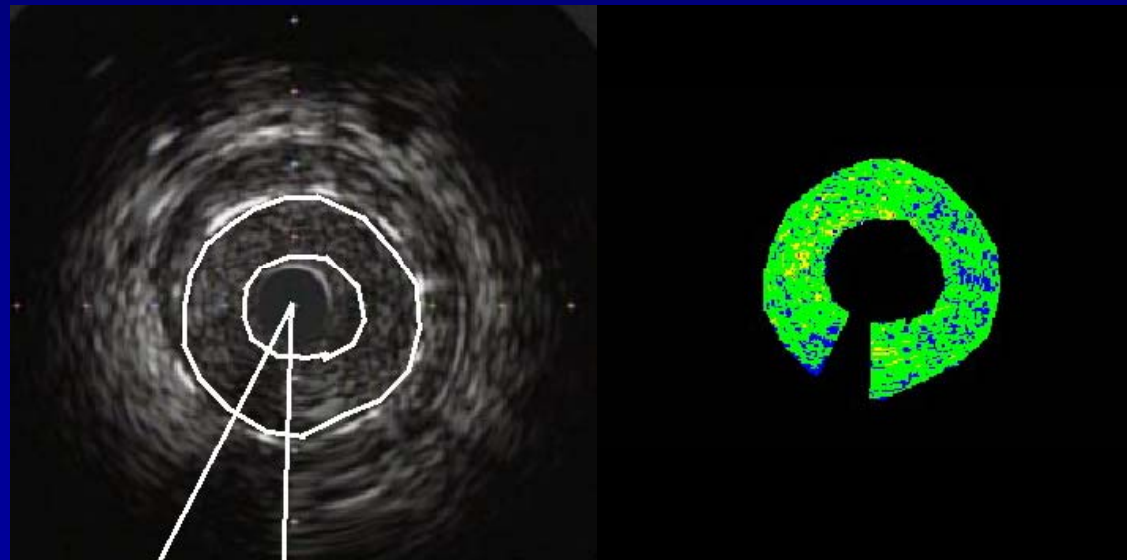
# Representative case (TLR site)

**DES**



Red	0.13%
Yellow	5.63%
Green	77.84%
Blue	16.4%

**BMS**



Red	0.37%
Yellow	8.05%
Green	75.08%
Blue	16.5%

# Baseline Characteristics 1

	DES (N=12)	BMS (N=16)	p-value
<b>Clinical</b>			
Age (years)	65±10	70±11	0.29
Gender, male (%)	9 (75)	13(81)	0.99
Acute coronary syndrome (%)	0 (0)	5 (31)	<b>0.053</b>
<b>Coronary Risk factors</b>			
Hypertension (%)	11(92)	11(69)	0.20
Dyslipidemia (%)	8 (67)	5 (31)	0.12
Diabetes mellitus (%)	6 (50)	6 (38)	0.51
Smoking (%)	3 (25)	5 (31)	0.99
On HD (%)	5 (42)	3 (19)	0.18
Previous MI (%)	5 (42)	2 (13)	0.10
Prior PCI or CABG(%)	10 (83)	9 (56)	0.22



## Baseline Characteristics 2

	DES (N=12)	BMS (N=16)	p-value
<b>Medication</b>			
Aspirin (%)	12(100)	16 (100)	-
Aspirin +Ticlopidine (%)	7 (58)	4 (25)	0.12
Aspirin + Clopidogrel (%)	5 (42)	6 (38)	0.99
ACE-I (%)	2 (17)	0 (0)	0.17
ARB (%)	5 (42)	7 (44)	0.91
Statin (%)	10 (83)	9 (56)	0.22
<b>Labo data</b>			
hsCRP	0.31±0.36	0.45±0.83	0.61
LDL-C (mg/dl)	89±26	82±30	0.52
HDL-C (mg/dl)	52±12	53±10	0.84
LDL/HDL ratio	1.8±0.8	1.6±0.5	0.30
HbA1c (%)	5.8±1.1	6.1±1.6	0.60

# Lesion and Procedural Characteristics

	<b>DES (N=13)</b>	<b>BMS (N=18)</b>	<b>p-value</b>
De novo lesion (%)	12(92)	18(100)	0.42
In-stent restenosis lesion (%)	1 (8)	0 (0)	0.42
Chronic total occlusion (%)	1 (8)	0 (0)	0.42
<b>Target vessel</b>			0.19
LAD (%)	8 (62)	10(56)	
LCX (%)	3 (23)	1 (6)	
RCA (%)	2 (15)	7(38)	
<b>Procedural characteristics</b>			
Stent diameter (mm)	2.9±0.2	3.2±0.3	<b>&lt;0.01</b>
Stent length (mm)	30.1±14.0	24.8±10.5	0.24
Max inflation pressure (atm)	19±3	20±3	0.77

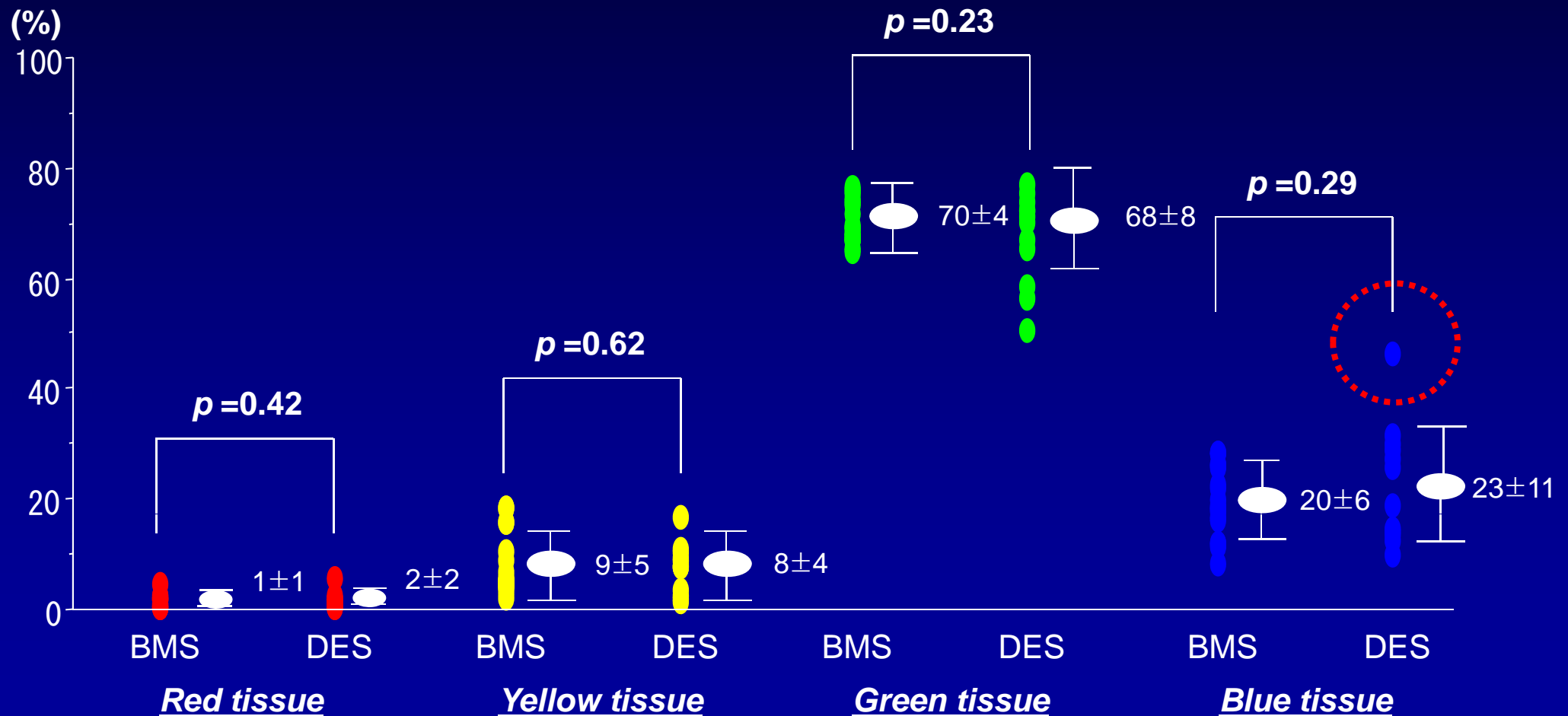
# Pattern of in-stent restenosis

	DES (N=13)	BMS (N=18)	p-value
			<b>&lt;0.001</b>
<b><i>Focal restenosis</i></b>			
proximal site	2	0	
stent body	8	2	
distal site	0	0	
<b><i>Diffuse restenosis</i></b>	3	16	

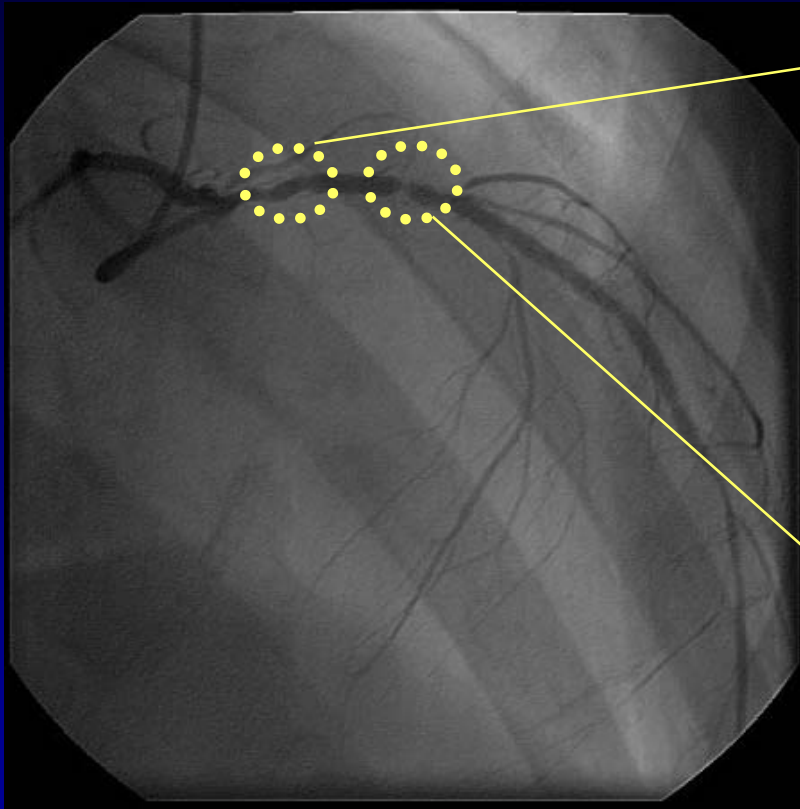
(Mehran's classification)



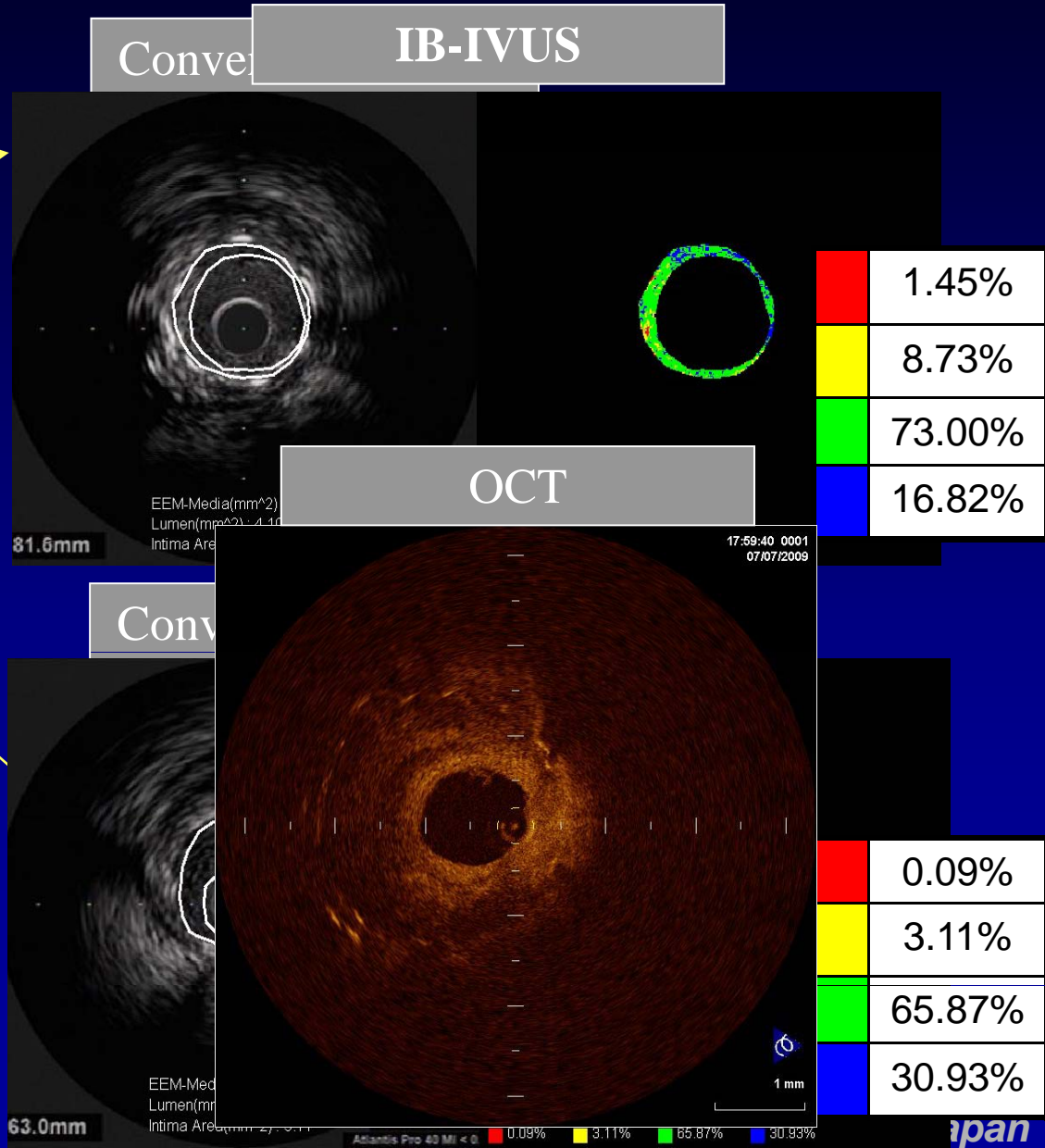
# Comparison of neointimal tissue components at TLR site



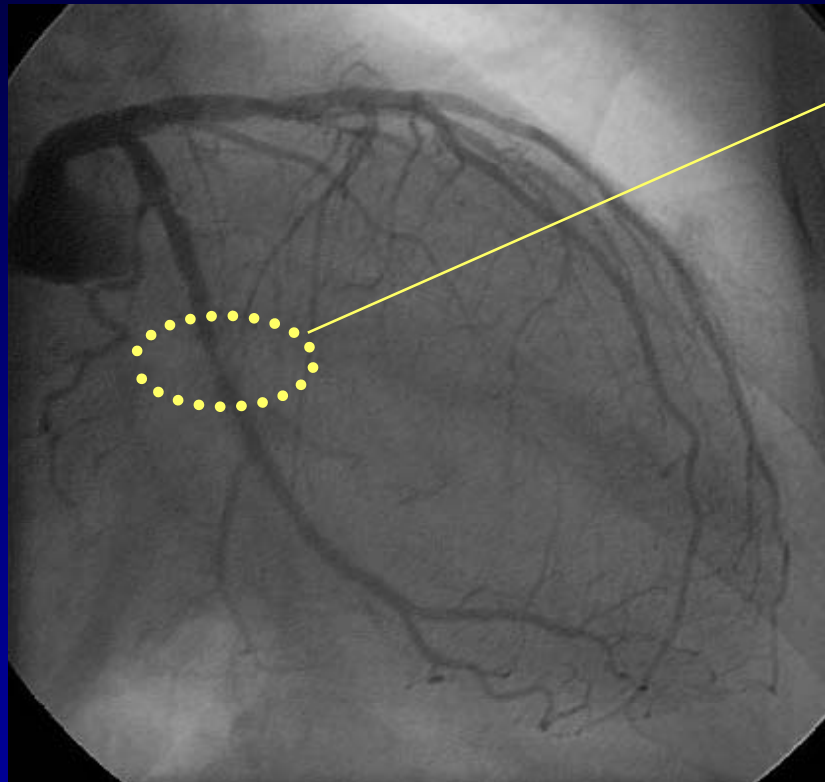
# IB-IVUS and OCT Findings - SES TLR case -



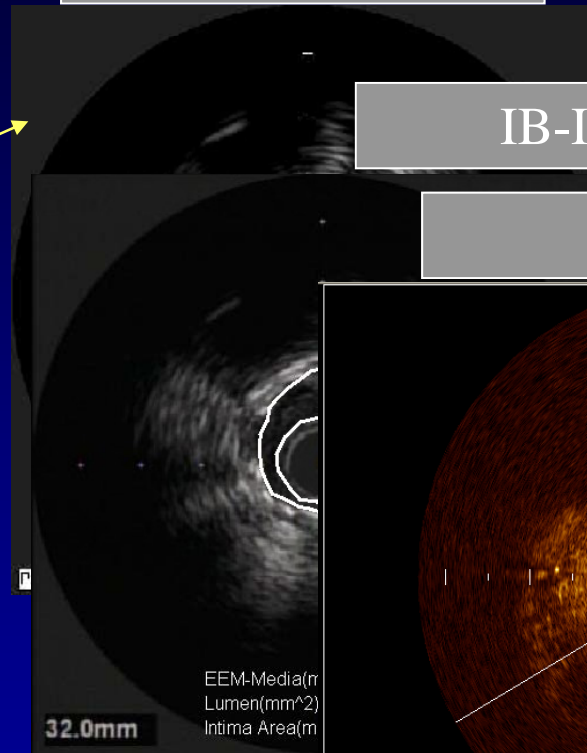
SES 3.0/23mm to #6  
SES 2.5/28mm to #6-7  
SES 2.5/28mm to #7



# IB-IVUS and OCT Findings - PES TLR case -

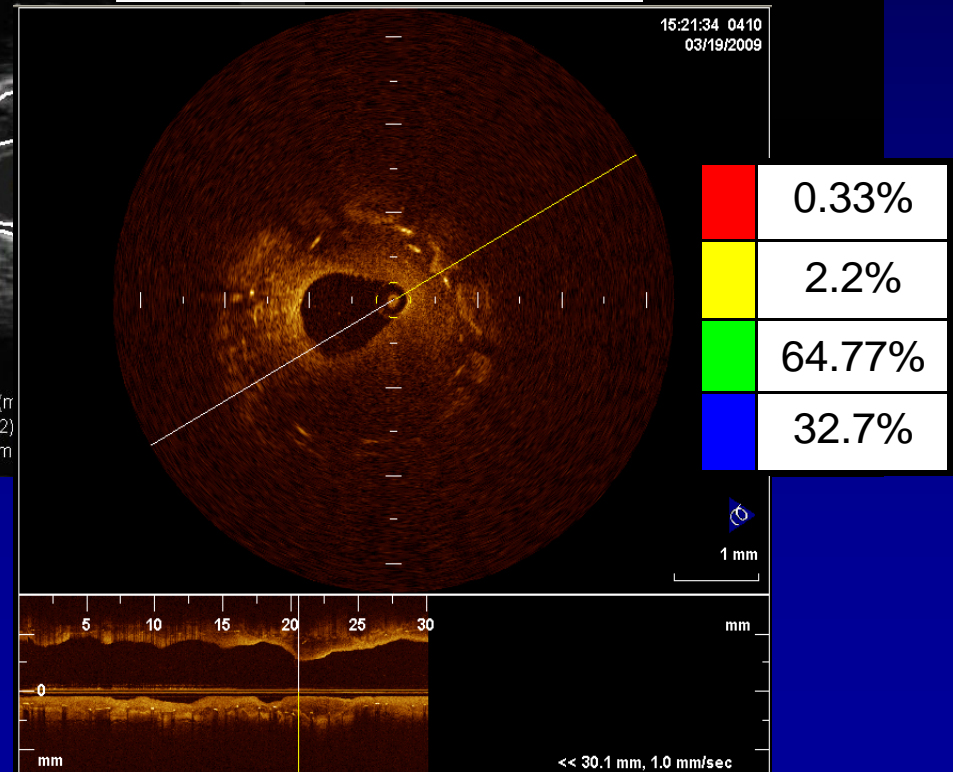


Conventional IVUS



IB-IVUS

OCT



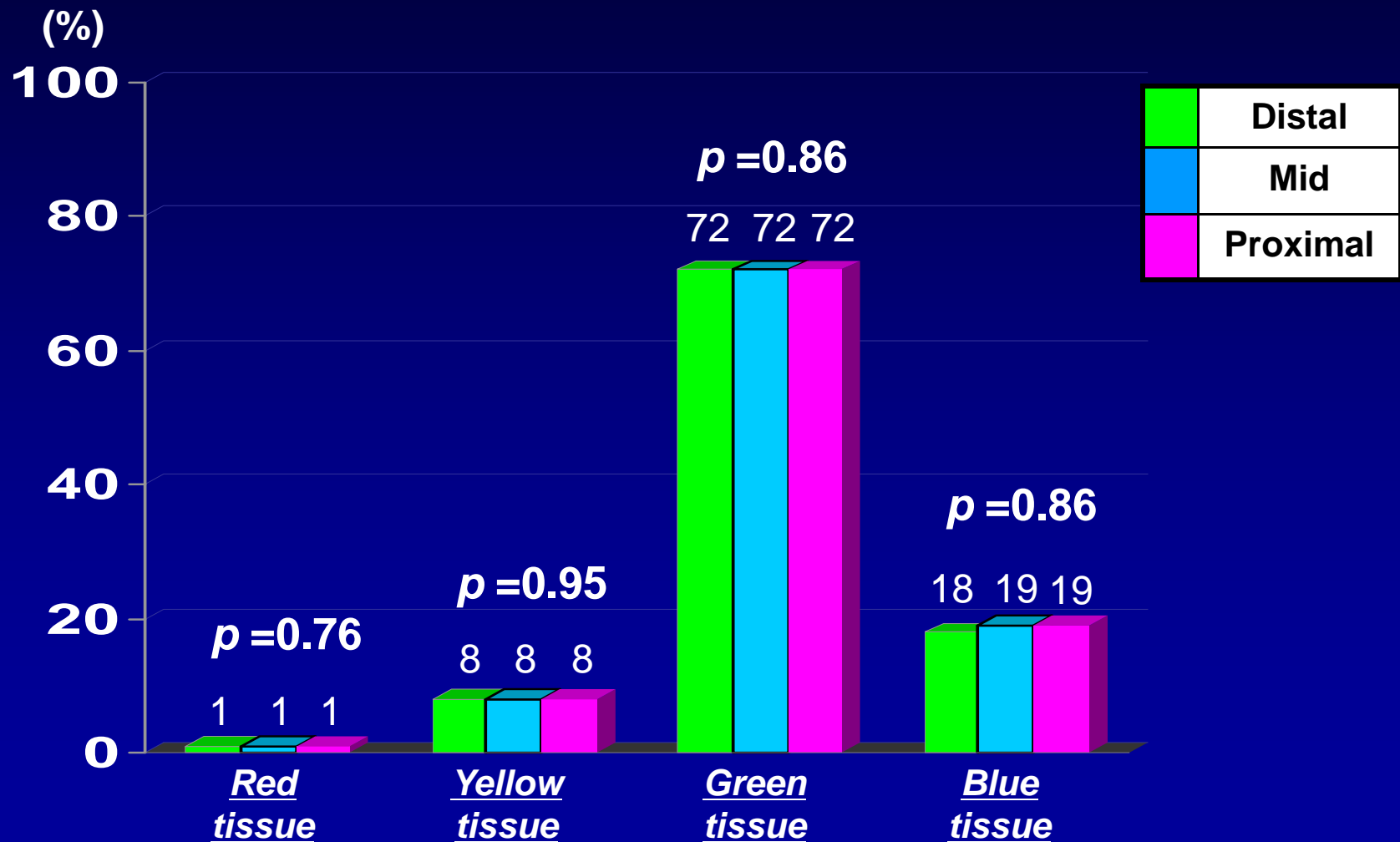
PES : 3.0/24mm to #13

PES : 2.5/20mm to #13-15

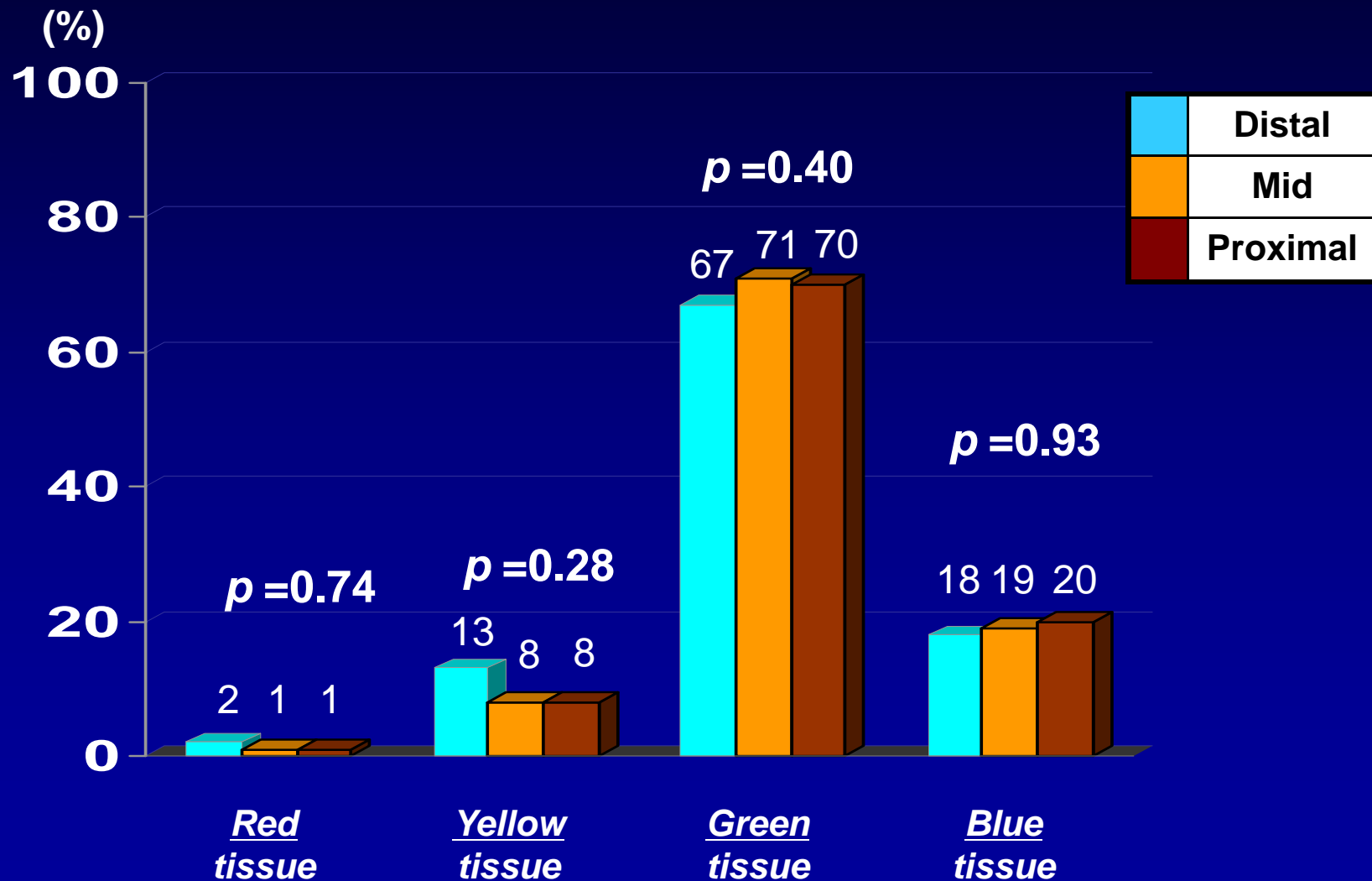




# Homogeneity of neointimal tissue characteristics in BMS group



# Homogeneity of neointimal tissue characteristics in DES group



# Summary

- ◆ The pattern of in-stent restenosis in DES group was mostly focal. On the other hand, the pattern of in-stent restenosis in BMS group was mostly diffuse proliferative.
- ◆ IB-IVUS analysis revealed that neointimal tissue after DES implantation was mainly composed of green (fibrotic) tissue at TLR site.
- ◆ There were no significant differences of tissue components at TLR site between DES and BMS.
- ◆ Furthermore, DES, as well as BMS, had homogenous neointimal tissue characteristics throughout the stent.

# *Study Limitation*

Small sample size

Patient selection bias

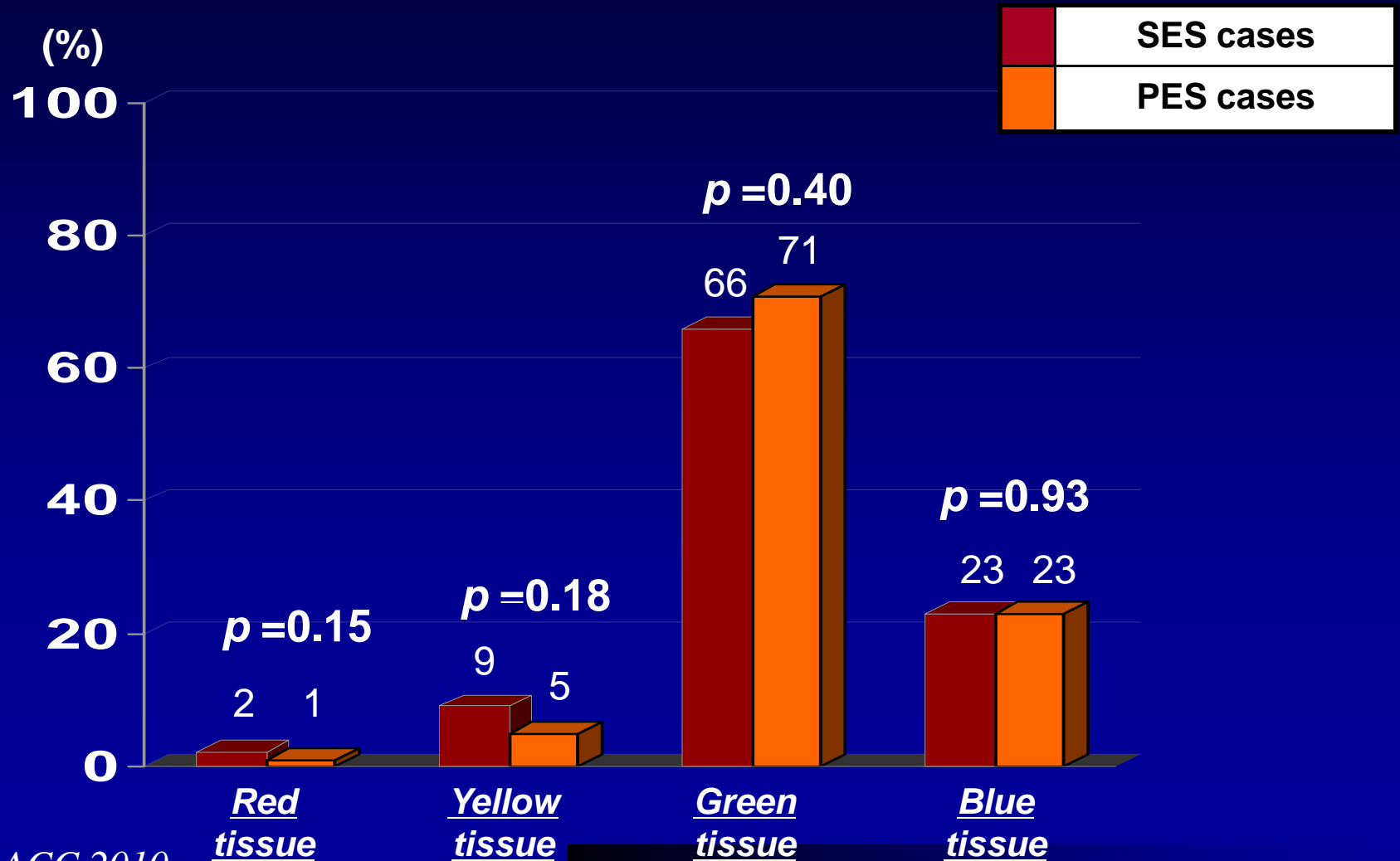


# Conclusions

- ◆ Neointimal tissue components after DES implantation were similar to BMS.
- ◆ Because of small sample size, we need further investigation to confirm these results.

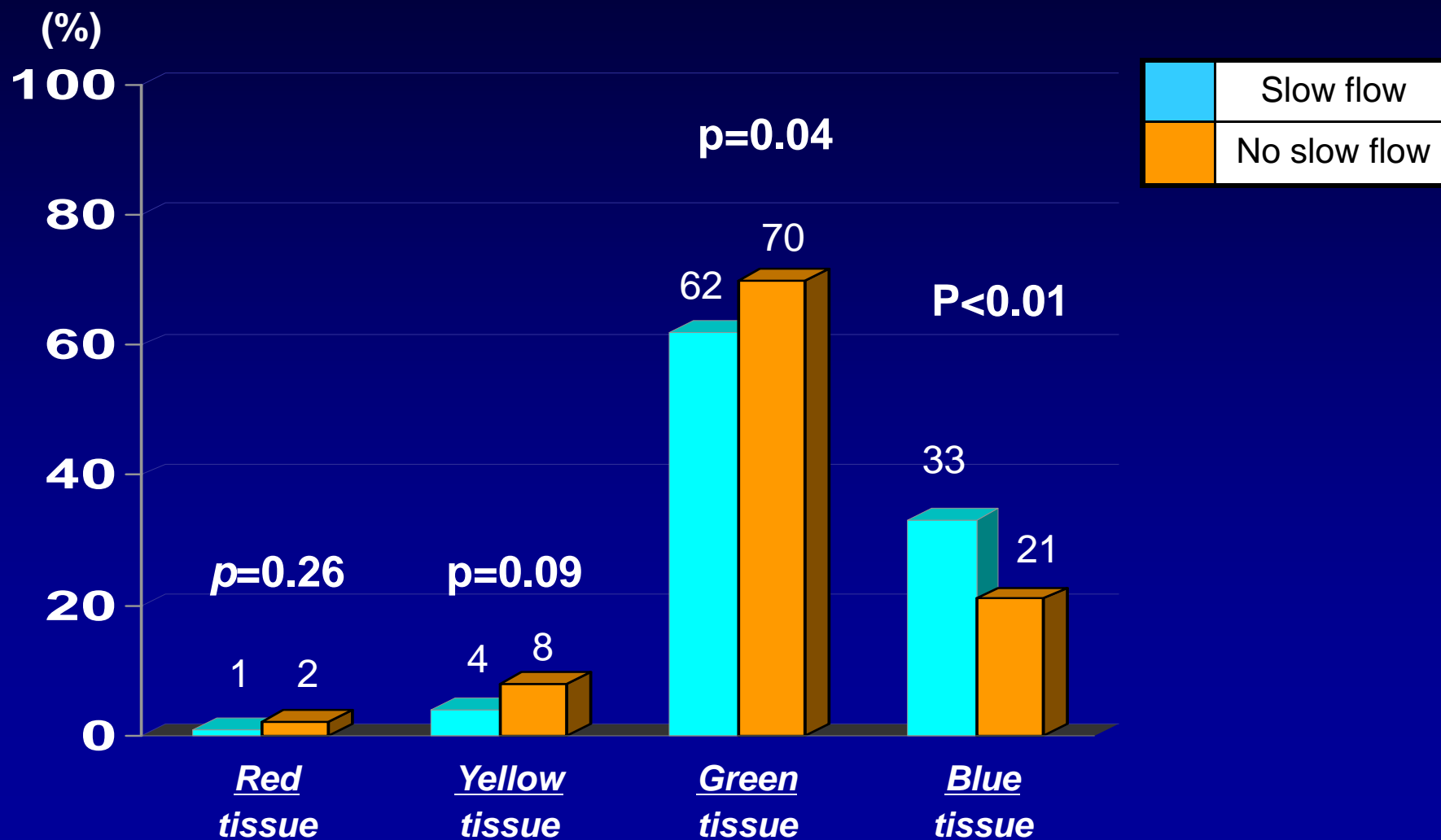
# Comparison of neointimal tissue components

at TLR site

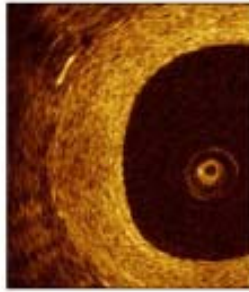


# Comparison of NI tissue components (at TLR site)

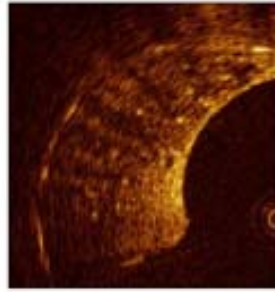
Group S (n=4) vs. Group N (n=11)



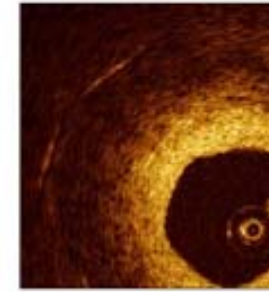
# Variety of DES neointimal tissue components by OCT



**Homogeneous:** restenotic tissue has uniform optical properties and does not show focal variations in backscattering pattern.

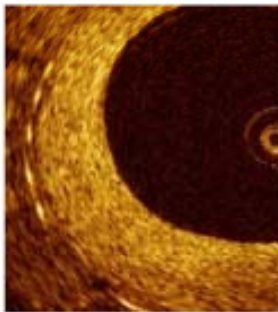


**Heterogeneous:** restenotic tissue has focally changing optical properties and shows various backscattering patterns

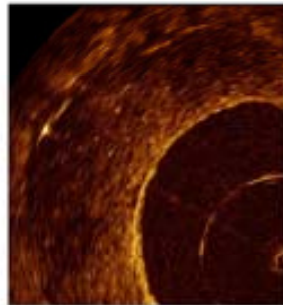


**Layered:** restenotic tissue consists of concentric layers with different optical properties: an adluminal high scattering layer and an abluminal low scattering layer

## Restenotic tissue backscatter

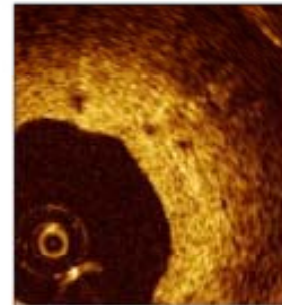


**High:** the majority of the tissue shows high backscatter and appears bright



**Low:** the majority of the tissue shows low backscatter and appears dark or black

## Microvessels visible



**Yes:** microvessels appear as well delineated low backscattering structures less than 200 micron in diameter that show a trajectory within the vessel



**No**



## *Objective 2*

*To Evaluate Serial Change in Persistent Tissue Component Using Integrated Backscatter  
Intravascular Ultrasound*

## *Impact of Neoadventitia (Periadventitia thickening) on Drug-Eluting Stent Restenosis*

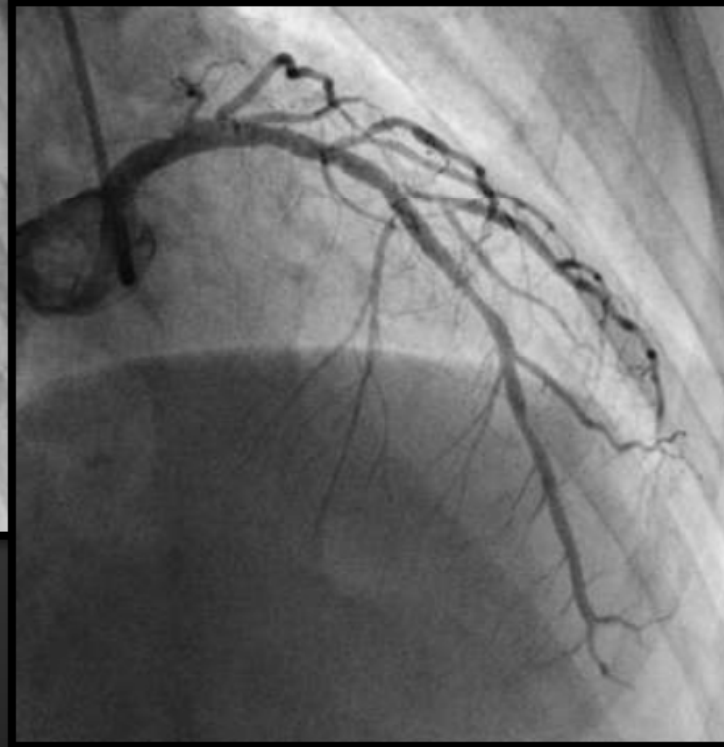
	<b>DES failure (N=45)</b>	<b>Patent DES (N=20)</b>	<b>p-value</b>
Stent length (mm)	30±13	21±7	<b>0.001</b>
EEM area (mm <sup>2</sup> )	12.8±4.0	13.6±5.1	0.53
Minimal lumen area (mm <sup>2</sup> )	2.5±0.8	3.1±1.4	<b>&lt;0.001</b>
MSA (mm <sup>2</sup> )	4.7±1.5	5.7±1.6	<b>0.01</b>
Max. IH area (mm <sup>2</sup> )	3.3±1.4	0.8±0.8	<b>&lt;0.001</b>
Neoadventitia area (mm <sup>2</sup> )	9.7±2.7	6.7±2.0	<b>&lt;0.001</b>

# Representative case (DES)

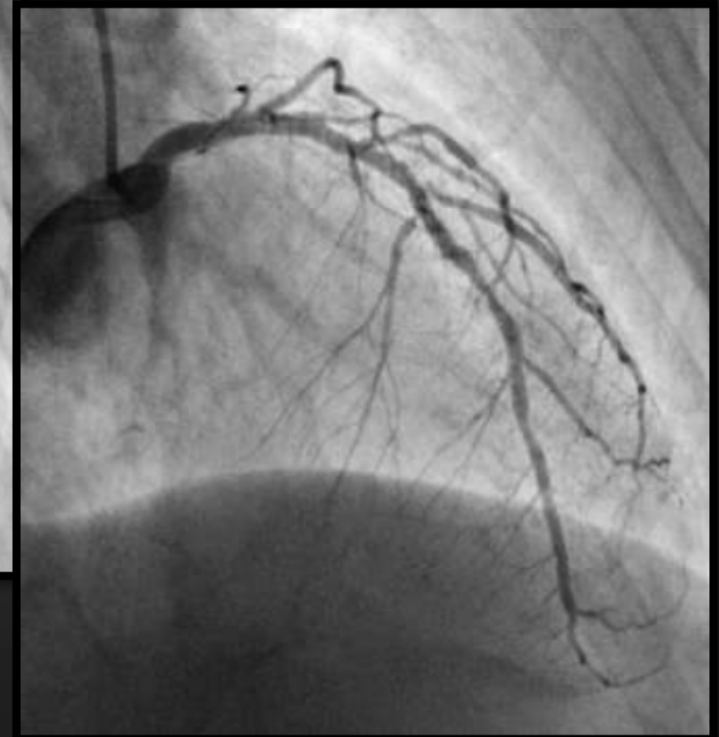
*Male 70's y/o LAD #6 3.0x28mm Cypher stent implantation*



*Immediately after DES implantation*



*At 10 month follow-up*



# Impact of DES on the persistent plaque compositions

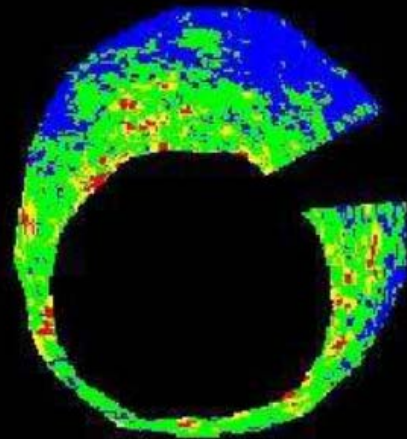
- serial IB-IVUS comparison -

Immediately after DES implantation



EEM area 16.8 mm<sup>2</sup>  
Peri-stent P+M area 9.2 mm<sup>2</sup>  
Stent area 7.6 mm<sup>2</sup>

% plaque volume of lipid: 26.3%



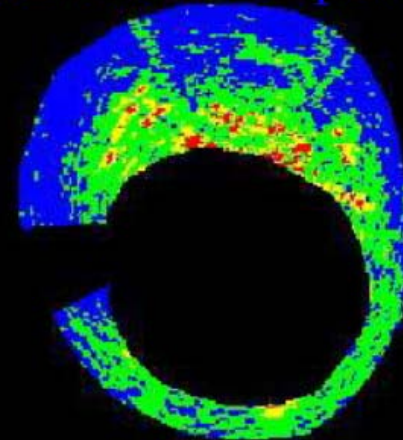
3.08% 12.19% 52.39% 32.34%

At 10 month follow-up



EEM area 19.1 mm<sup>2</sup>  
Peri-stent P+M area 11.5 mm<sup>2</sup>  
Stent area 7.6 mm<sup>2</sup>

% plaque volume of lipid: 38.3%



2.29% 6.83% 44.98% 45.91%

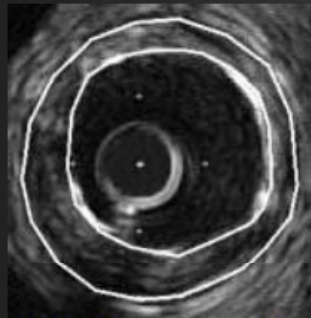


# Impact of BMS on the persistent plaque compositions

- serial IB-IVUS comparison -

Male 80's y/o LAD #7 3.0x25mm Duraflex stent implantation

Baseline



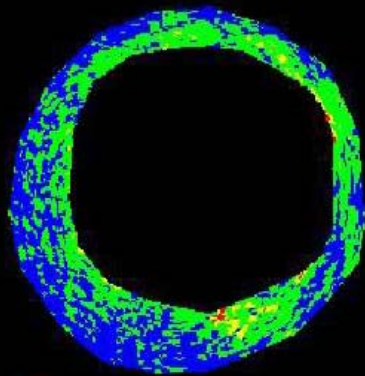
EEM area 14.6 mm<sup>2</sup>  
Peri-stent P+M area 6.5 mm<sup>2</sup>  
Stent area 8.1 mm<sup>2</sup>

At 10 month follow-up



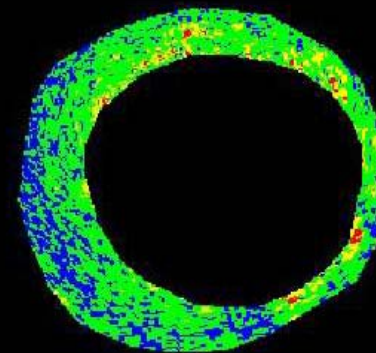
EEM area 14.4 mm<sup>2</sup>  
Peri-stent P+M area 6.4 mm<sup>2</sup>  
Stent area 8.0 mm<sup>2</sup>

% plaque volume of lipid: 45.6%



0.868% 50.725%  
3.02% 45.387%

% plaque volume of lipid: 20.1%



1.09% 8.50% 66.96% 23.44%

# Baseline Characteristics

	BMS (n=20)	DES (n=22)	p Value
Age, yrs	66.3±9.3	68.5±8.6	0.41
Male gender, n (%)	15 (75)	21 (95)	0.15
Smoking, n (%)	12 (60)	15 (68)	0.82
Diabetes mellitus, n (%)	10 (50)	9 (41)	0.55
Hypertension, n (%)	12 (60)	12 (55)	0.72
Hypercholesterolemia, n (%)	11 (55)	10 (45)	0.54
Unstable angina, n (%)	8 (40)	9 (41)	0.99
Previous MI, n (%)	6 (30)	5 (23)	0.85
Total cholesterol, mg/dl	188.0±47.6	180.8±28.7	0.55
LDL-cholesterol, mg/dl	116.4±38.8	110.2±28.1	0.56
HDL-cholesterol, mg/dl	48.2±10.8	47.0±10.6	0.71
Triglyceride, mg/dl	153.0±71.0	122.8±68.0	0.17
hs-CRP, mg/dl	0.32±0.36	0.29±0.36	0.79
Troponin-I ≥ 0.1 ng/ml	7 (35)	3 (14)	0.21
Prescription at discharge			
Statin, n (%)	19 (95)	19 (86)	0.67
ACEI/ARB, n (%)	13 (65)	15 (68)	0.99

# Angiographic Characteristics

	BMS (n=20)	DES (n=22)	p Value
Treated vessel			0.24
LAD, n (%)	7 (35)	13 (59)	
LCX, n (%)	4 (20)	4 (18)	
RCA, n (%)	9 (45)	5 (23)	
Type of lesion			0.11
A/B1, n (%)	14 (70)	9 (41)	
B2/C, n (%)	6 (30)	13 (59)	
Location of lesion			0.32
Proximal, n (%)	9 (45)	10 (45)	
Mid, n (%)	6 (30)	10 (45)	
Distal, n (%)	2 (10)	2 (9)	
Reference vessel diameter, mm	2.87±0.33	2.81±0.46	0.59
Minimum vessel diameter, mm	1.24±0.28	1.15±0.33	0.35
% diameter stenosis, %	56.4±9.9	58.8±10.4	0.44
Lesion length, mm	14.7±6.4	17.2±8.4	0.30
Average stent diameter, mm	3.30±0.25	3.10±0.36	0.04
Total stent length, mm	18.8±7.8	23.2±9.7	0.11

## *IVUS Measurements at Baseline and Follow-up*

	Baseline	Follow-up	p Value
<b><u>BMS</u></b>			
Vessel volume, mm <sup>3</sup>	144.2±22.3	140.6±15.7	0.21
Stent volume, mm <sup>3</sup>	91.3±11.4	90.4±12.2	0.64
Peristent plaque volume, mm <sup>3</sup>	53.1±13.0	50.4±6.6	0.17
Lumen volume, mm <sup>3</sup>	91.3±11.4	56.4±10.5	<0.001
Intimal hyperplasia volume, mm <sup>3</sup>	-	34.9±11.7	-
<b><u>DES</u></b>			
Vessel volume, mm <sup>3</sup>	143.3±40.0	154.1±42.0	<0.001
Stent volume, mm <sup>3</sup>	87.0±22.5	88.8±24.3	0.06
Peristent plaque volume, mm <sup>3</sup>	56.3±21.4	65.4±23.2	<0.001
Lumen volume, mm <sup>3</sup>	87.0±22.5	74.5±20.1	<0.01
Intimal hyperplasia volume, mm <sup>3</sup>	-	11.1±6.8	-

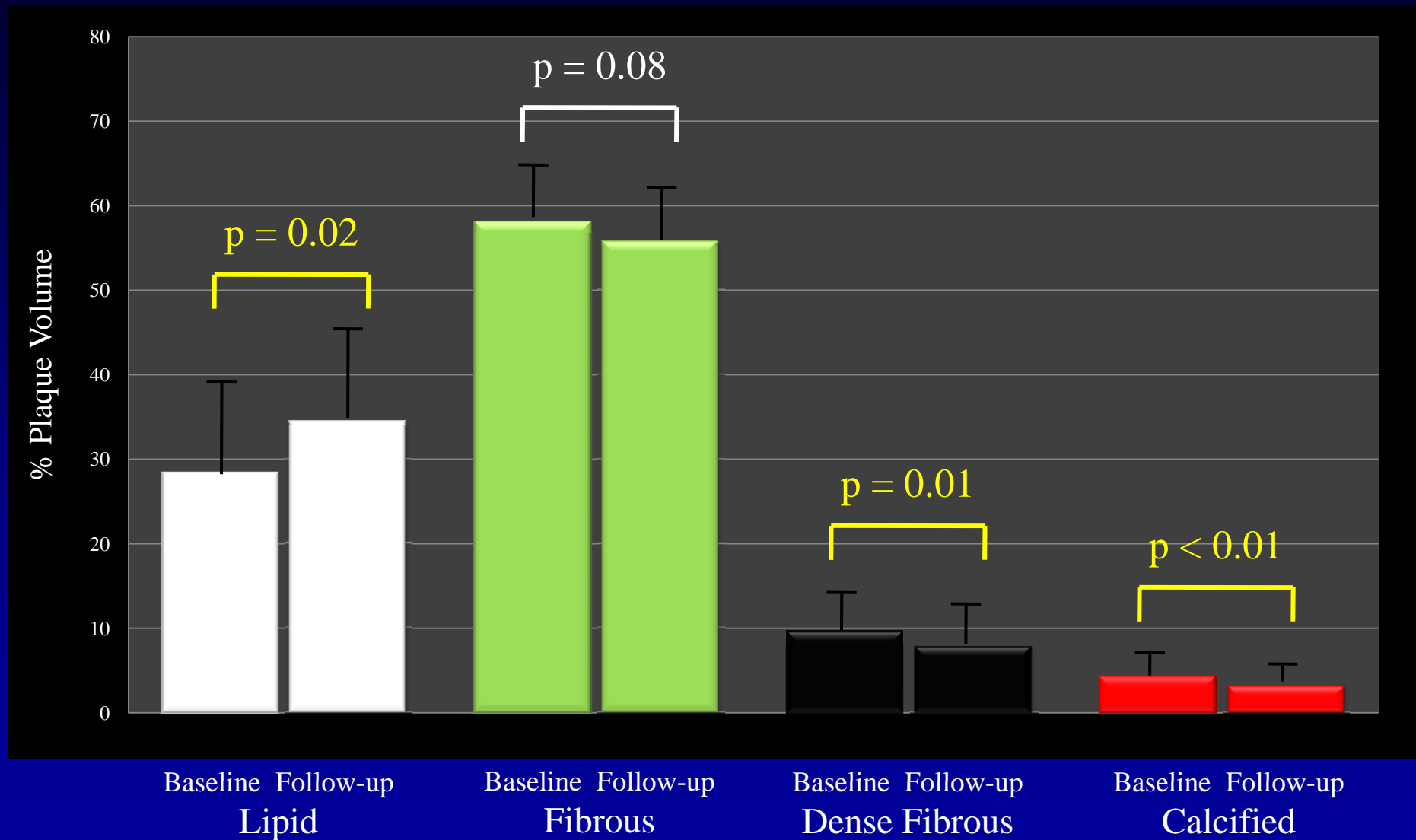


# Comparison of Vessel Responses between BMS and DES

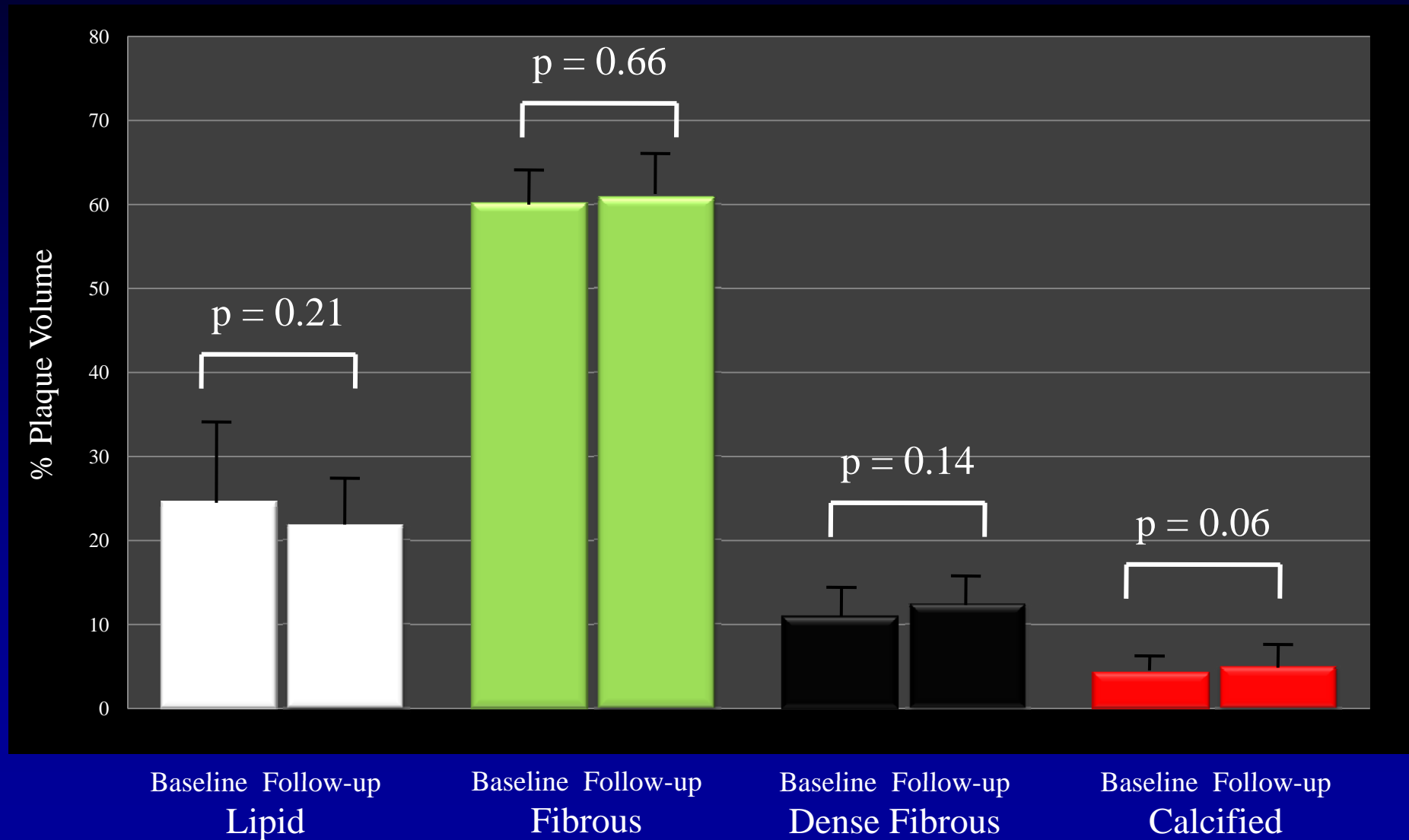
- Serial IVUS comparison -

	BMS (n=20)	DES (n=22)	pValue
$\Delta$ Vessel volume, mm <sup>3</sup>	-3.7±12.7	10.8±10.7	<0.001
$\Delta$ Persistent plaque volume, mm <sup>3</sup>	-2.7±8.6	9.1±9.1	<0.001
Incomplete stent apposition (ISA)			
Late acquired ISA, n (%)	0 (0)	4 (18)	0.14
Persistent ISA, n (%)	1 (5)	2 (9)	0.93
Resolved ISA, n (%)	3 (15)	0 (0)	0.20

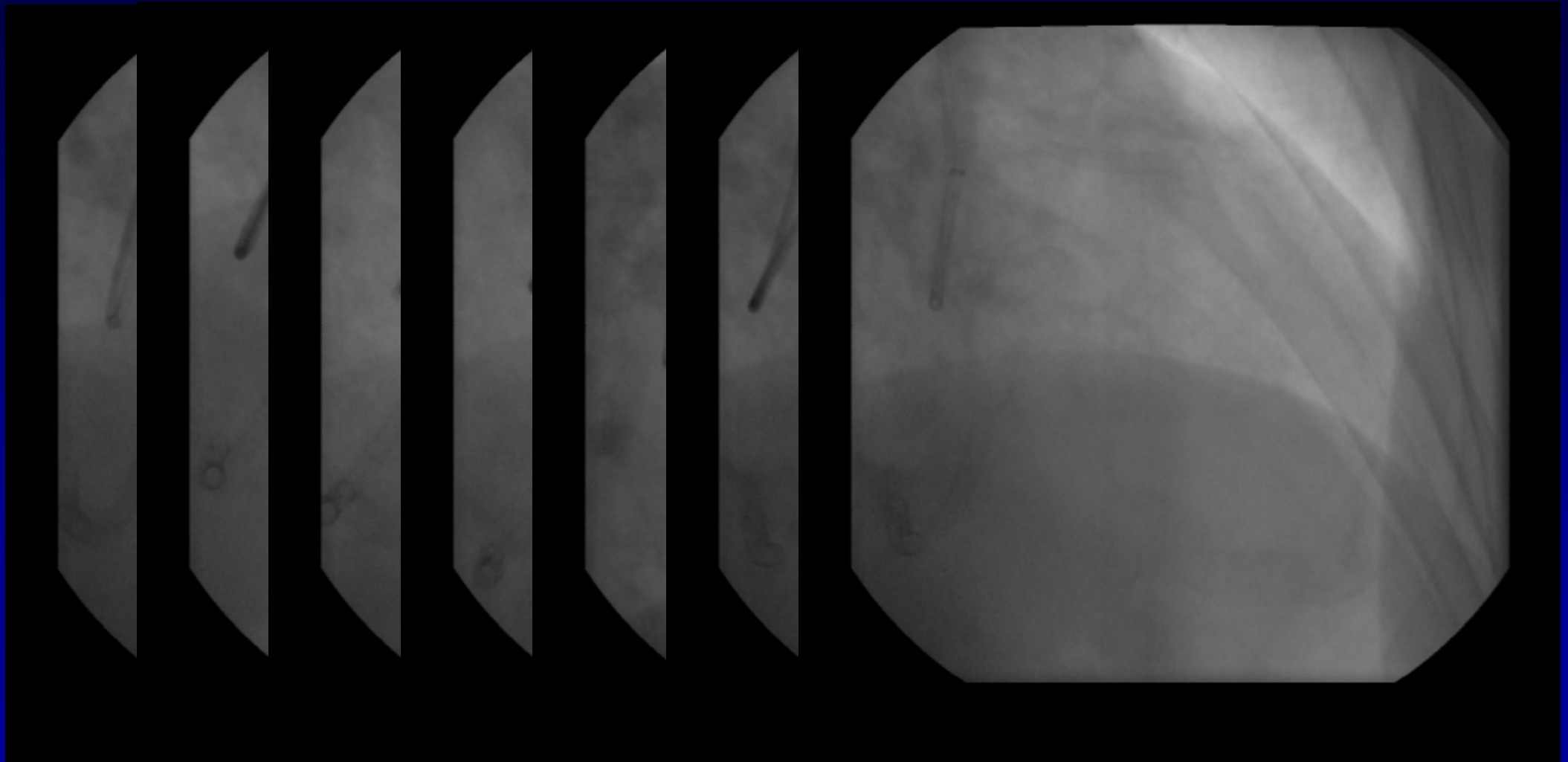
# Changes of Plaque Component Fraction in DES



# Changes of Plaque Component Fraction in BMS

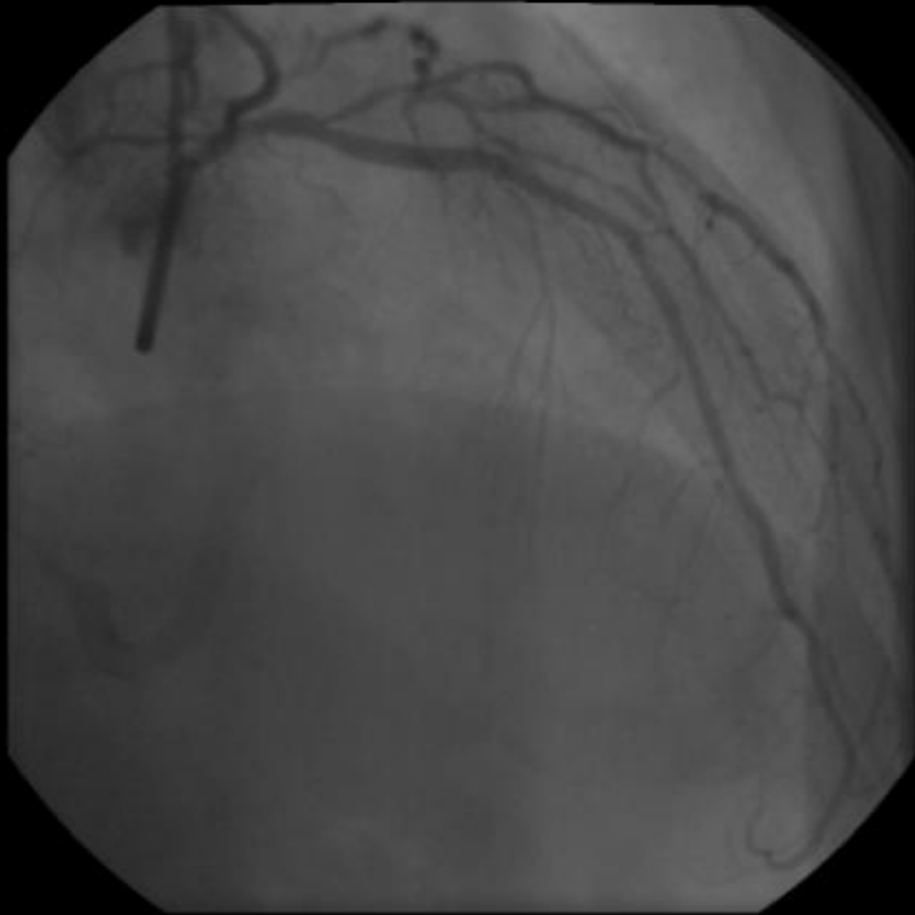


# Case (ENDEAVOR stent: 2<sup>nd</sup> Generation DES)





# ENDEAVOR stent: 2<sup>nd</sup> Generation DES

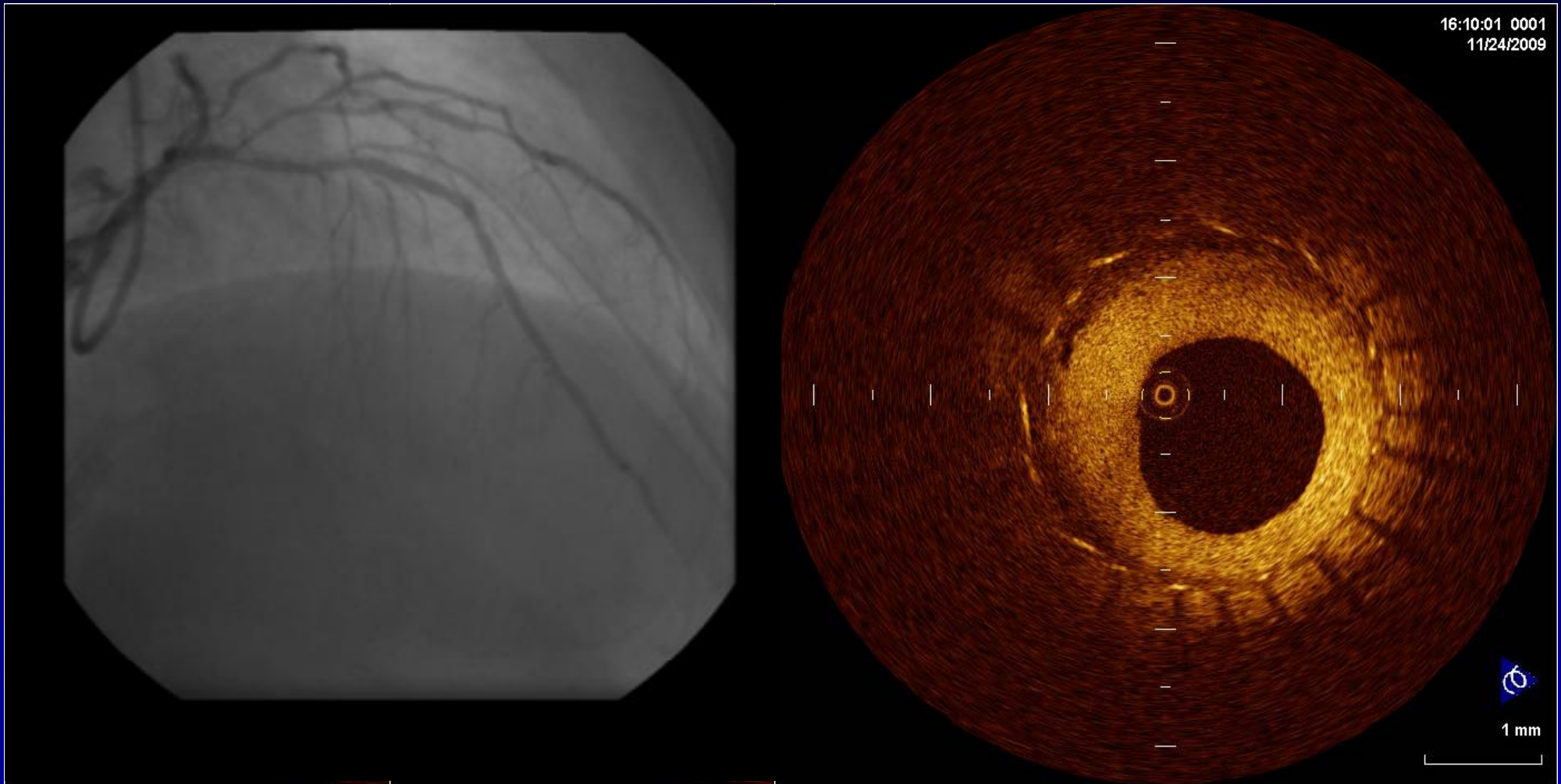


Post stenting (Final)

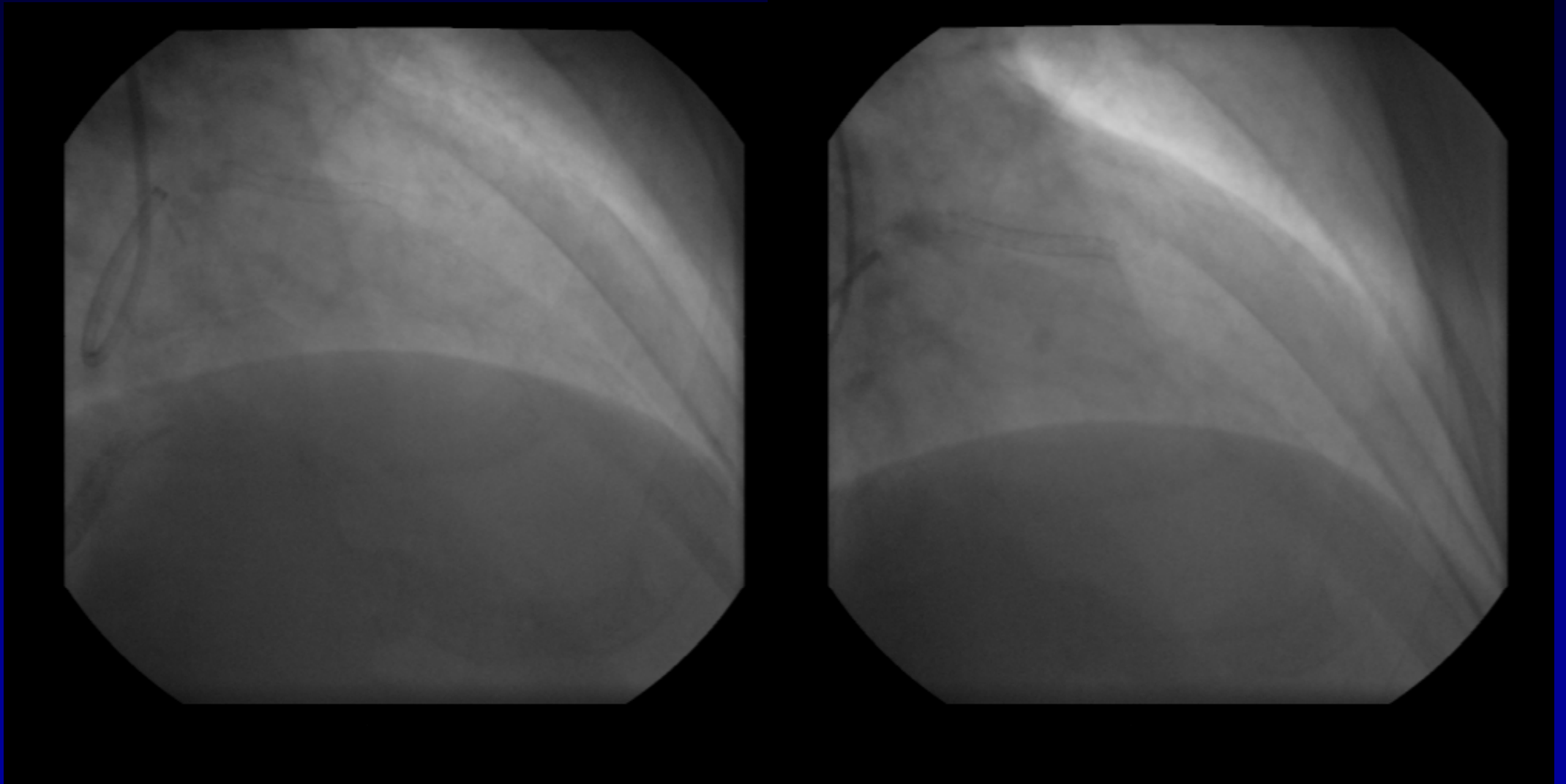


6-month follow-up

# ENDEAVOR stent: 2<sup>nd</sup> Generation DES (6-month follow-up)

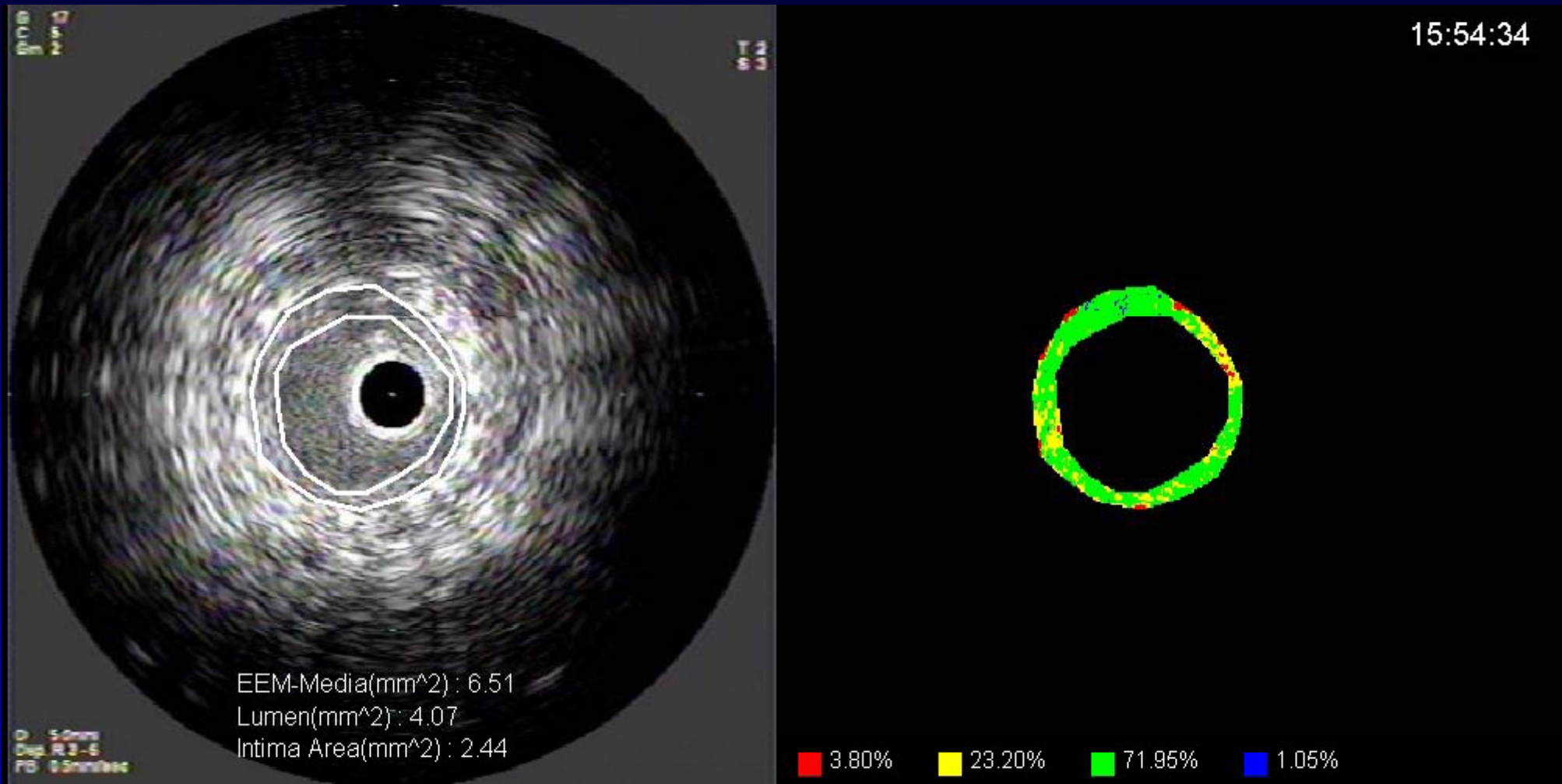


# ENDEAVOR stent: 2nd Generation DES (6-month follow-up)



# ENDEAVOR stent: 2nd Generation DES

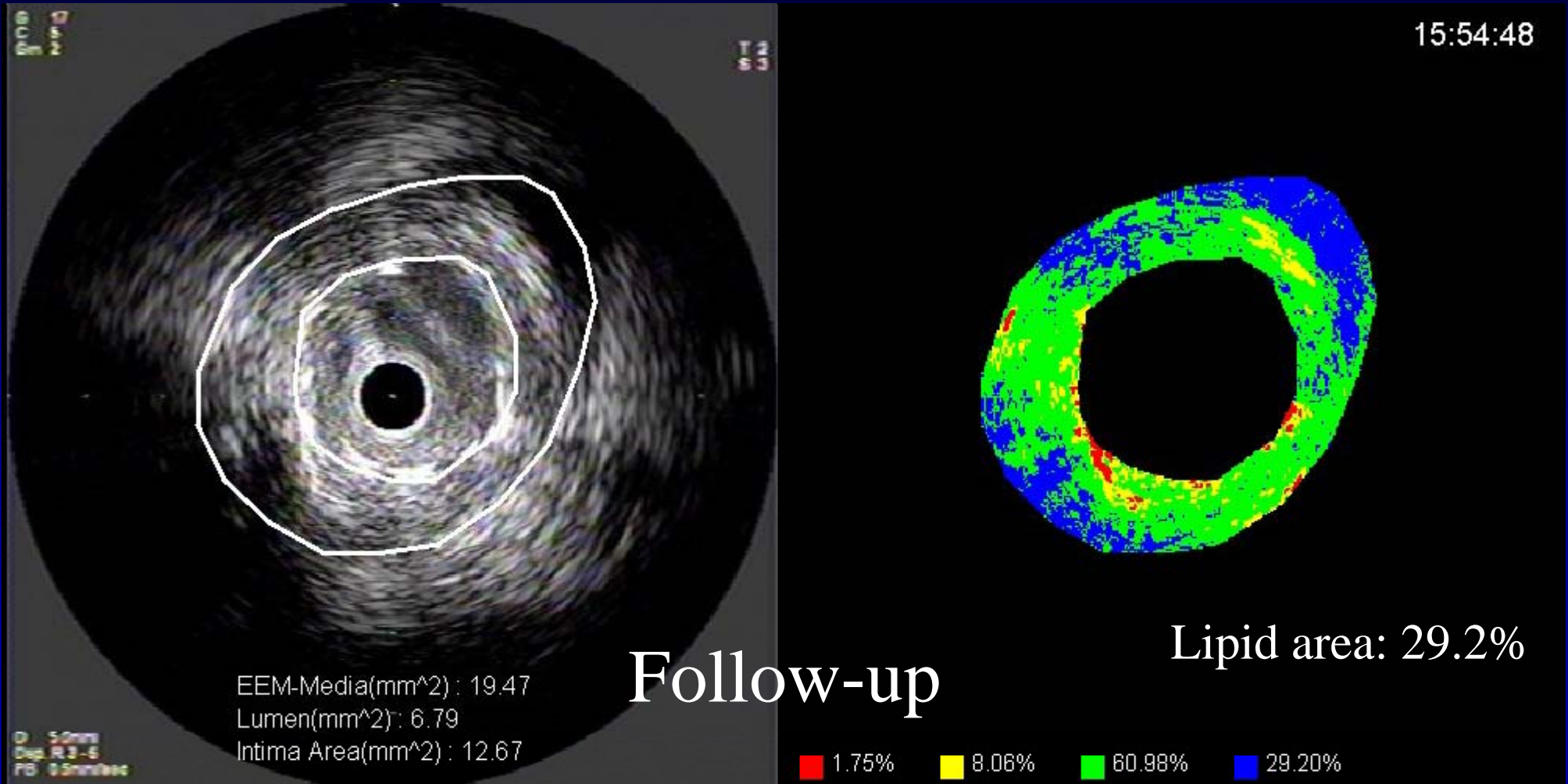
## Neointima





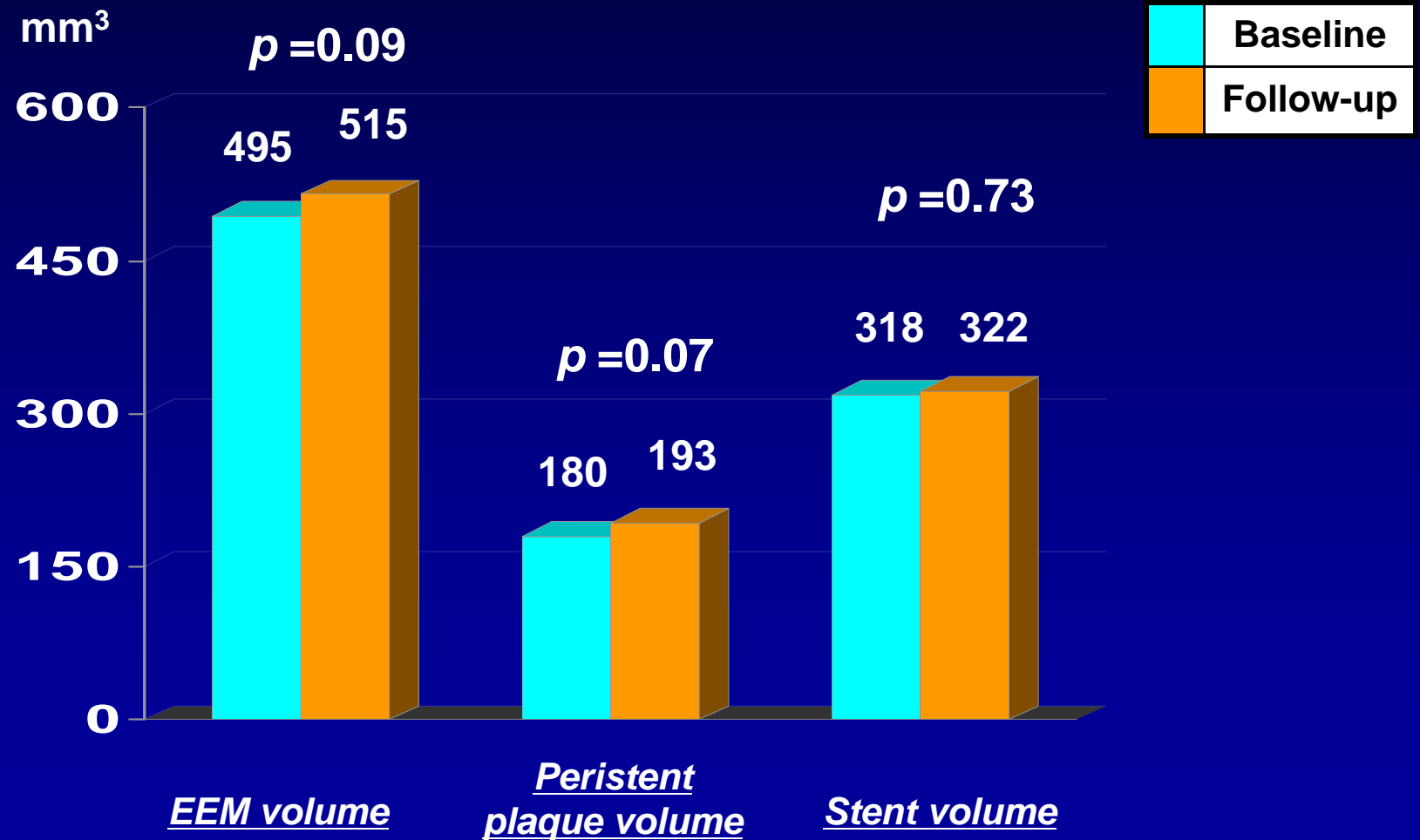
# ENDEAVOR stent: 2nd Generation DES

## Peristent plaque

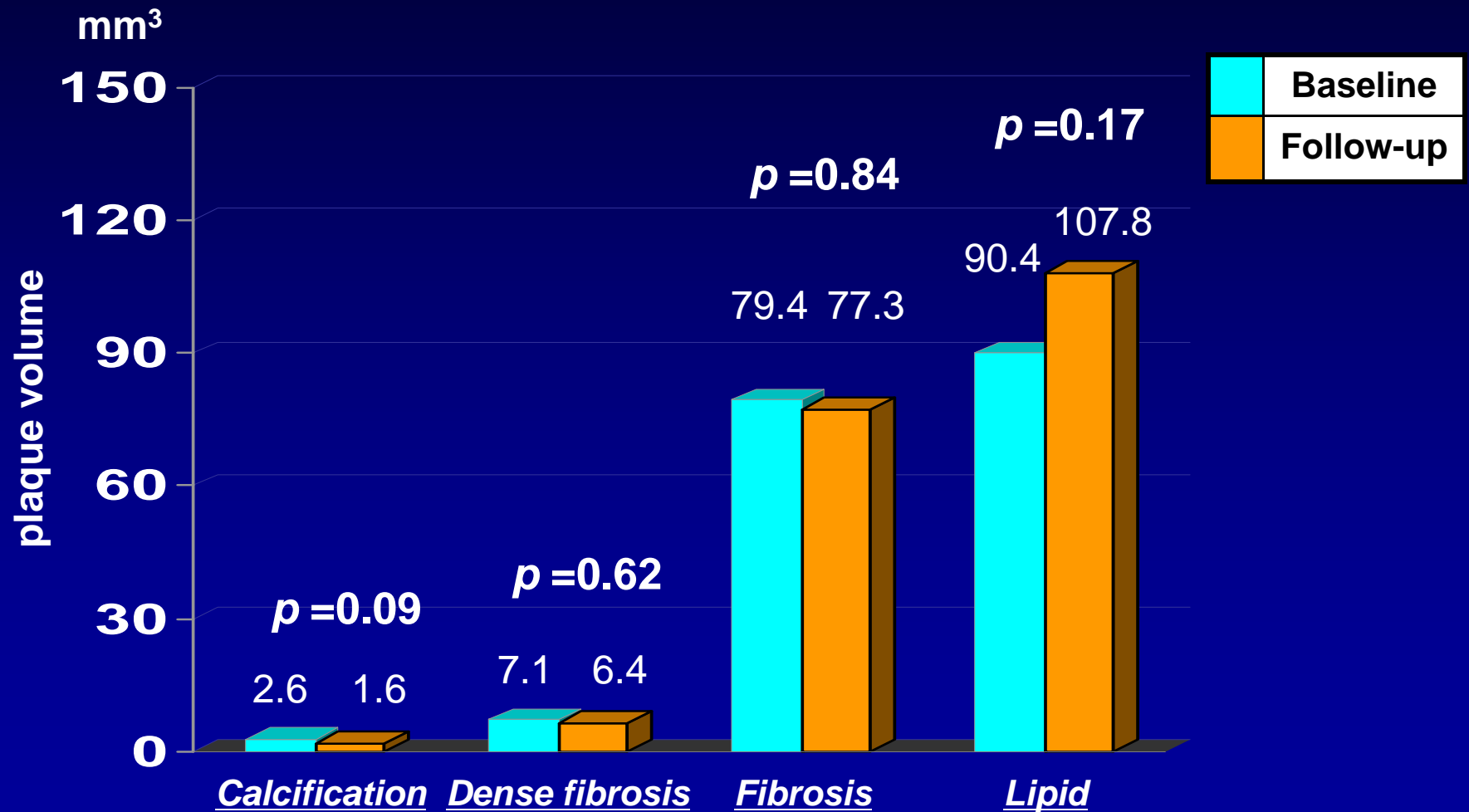




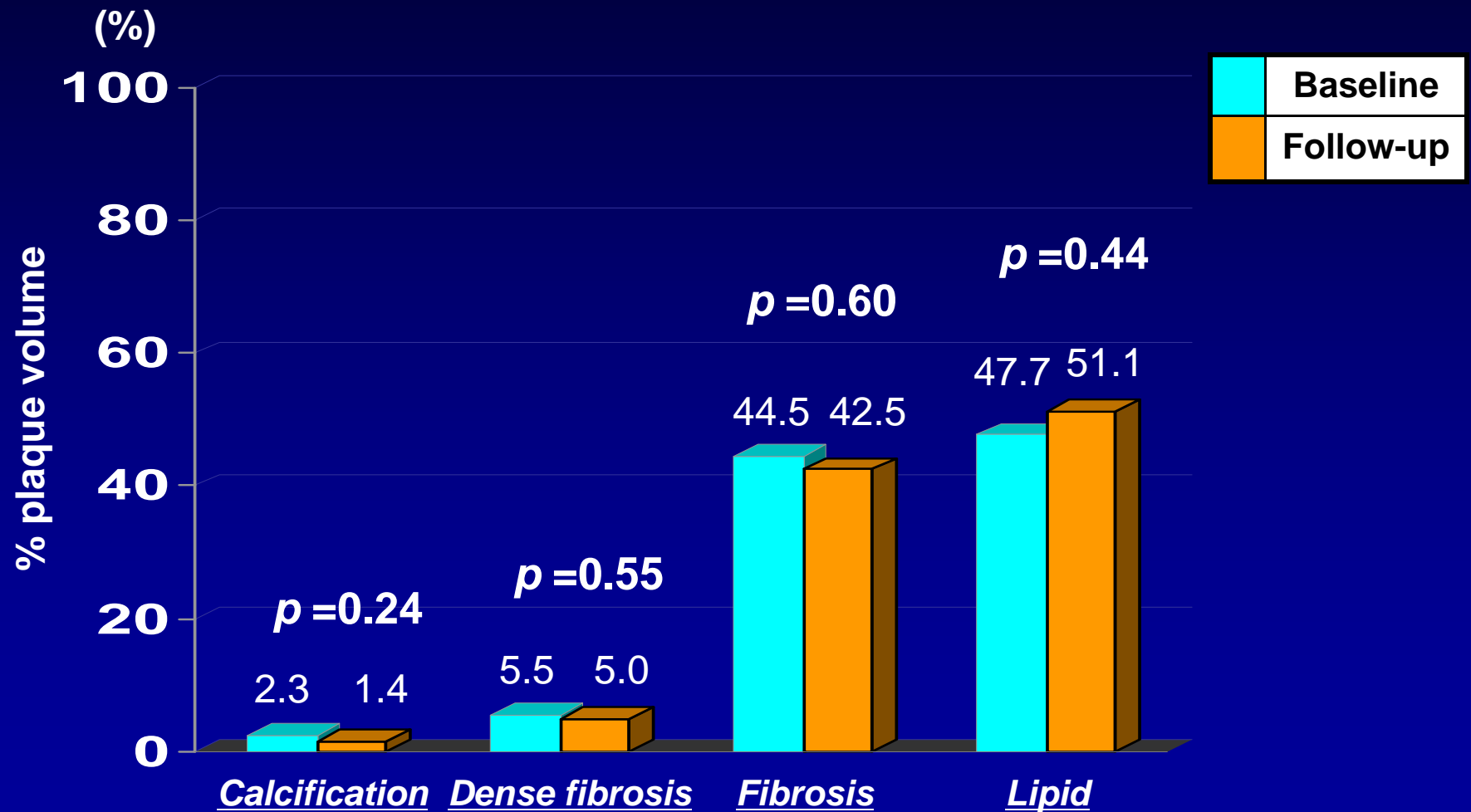
# Volumetric IVUS analysis in BMS (N=4)



# Serial change of persistent plaque components in BMS (N=4)

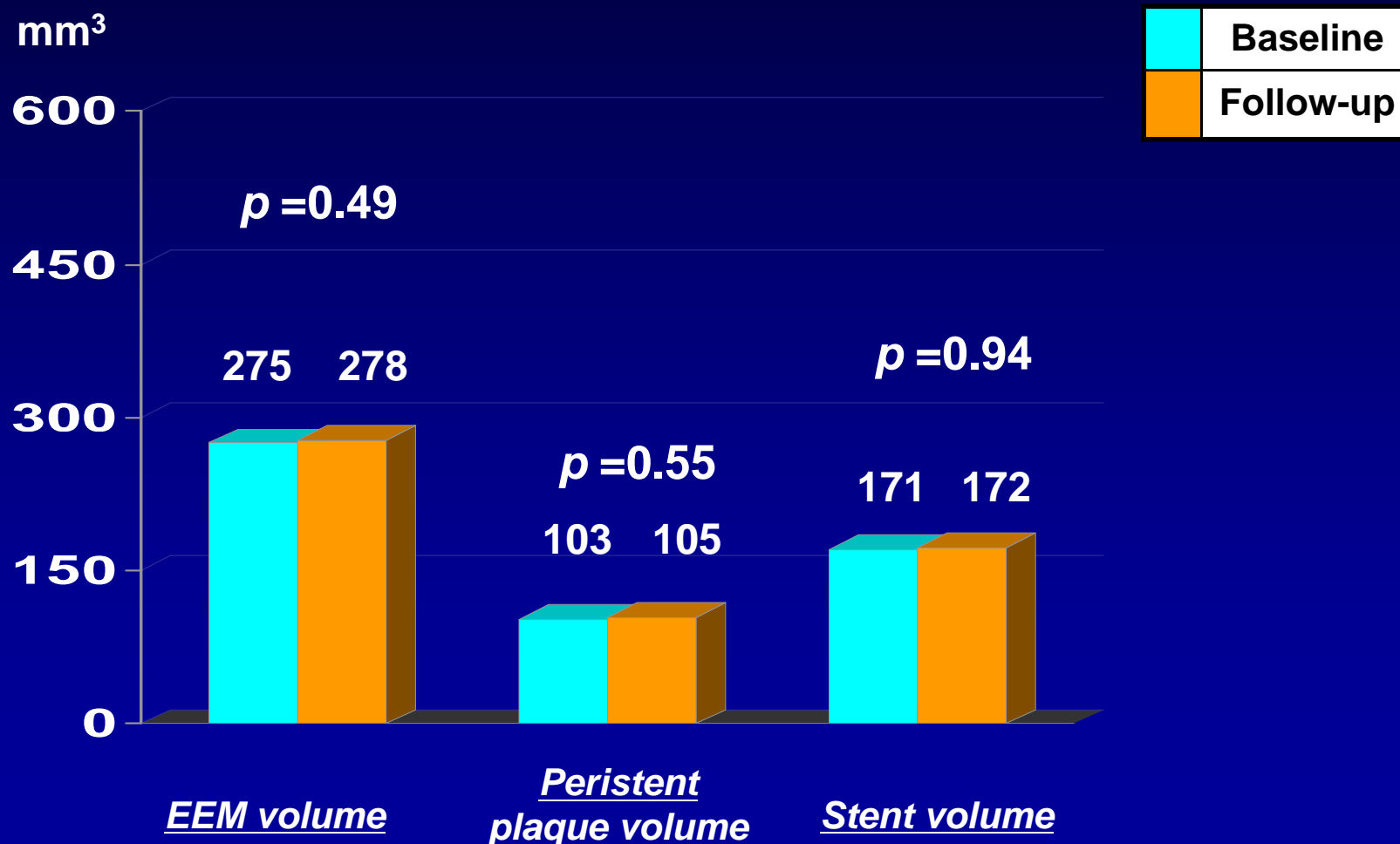


# Serial change of persistent plaque components in BMS (N=4)



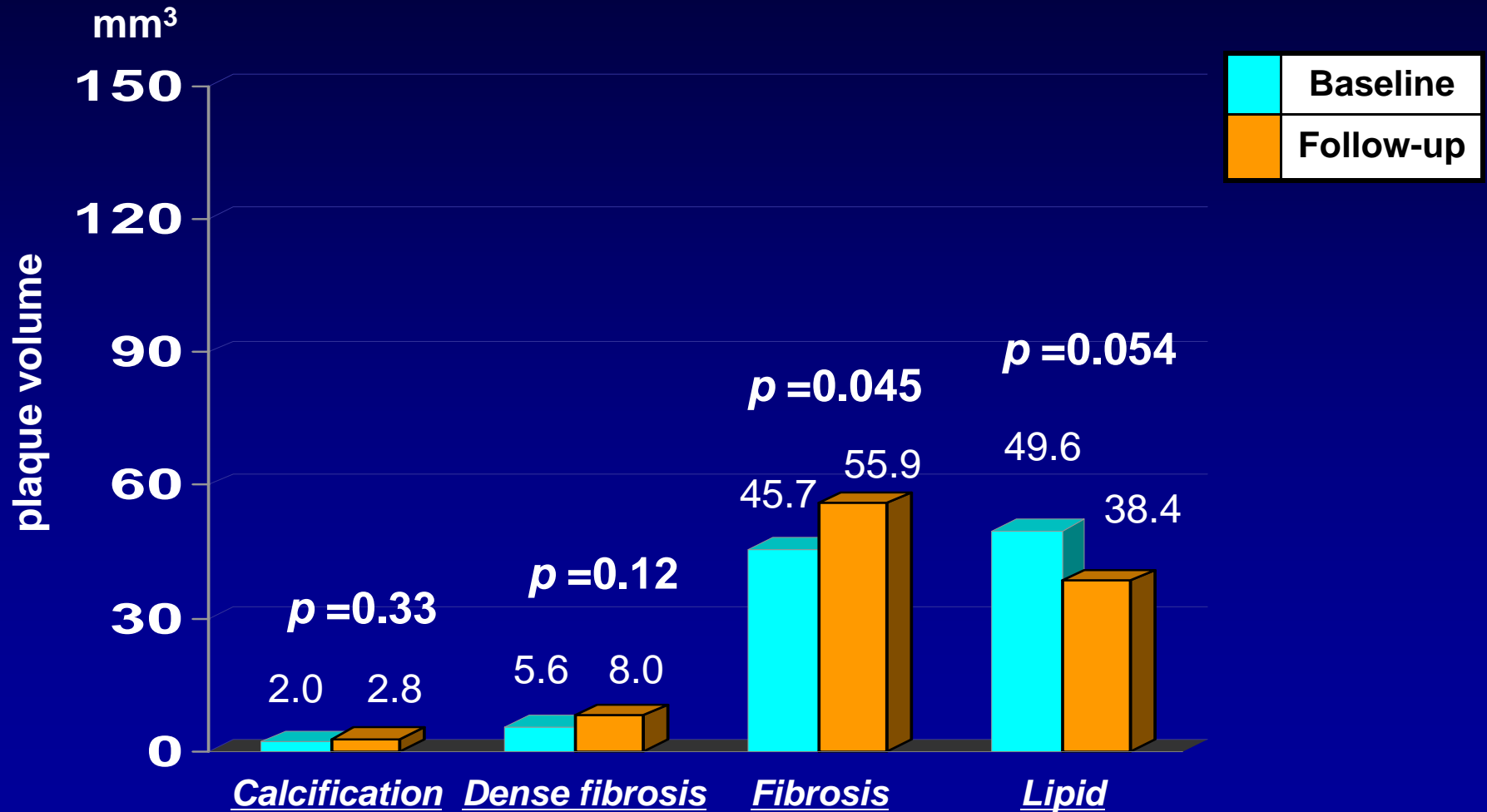
# Volumetric IVUS analysis

ENDEAVOR stent (N=9)



# Serial change of persistent plaque components

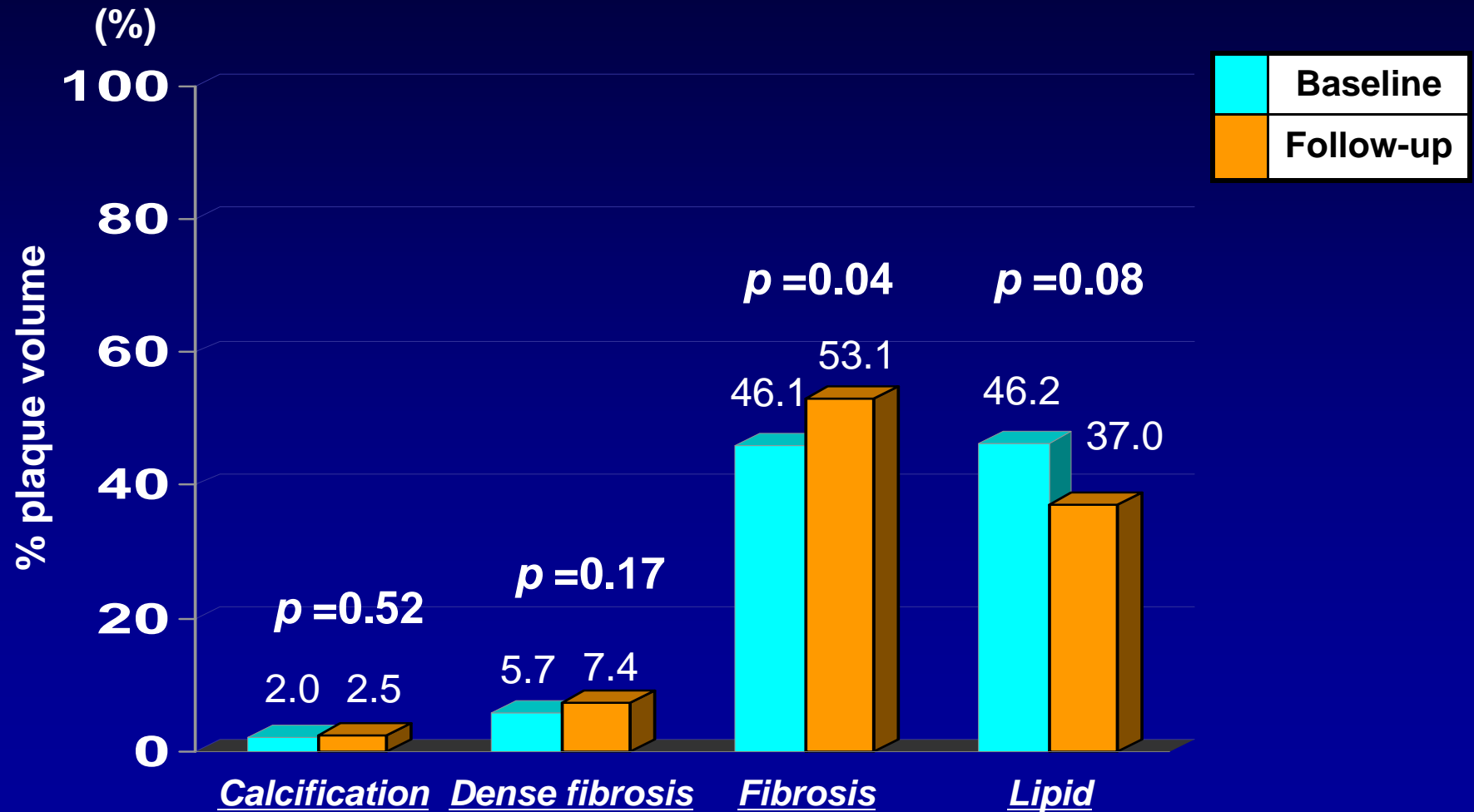
ENDEAVOR stent (N=9)





# Serial change of persistent plaque components

ENDEAVOR stent (N=9)



# Summary

- On average, there were no significant differences of neointimal tissue components (mainly composed of fibrotic tissue) at TLR site between DES and BMS as assessed by IB-IVUS.
- However, there were some few cases which had abnormal neointimal tissue components (vulnerable neointima) after DES implantation.
- Compared to BMS, DES caused positive remodeling and affected tissue characteristics of persistent plaque as assessed by IB-IVUS.
- Second generation DES (ENDEAVOR stent) may have a favorable influence on coronary arterial healing process after DES implantation.

## *Conclusion*

Compared to BMS, DES had affected tissue characteristics of instant neointimal tissue and persistent coronary plaque components as assessed by IB-IVUS.

Second generation DES may be potentially safe, from the point of view of chronic arterial response to DES implantation.



*Thank you for your attention!*

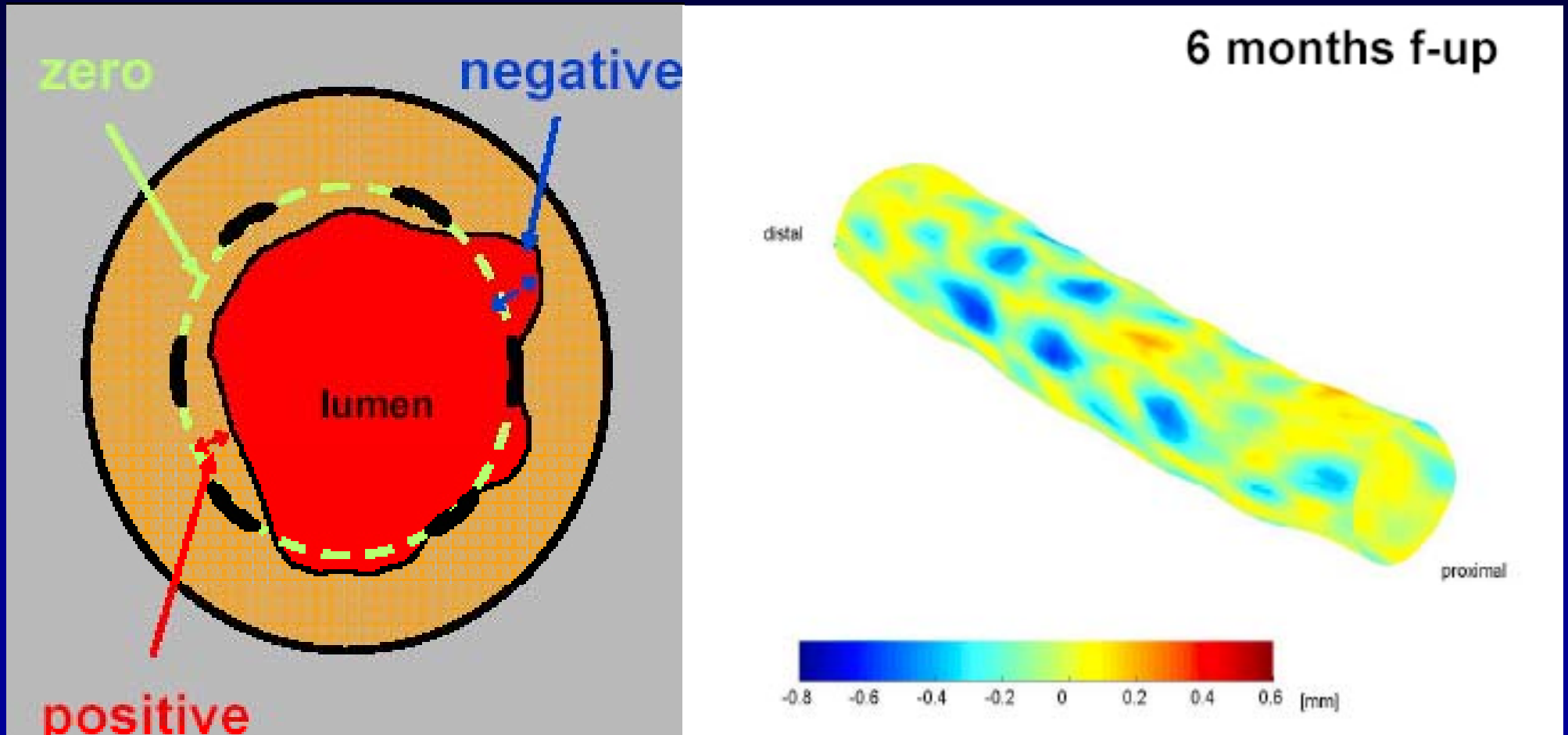
*KSC - JCS Joint Symposium 2010*





# Heterogeneity of Neointimal Coverage

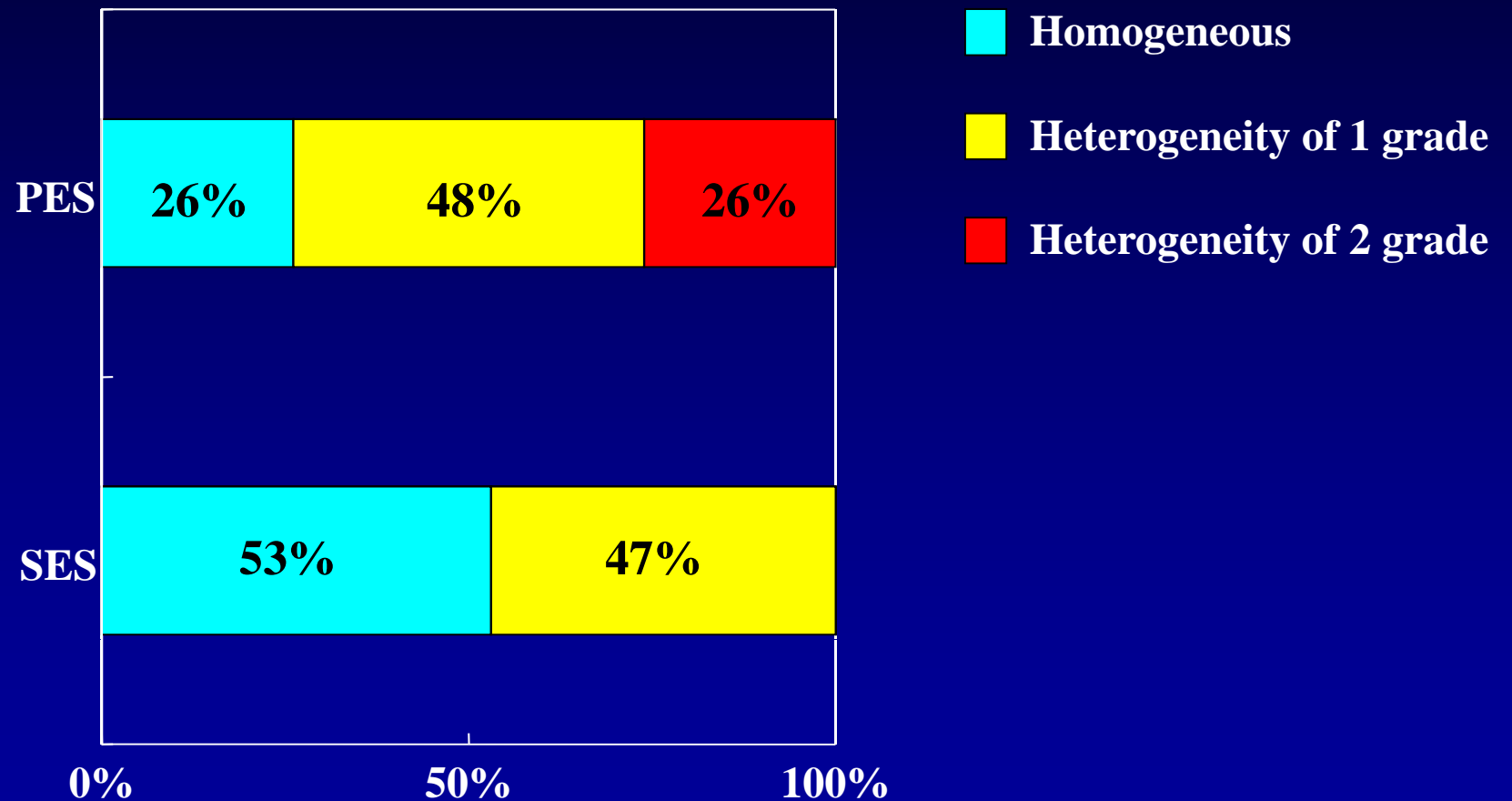
## Outpouching or Cavities





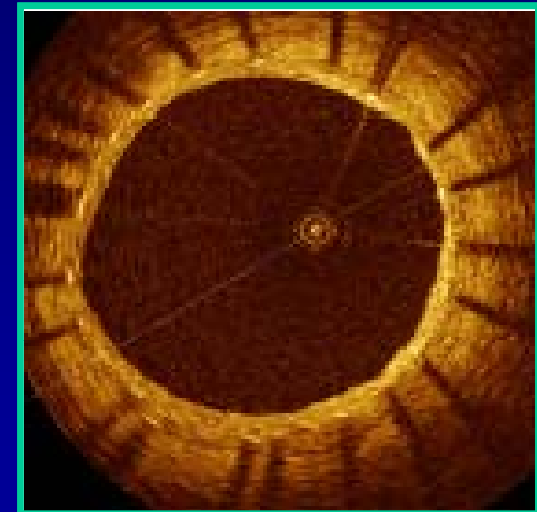
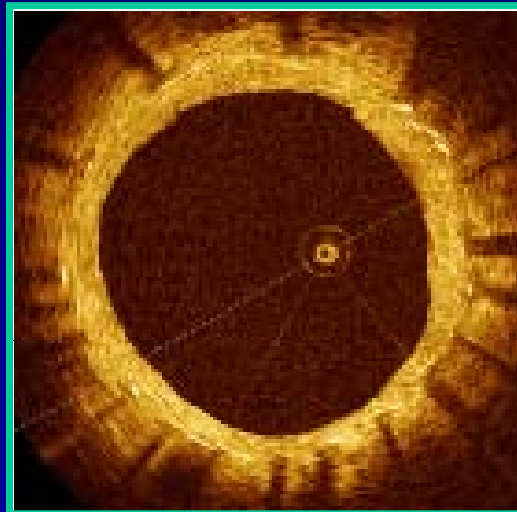
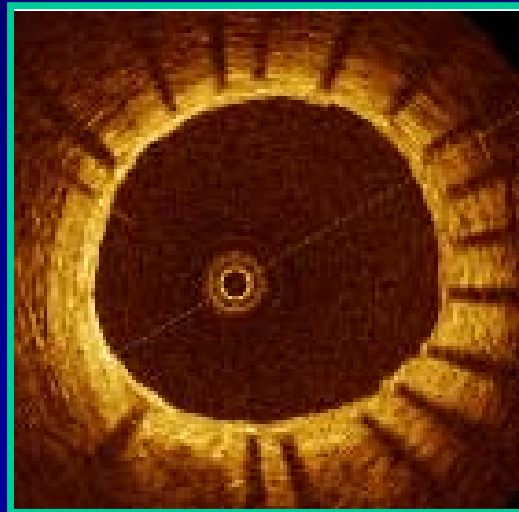
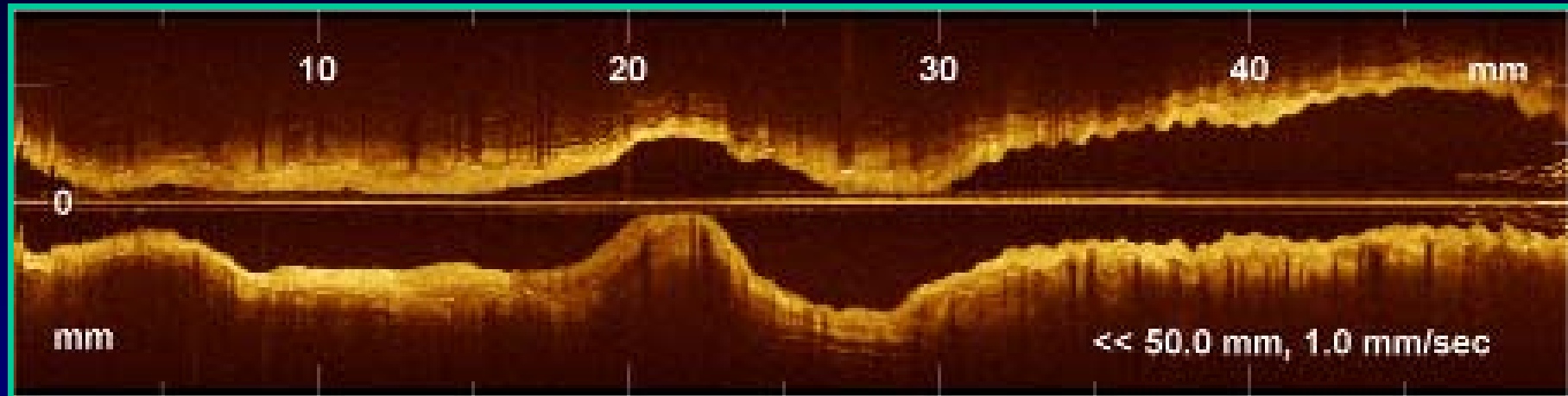
# Heterogeneity of NIC Grades: Angioscopy

## PES vs. SES



# OCTによる新生内膜被覆の評価

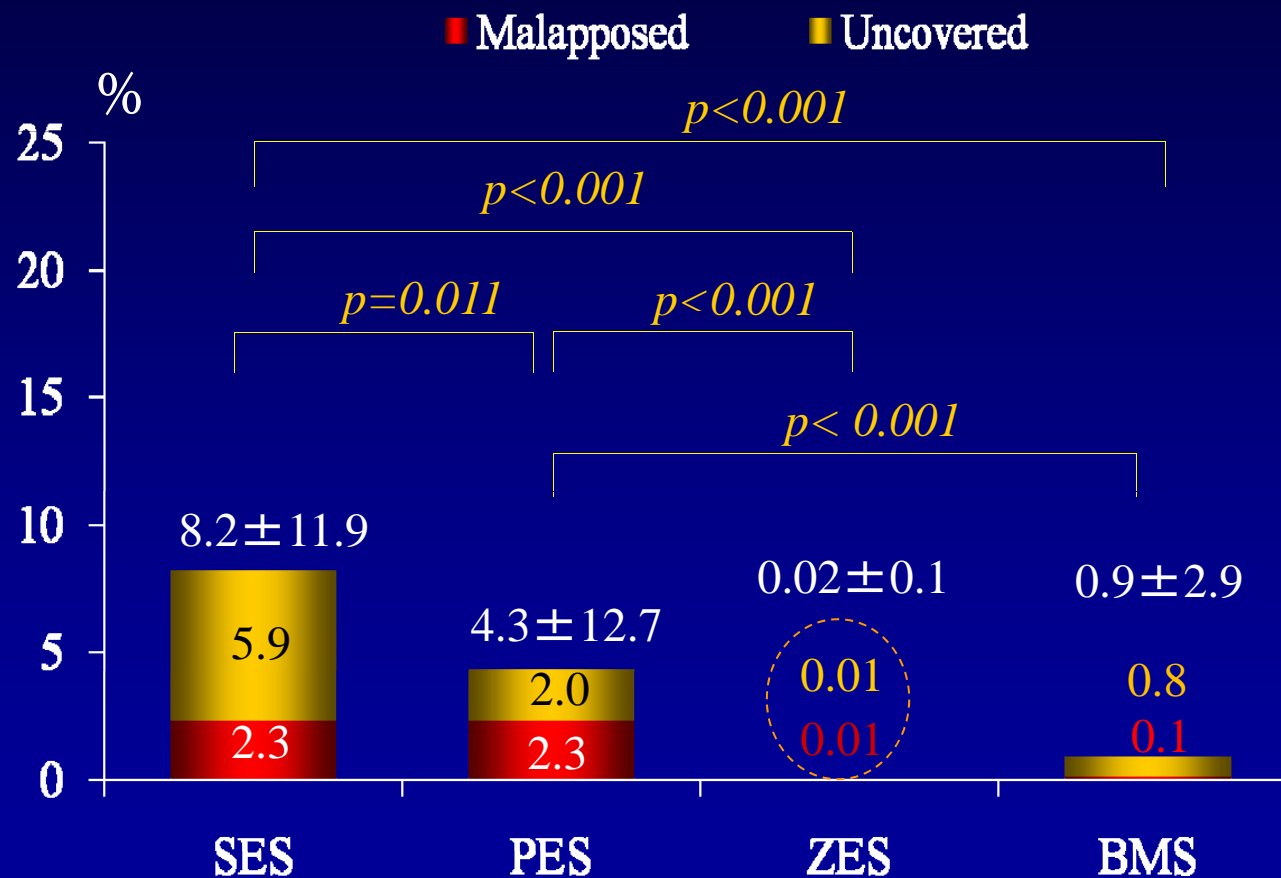
ステント留置後6カ月後 (Endeavor stent: n=44)



Endeavor 24,076ストラットが100%均一に被覆されていた

# OCTによる被覆評価

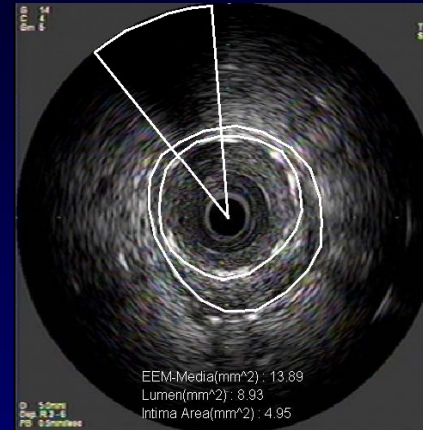
各種DESのステント非被覆およびステント不圧着の割合



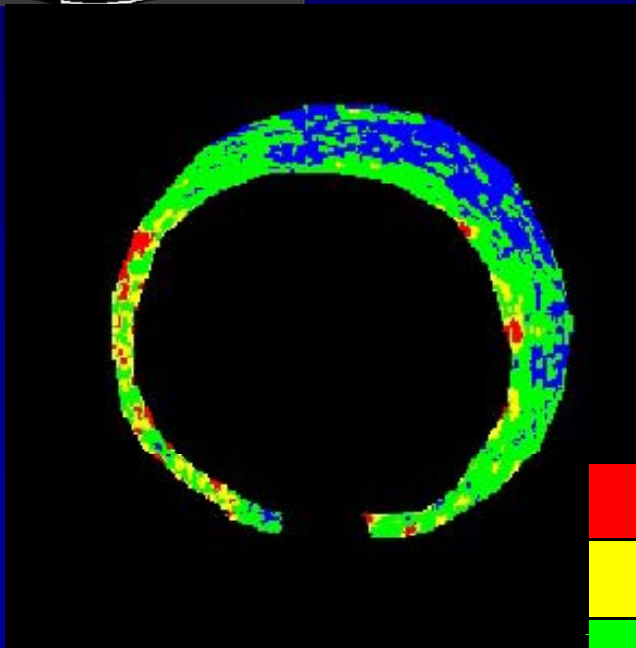
# Representative case (BMS)



EEM:	14.49mm <sup>2</sup>
Periplaque:	4.90mm <sup>2</sup>
Stent:	9.59mm <sup>2</sup>

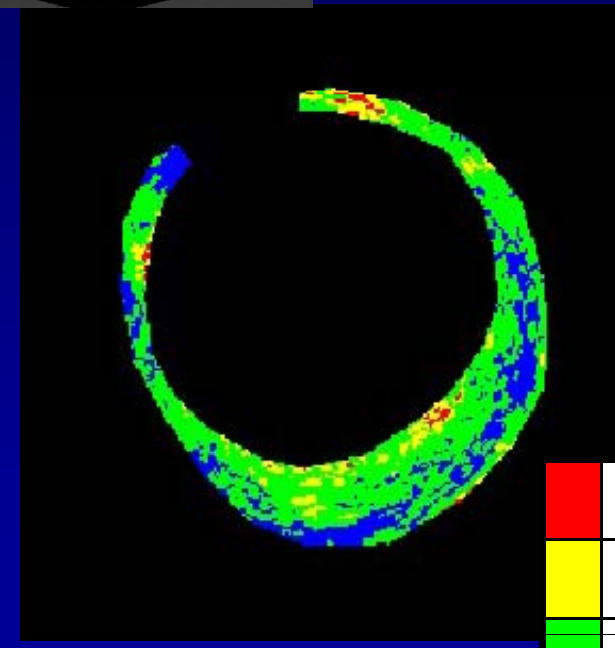


EEM:	13.89mm <sup>2</sup>
Periplaque:	4.95mm <sup>2</sup>
Stent:	8.93mm <sup>2</sup>



**Baseline**

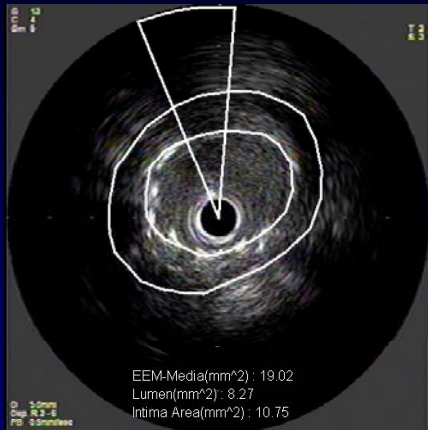
	3.67%
	10.93%
	57.53%
	27.87%



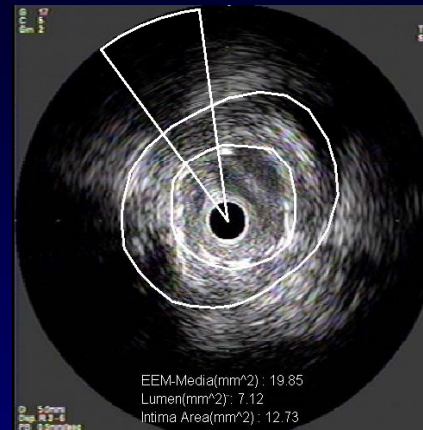
**Follow up**

	1.67%
	9.44%
	65.58%
	23.32%

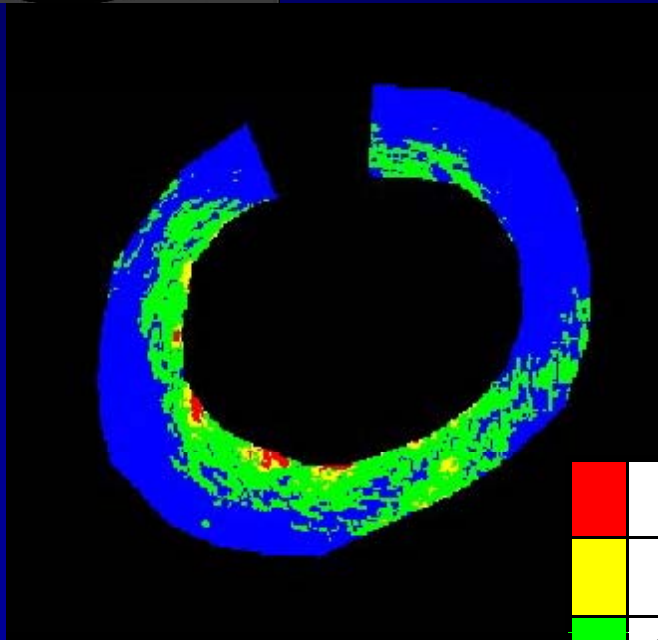
# Representative case (DES)



EEM: 19.02mm<sup>2</sup>  
Periplaque: 8.27mm<sup>2</sup>  
Stent: 10.75mm<sup>2</sup>

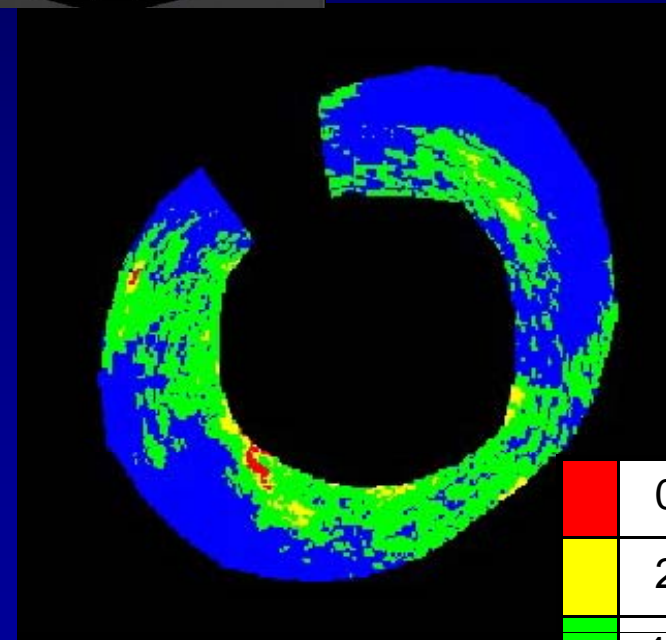


EEM: 19.85mm<sup>2</sup>  
Periplaque: 7.12mm<sup>2</sup>  
Stent: 12.73mm<sup>2</sup>



Baseline

Red	0.87%
Yellow	2.37%
Green	32.75%
Blue	64.02%



Follow up

Red	0.52%
Yellow	2.81%
Green	41.16%
Blue	55.51%