The Favorable Effects of Statin after Stenting: *OCT Study*

Jung-Sun Kim, MD, Ph D

Division of Cardiology, Severance Cardiovascular Hospital

Yonsei University College of Medicine

The authors have no financial conflicts of interest to disclose concerning the presentation.

Agenda

1. Stent Strut Coverage

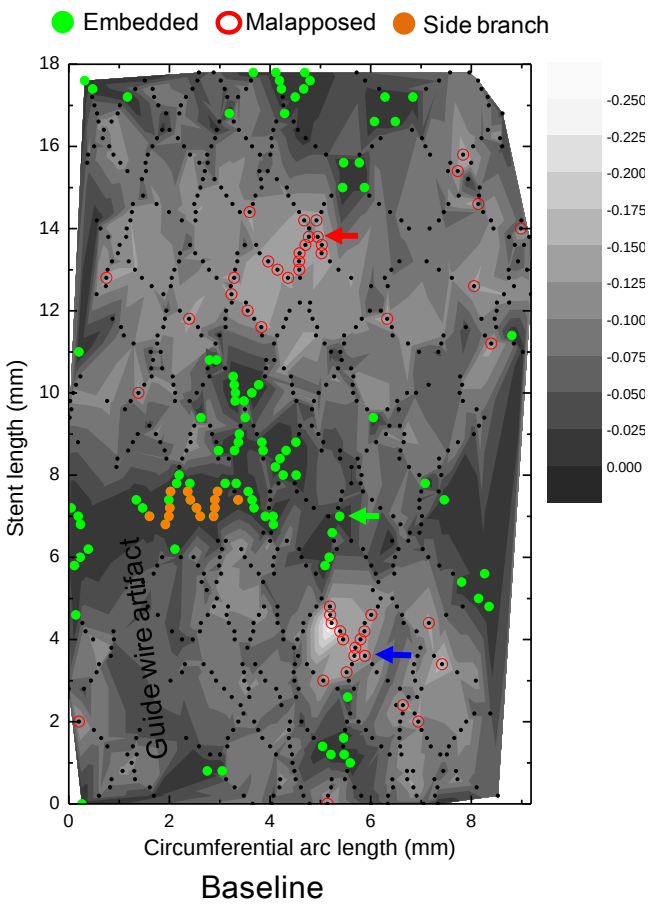
2. Neointimal Characteristics

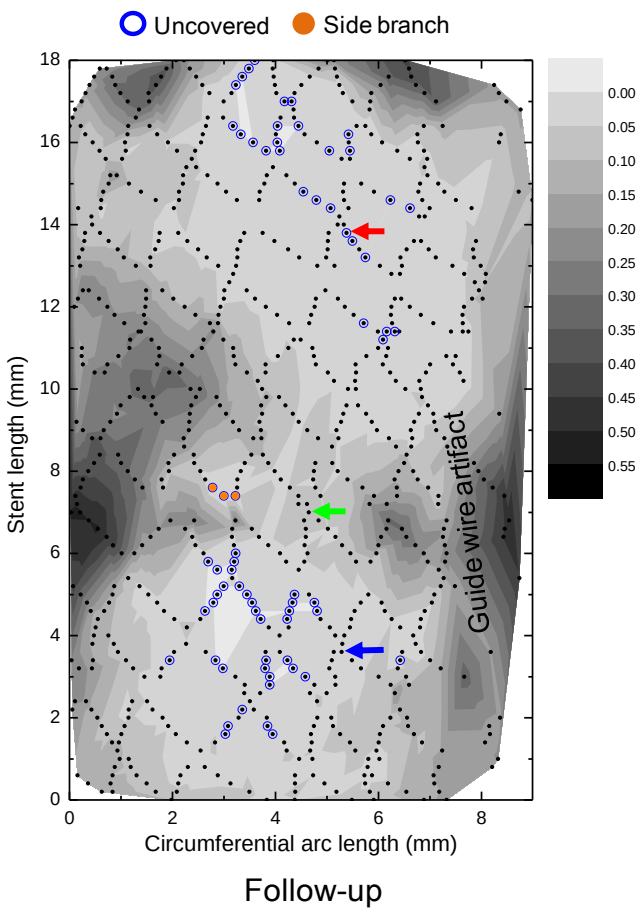
Agenda

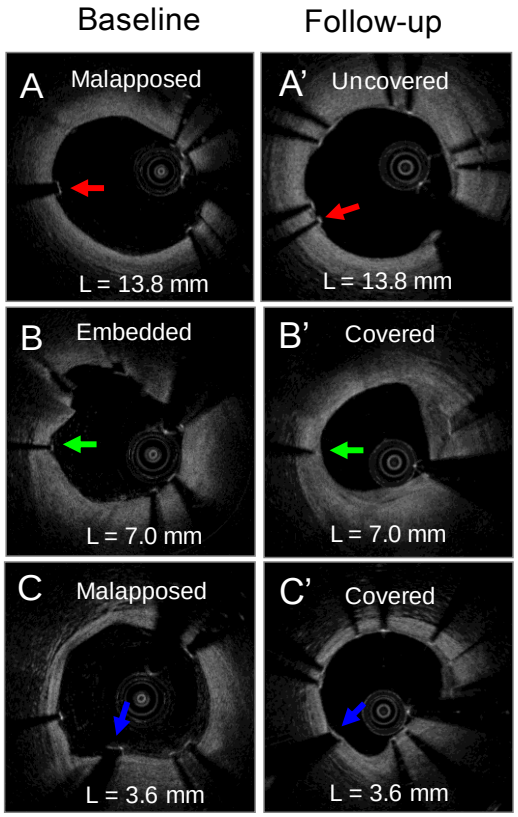
1. **Stent Strut Coverage**

2. **Neointimal Characteristics**

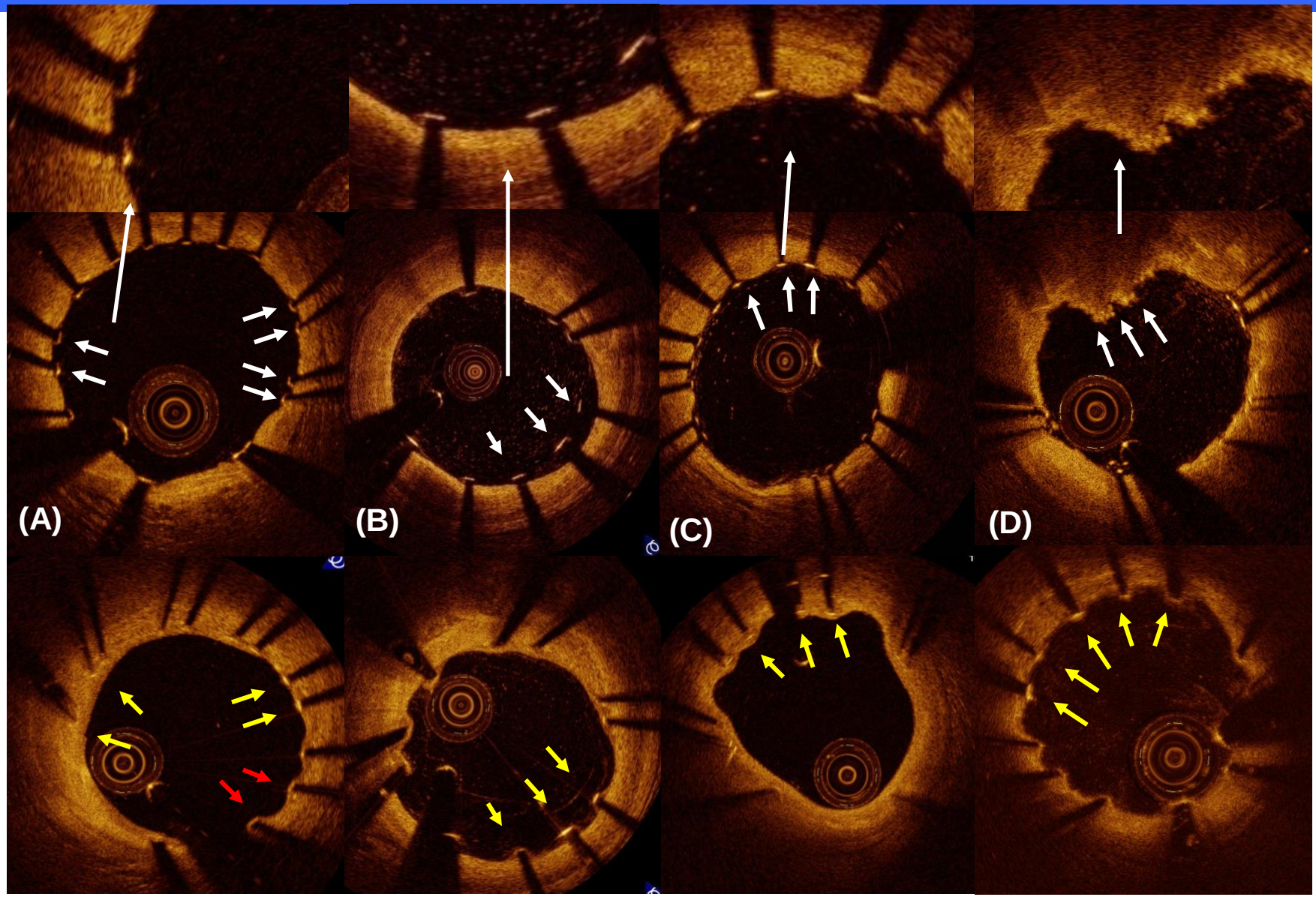
Strut Level Analysis



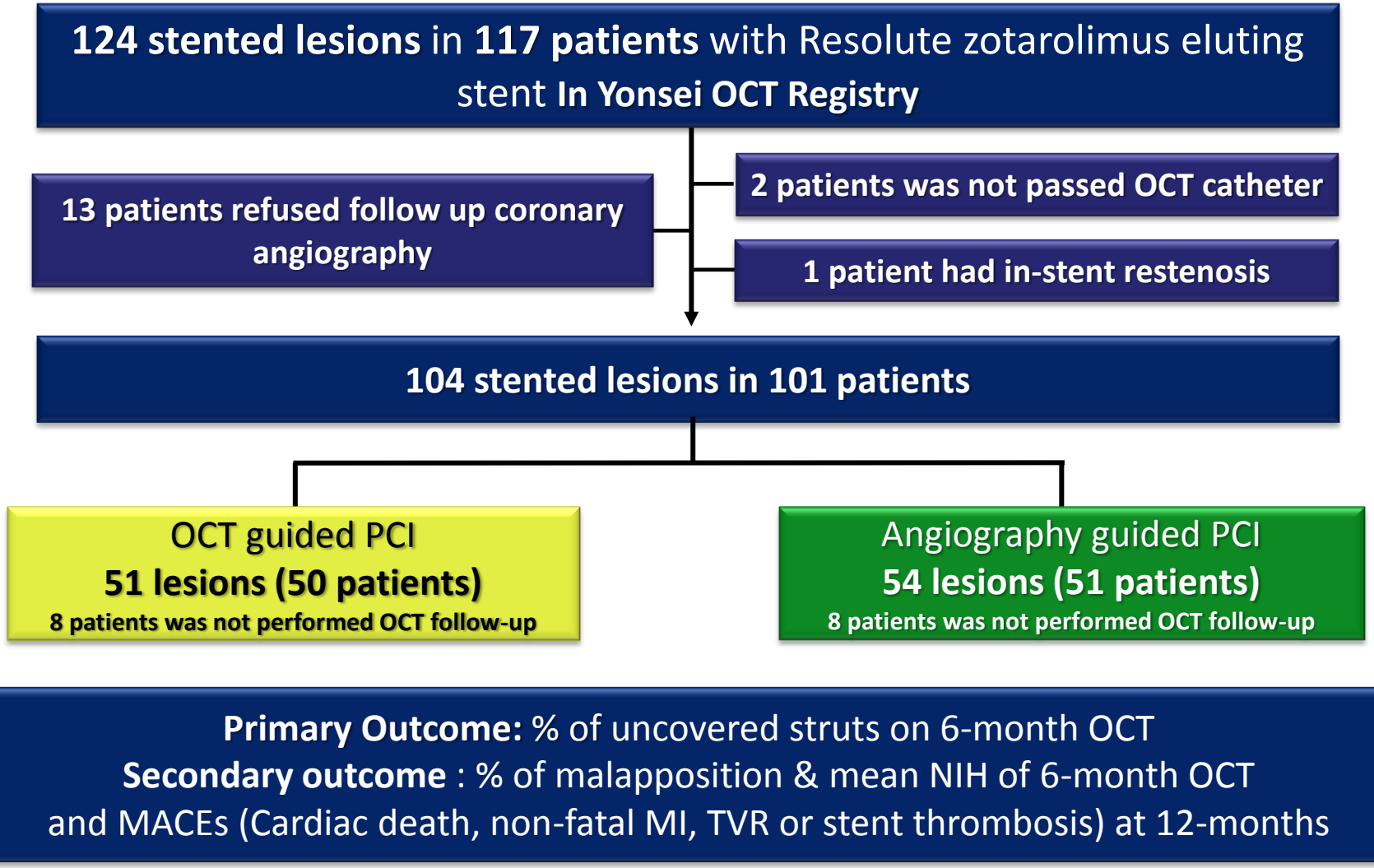




Kim JS, Ha J, Hong MK, et al. J Am Coll Cardiol Interv 2014


Post-intervention
Follow-up
(A)
(B)
(C)
(D)

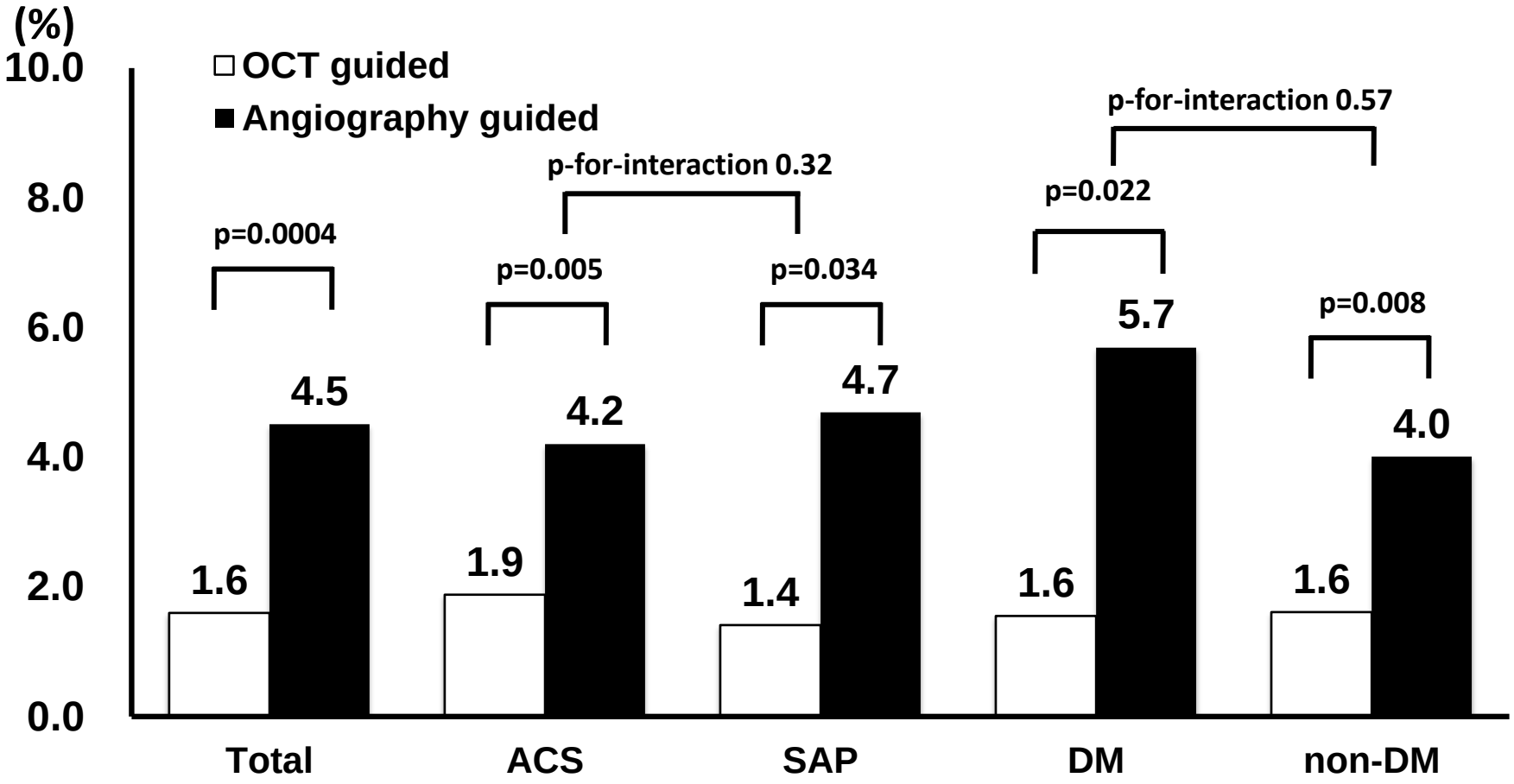
Constant Trial



Primary Outcome: % of uncovered struts on 6-month OCT
Secondary outcome : % of malapposition & mean NIH of 6-month OCT and MACEs (Cardiac death, non-fatal MI, TVR or stent thrombosis) at 12-months

Kim JS, Hong MK, et al. Rev Esp Cardiol 2015

Rate of uncovered struts

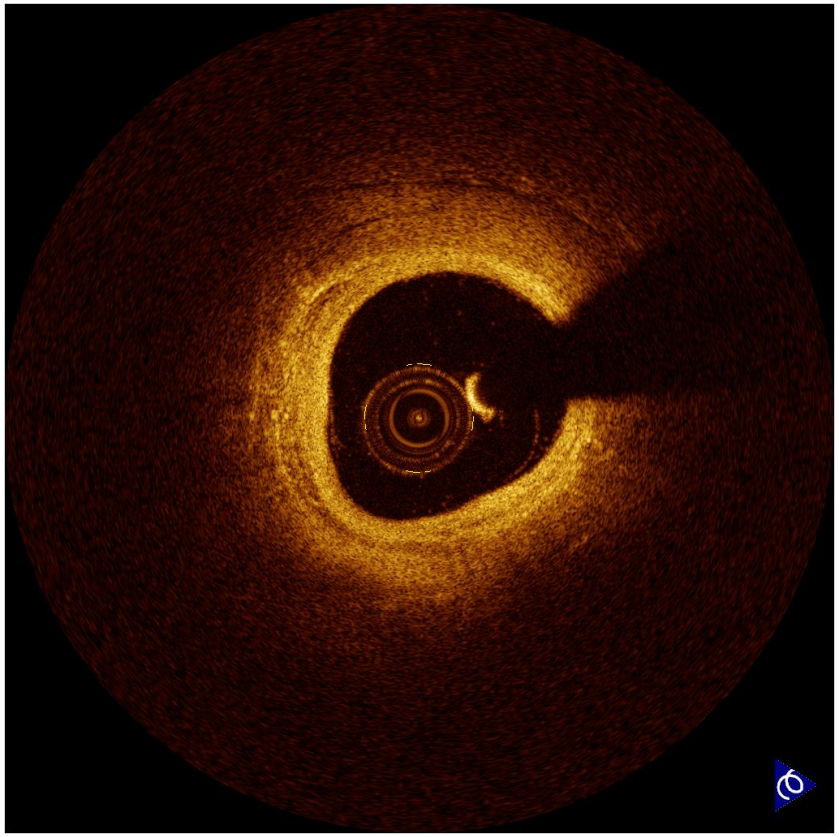


Kim JS, Hong MK, et al. Rev Esp Cardiol 2015

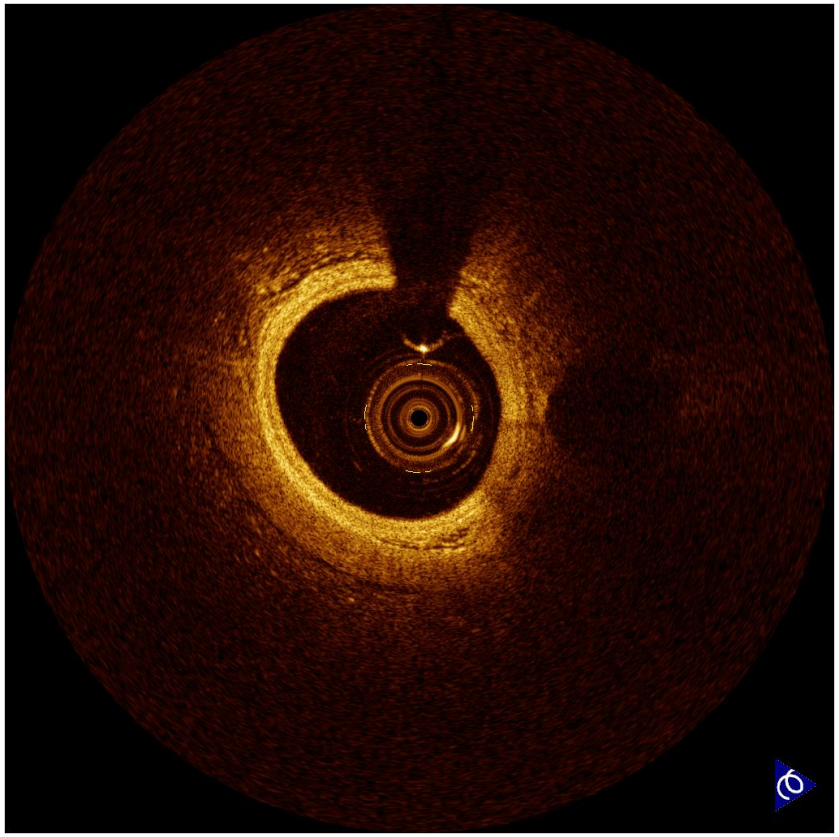
5153848 Yoon OO Unstable angina

Biolimus eluting stent 3.0x24 at pLAD

POST OCT



3 month FU OCT



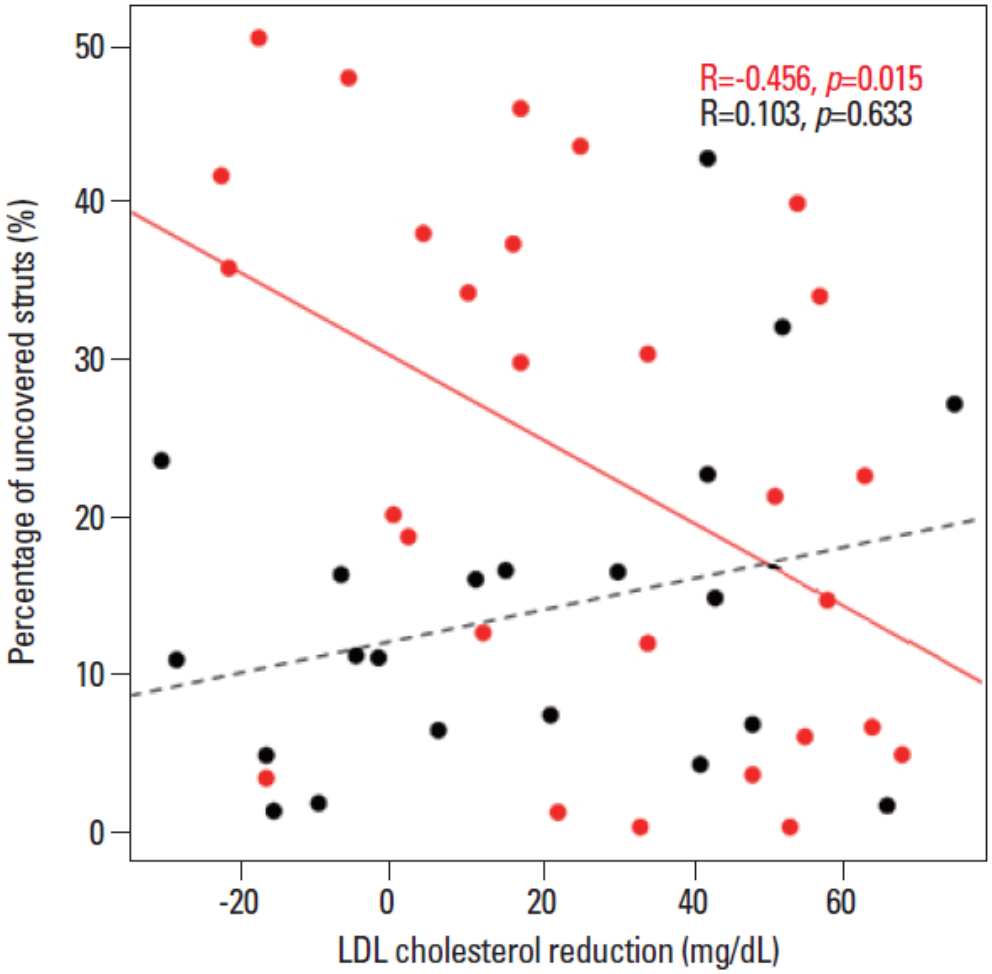
Uncovered stent struts: 0 %

OCT guidance can improve the stent strut coverage.

Then,

What is the further modality to improve stent healing process ?

Is statin possible option to enhance a stent strut coverage ?



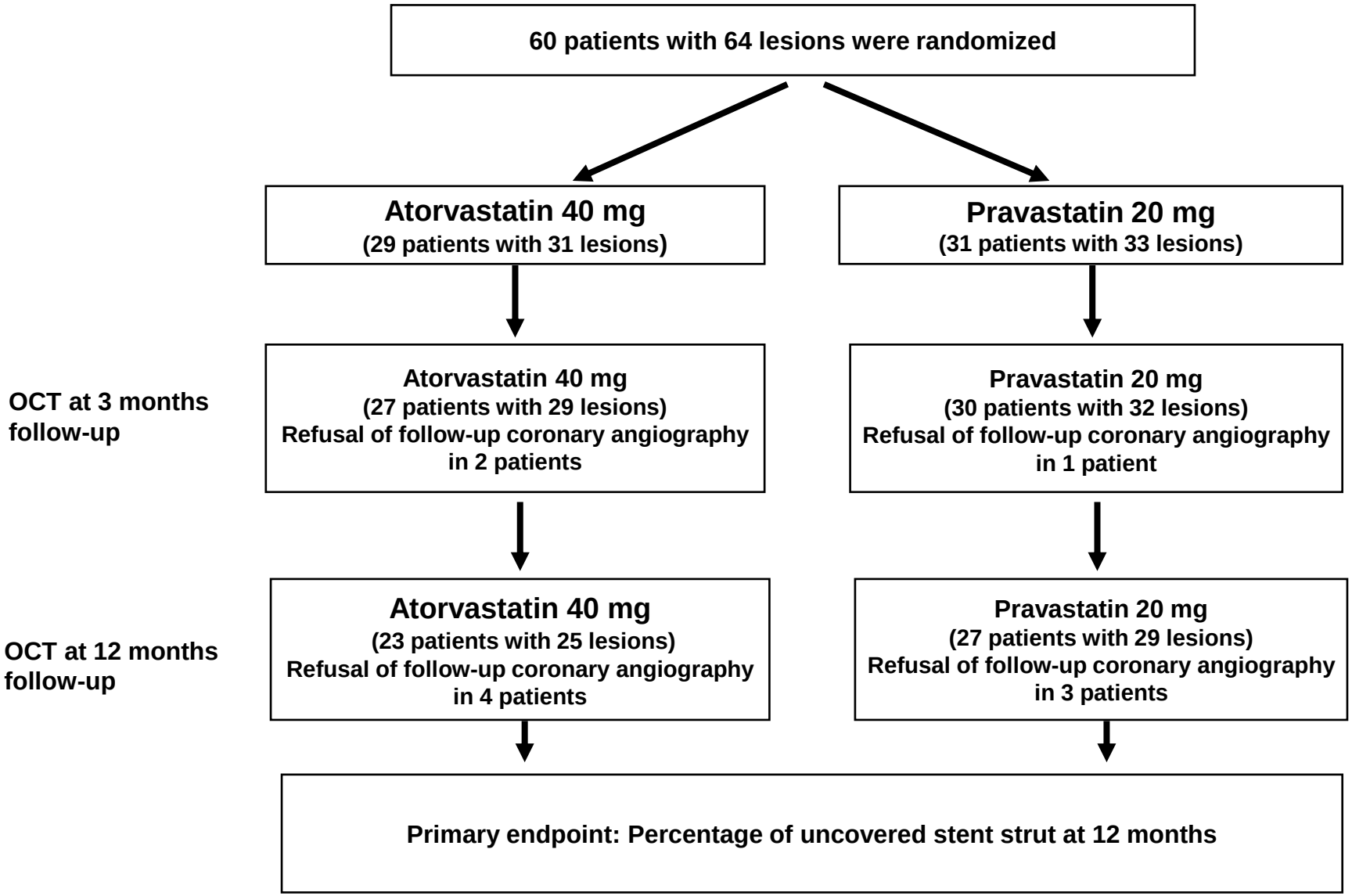
BES

SES

This study revealed a protective effect of statins against delayed strut coverage in patients with SES who achieved lower LDL cholesterol levels (especially less than 70 mg/dL).

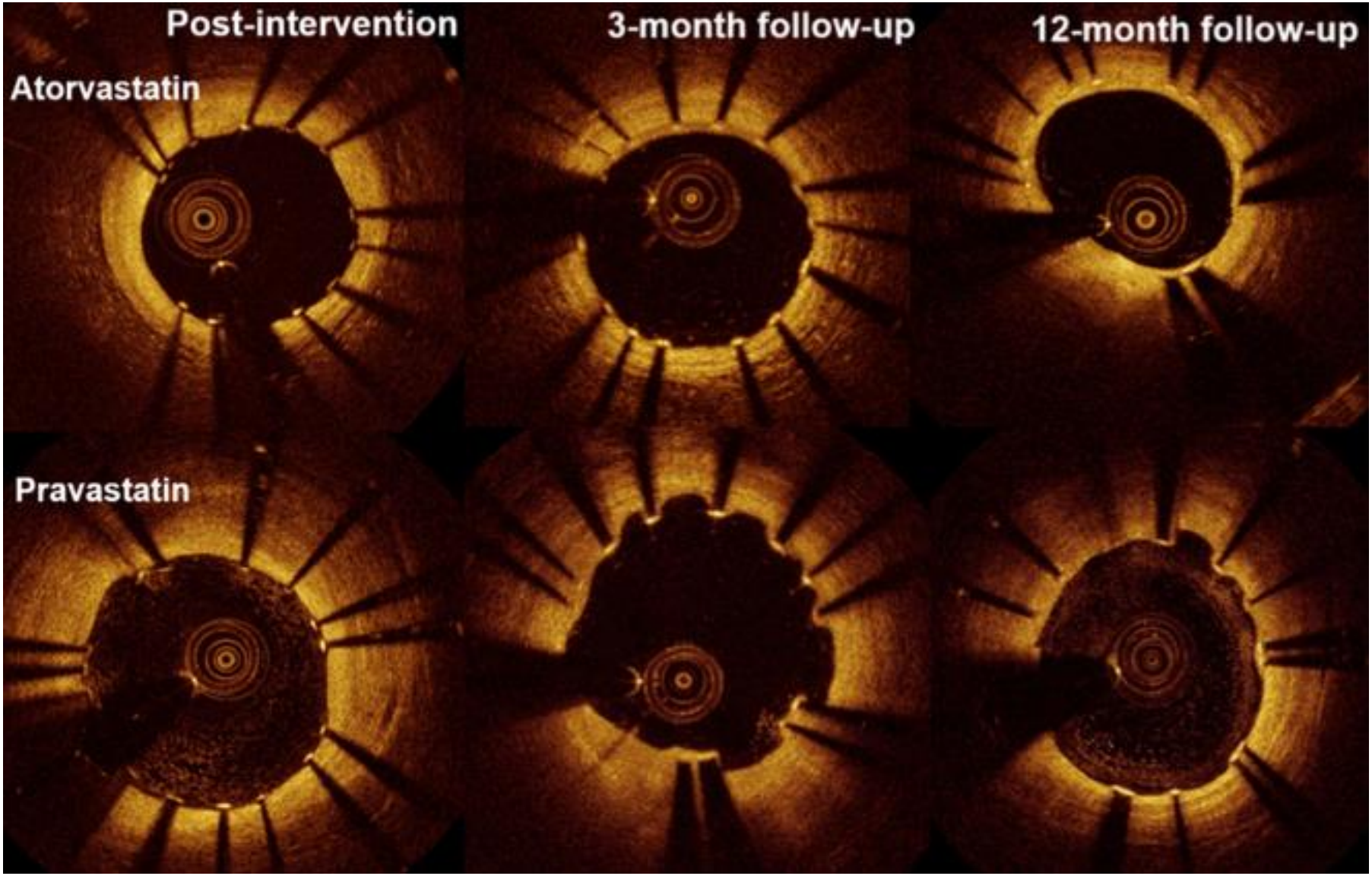
Suh Y, Hong MK, et al, YMJ 2015

Effect of high-dose statin therapy on drug-eluting stent strut coverage

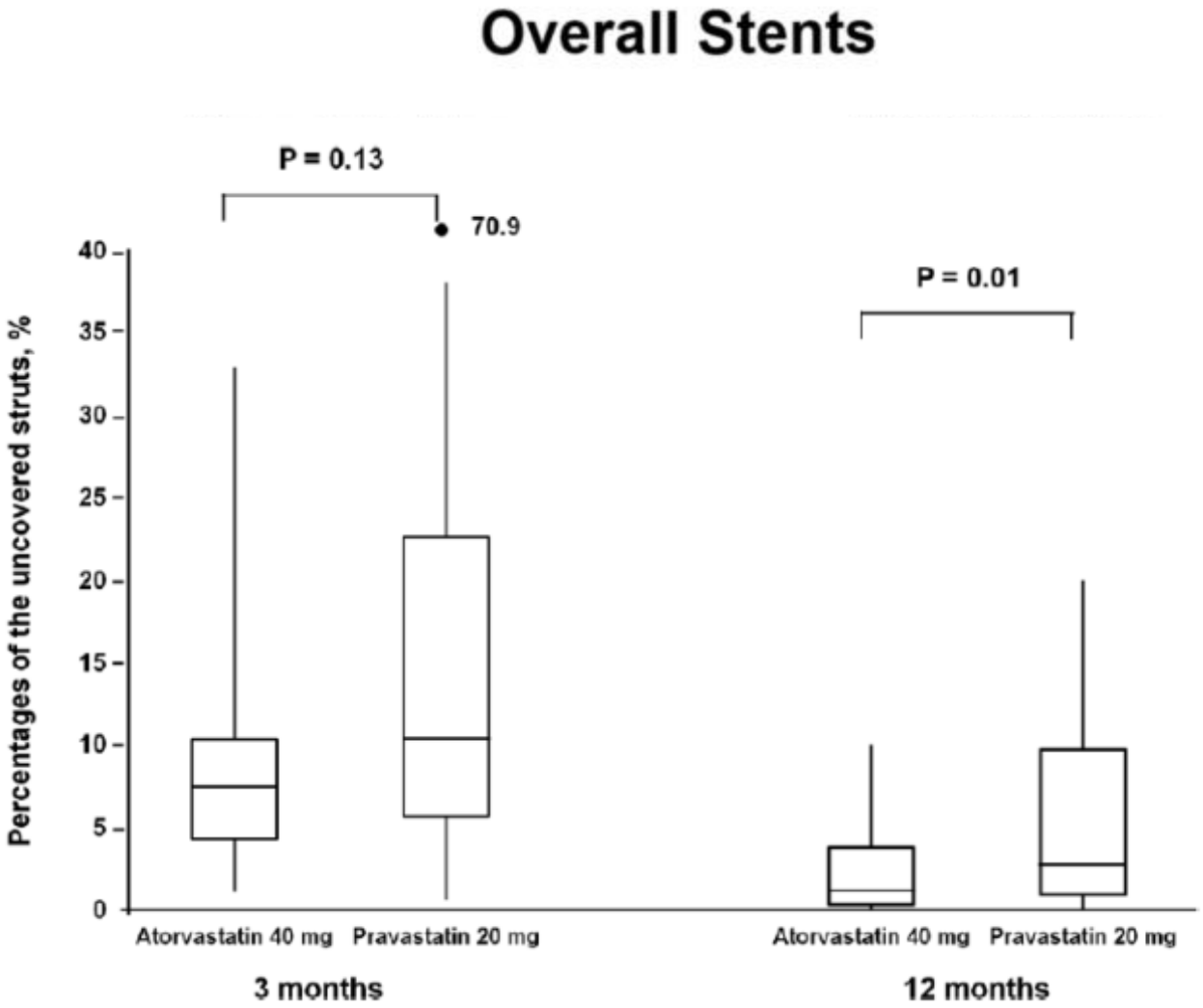


Kim JS, Kim JH, Hong MK, et al. ATBV 2015

Optical coherence tomography images on the atorvastatin and pravastatin groups



Serial change in the uncovered struts among the statins, stents and time interval (3 and 12 months follow-up)



Kim JS, Kim JH, Hong MK, et al. ATBV 2015

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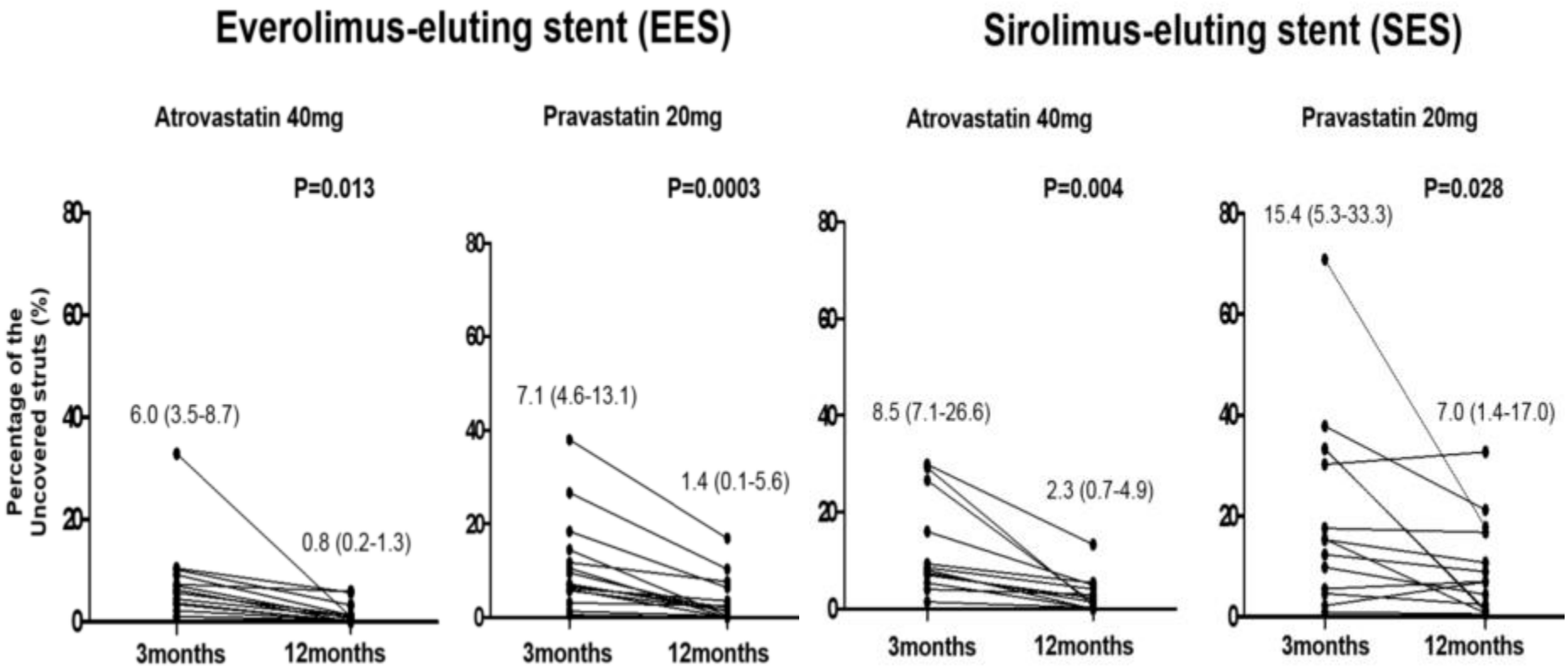


Kim JS, Kim JH, Hong MK, et al. ATBV 2015

OCT guidance can improve the stent strut coverage.

In addition,

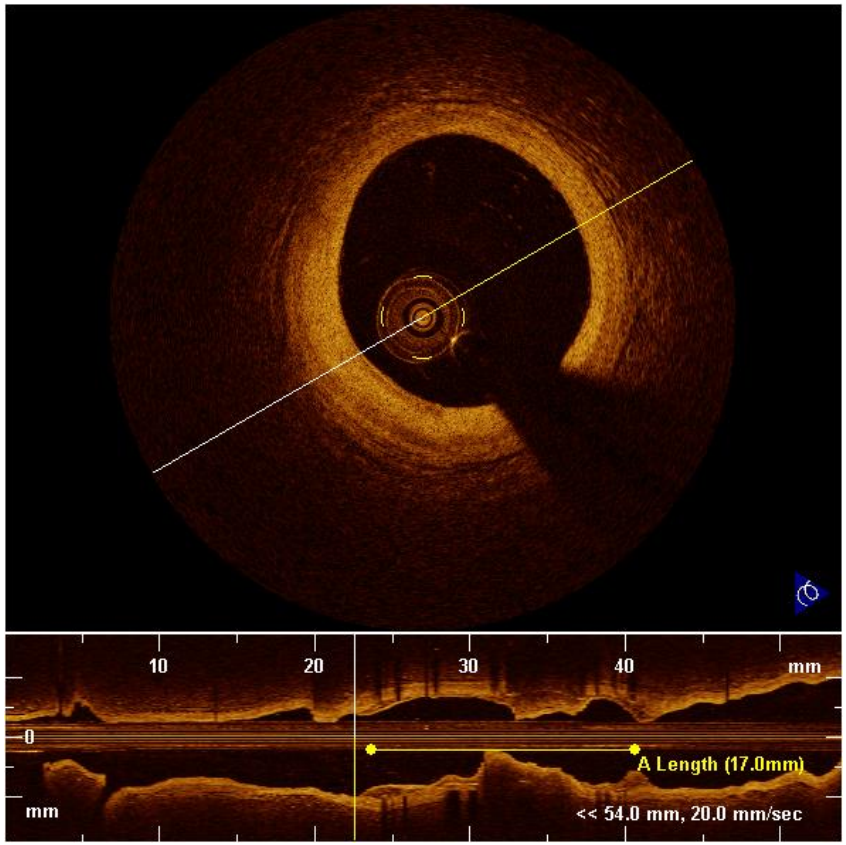
Optimal statin treatment may play a beneficial role on improve stent strut coverage.

Agenda

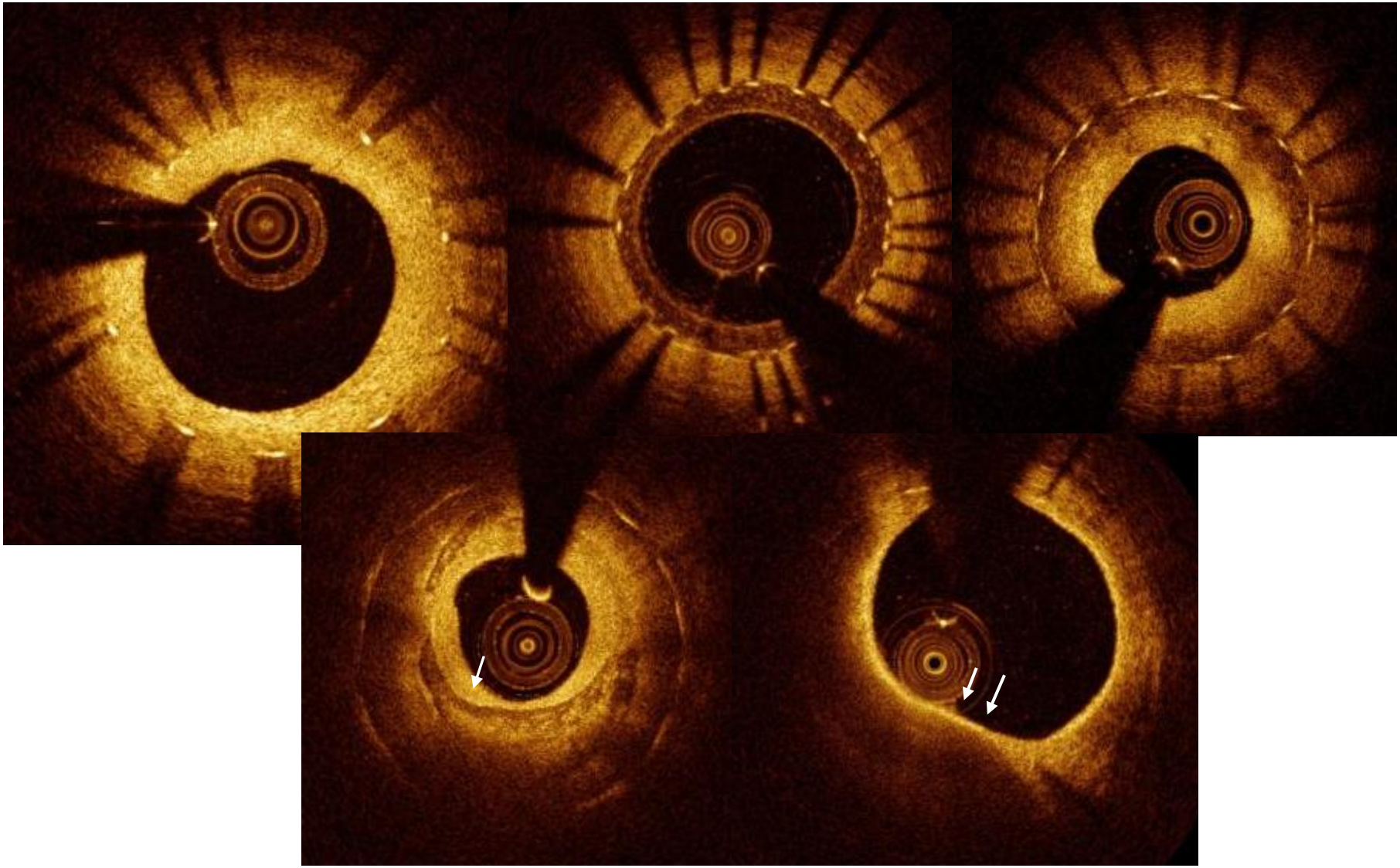
1. Stent Strut Coverage

2. **Neointimal Characteristics**

OCT Can Provide Qualitative Information of Neointima



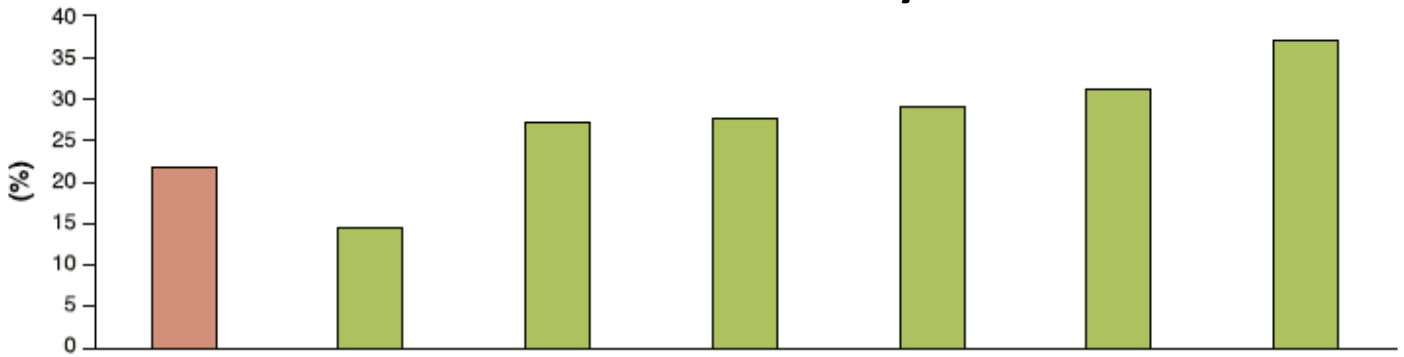
Abnormal Neointima



Text Book; Cardiovascular OCT Imaging: Late stent change, Kim JS, Hong MK, Jang Y

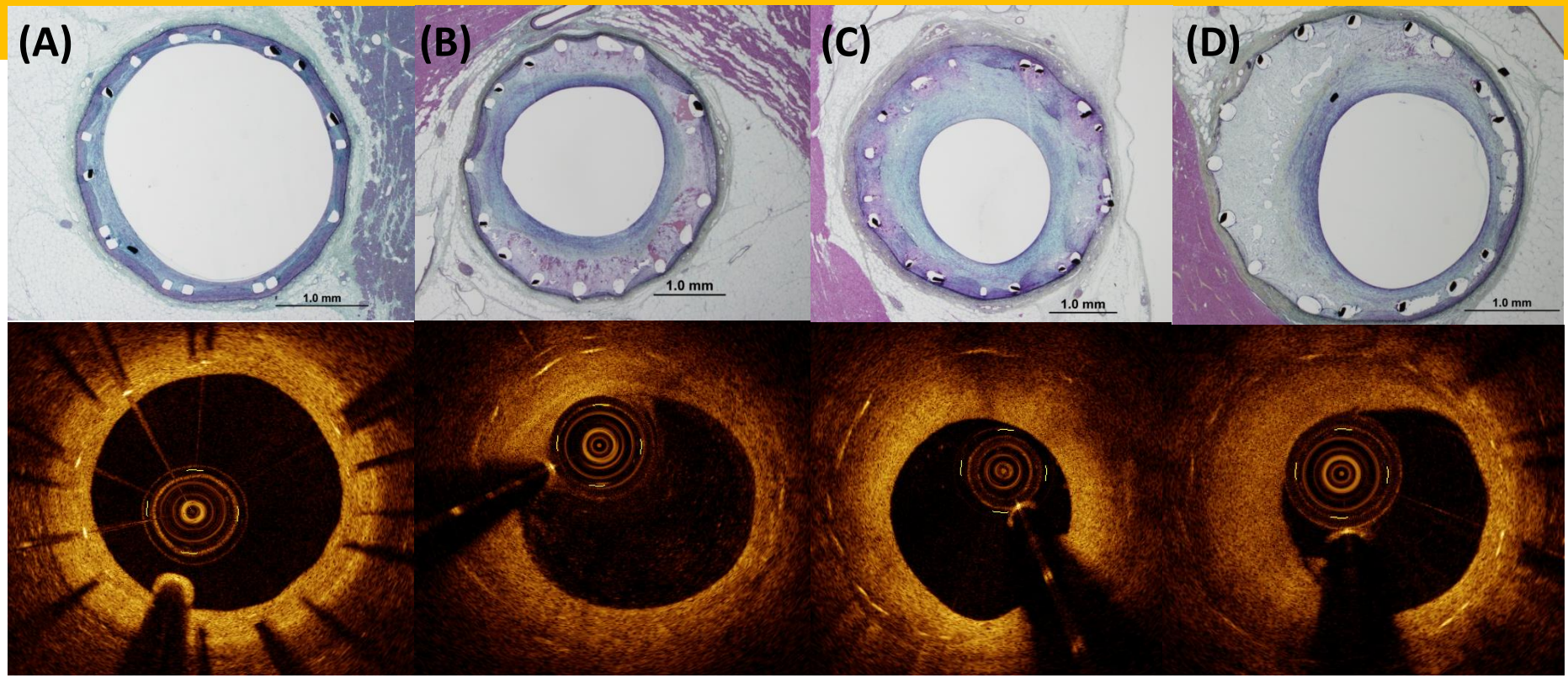
Prevalence of Heterogeneous Neointima & Neoatherosclerosis

Prevalence 20-30 % according to clinical population of patients, stent age or definition of each study



Duration	8-9 Months	9 Months	22 Months (median)	24 Months	7 Months (median)	12 Months (median)	<9 Months
Type of DES	1st & 2nd Generation	1st & 2nd Generation	1st & 2nd Generation	1st & 2nd Generation	2nd Generation	1st Generation	1st & 2nd Generation
Type of Study	OCT	OCT	OCT	OCT	Histology	Histology	OCT
Definition of Neoathero-sclerosis or OCT Heterogeneous Pattern	Heterogeneous neointima, focally changing optical properties and various backscattering patterns	Lipid laden neointima	Lipid laden neointima calcification, or TCFA	Lipid laden neointima	Clusters of foamy macrophages within the neointima with/without necrotic core formation	Clusters of foamy macrophages within the neointima with/without necrotic core formation	Lipid laden neointima
Type of Lesion	Percent NIH CSA 18.8%	Percent NIH CSA 18.7±11.3%	>50 stenosis	Percent NIH CSA 23.4±14.5%	Autopsy	Autopsy	Stable AP (73%) & NSTEMI (27%)
Published Year	2014	2012	2013	2012	2013	2011	2012
Reference	Kim et al. (9)	Kim at al. (8)	Lee et al. (12)	Kim et al. (8)	Otsuka et al. (10)	Nakazawa et al. (4)	Yonetsu et al. (11)

Kenichi S, Virmani R, et al. J Am Coll Cardiol Img 2014

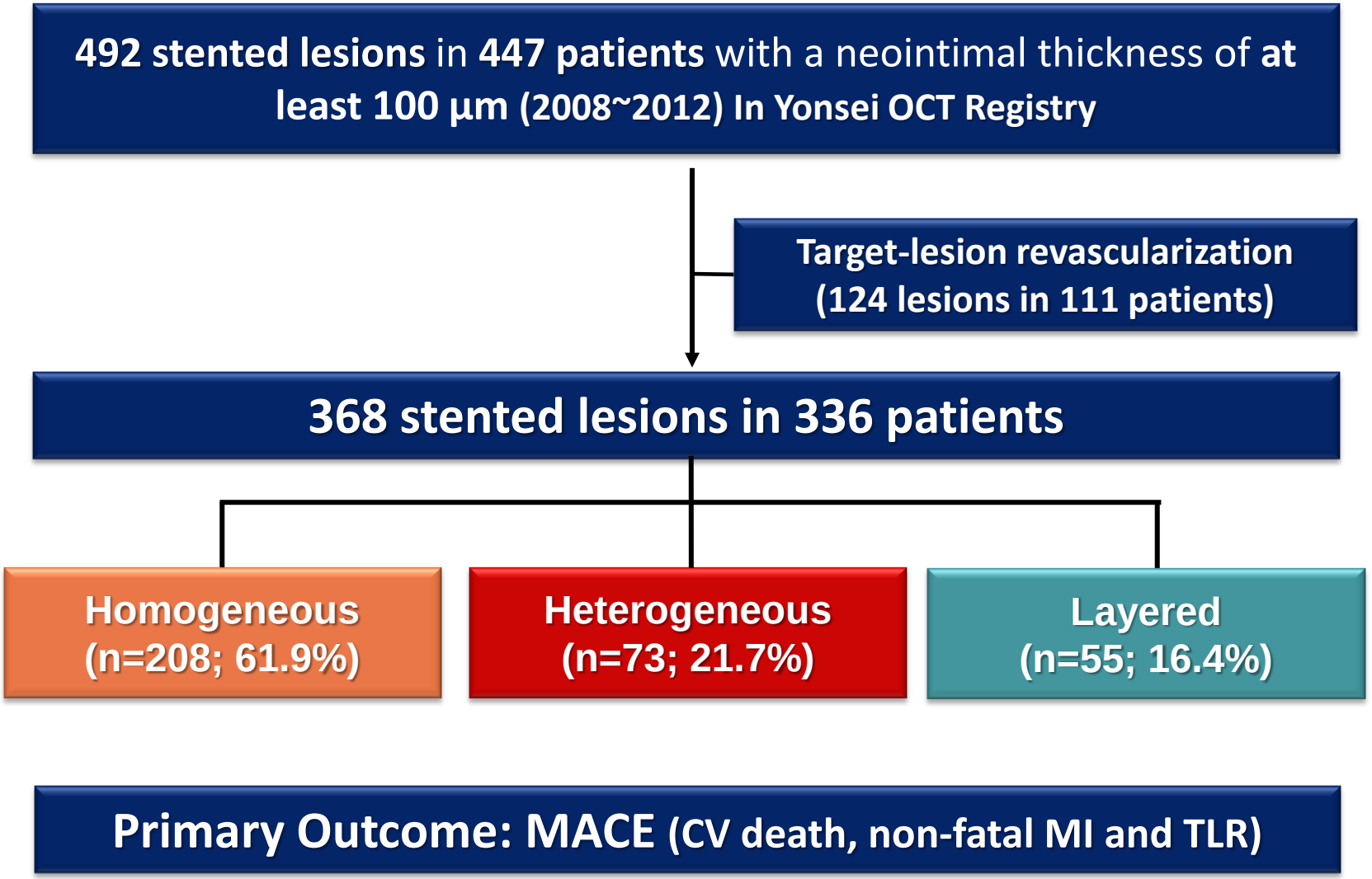


Representative images of OCT and histologic sections.

(A) **Homogeneous** neointimal pattern in OCT has a collagen rich neointima (bluish color) (B) **heterogeneous** neointimal pattern shows lots of loose connective tissue (grey color) and fibrin (pink color) (C) **layered neointimal** pattern shows thick neointima, external elastic laminal rupture and peristrut inflammation (D) **neovascularization** is shown in the middle of neointima.

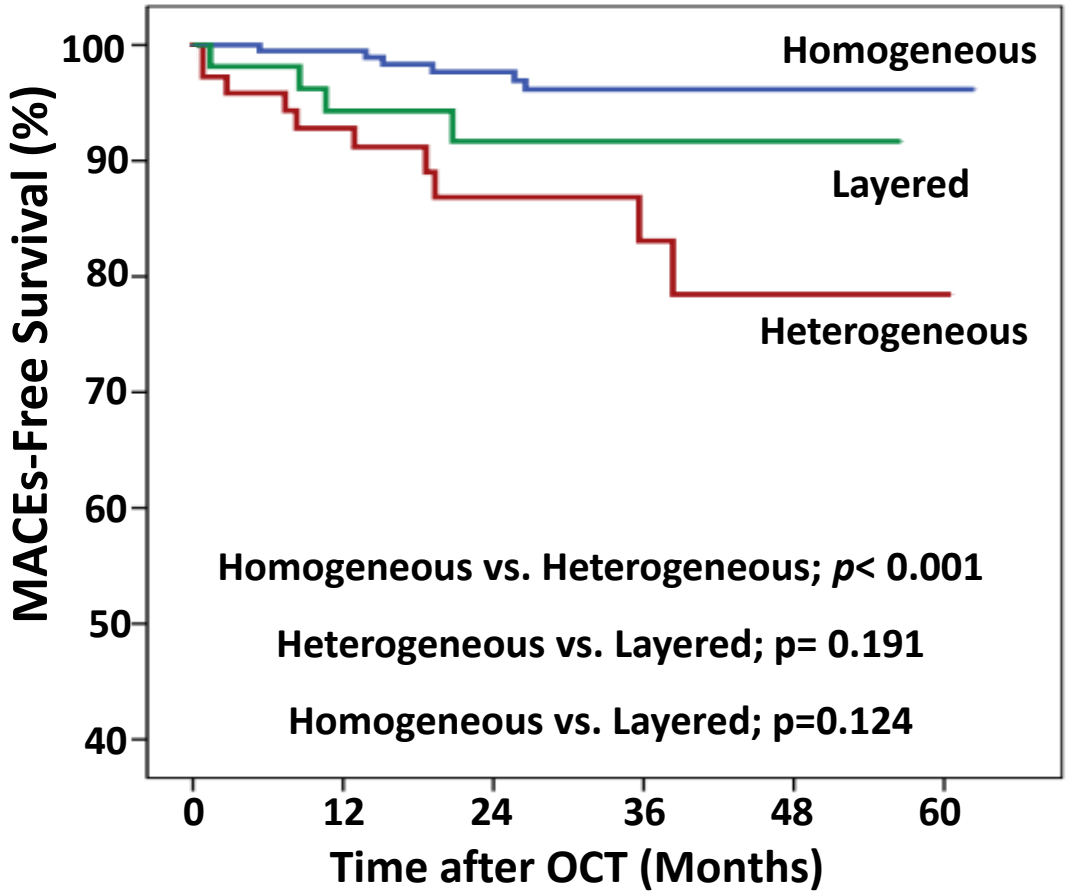
Kim JS, Granada JF, et al. Eur Heart J Cardiovasc Imaging 2013

The Clinical Implication of Neointimal Characteristics



Kim JS, Lee JH, Hong MK, et al. J Am Coll Cardiol Imag 2014

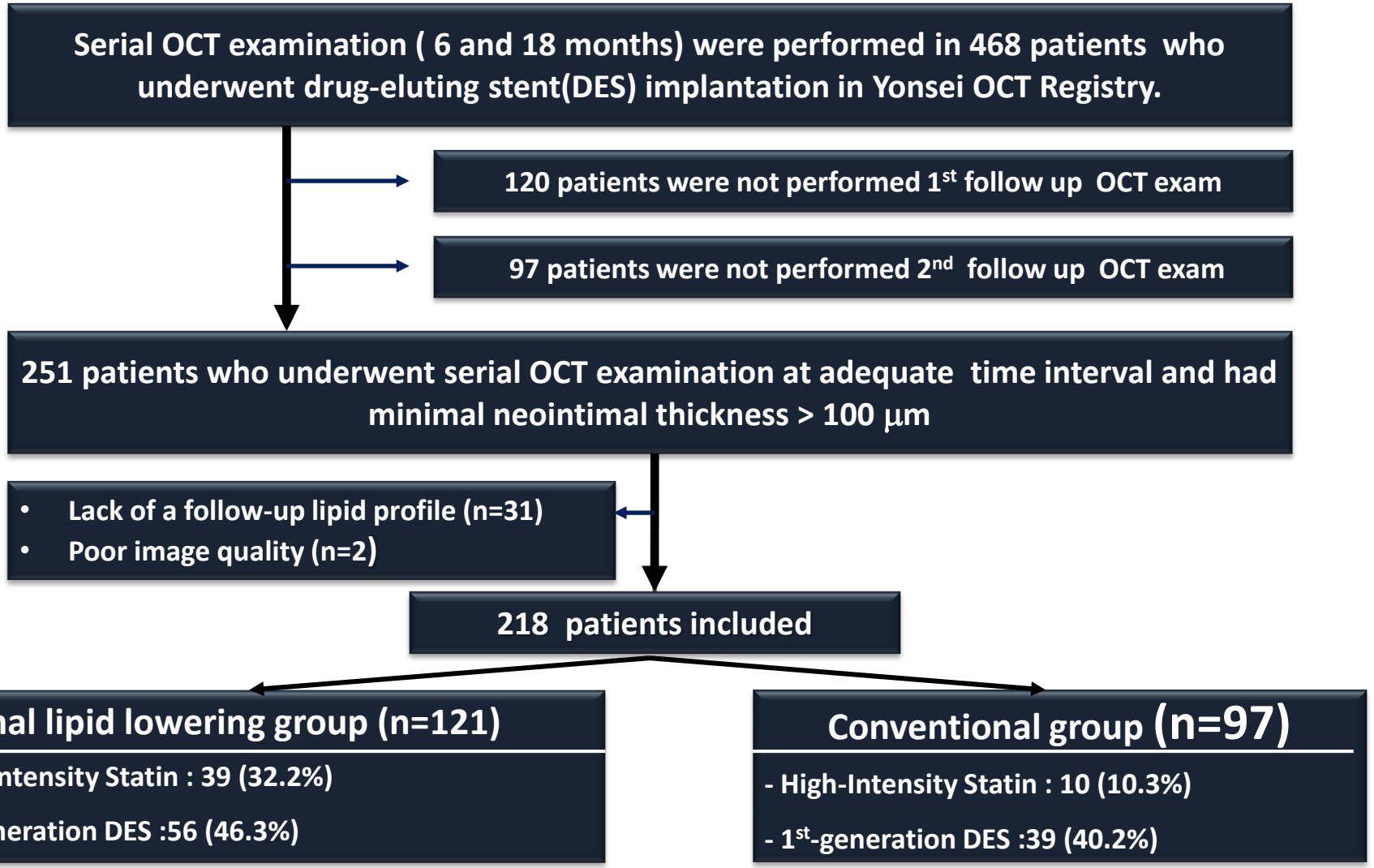
Heterogeneous Pattern of Neointima has adverse clinical outcome



Homogeneous (n)	208	187	132	100	49	2
Layered (n)	55	49	33	22	6	0
Hetero (n)	73	59	34	22	8	1

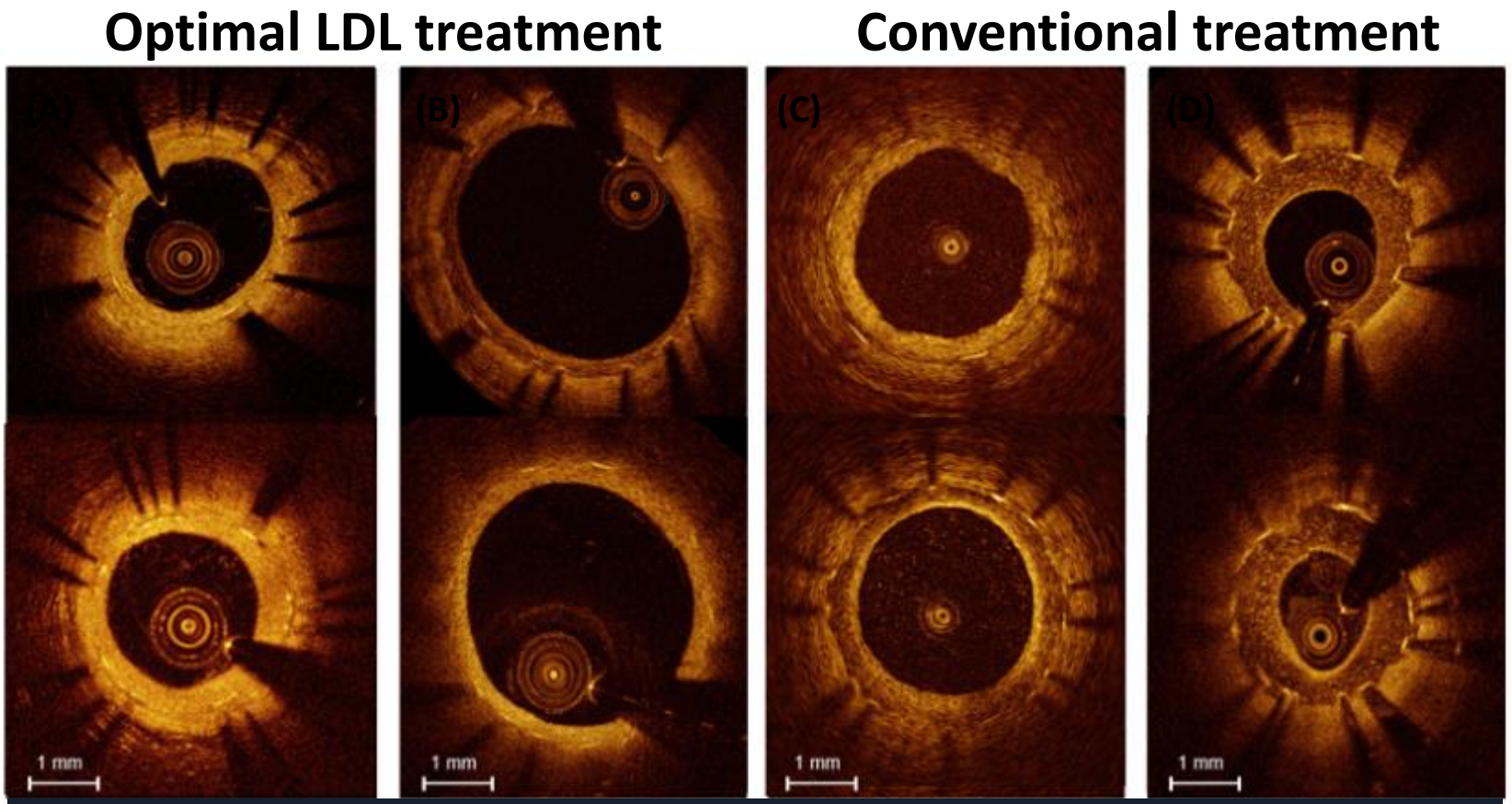
Kim JS, Lee JH, Hong MK, et al. J Am Coll Cardiol Imag 2014

How can we modify the neointimal characteristics ?



Jang JY, Kim JS, Hong MK, et al. Atherosclerosis 2015

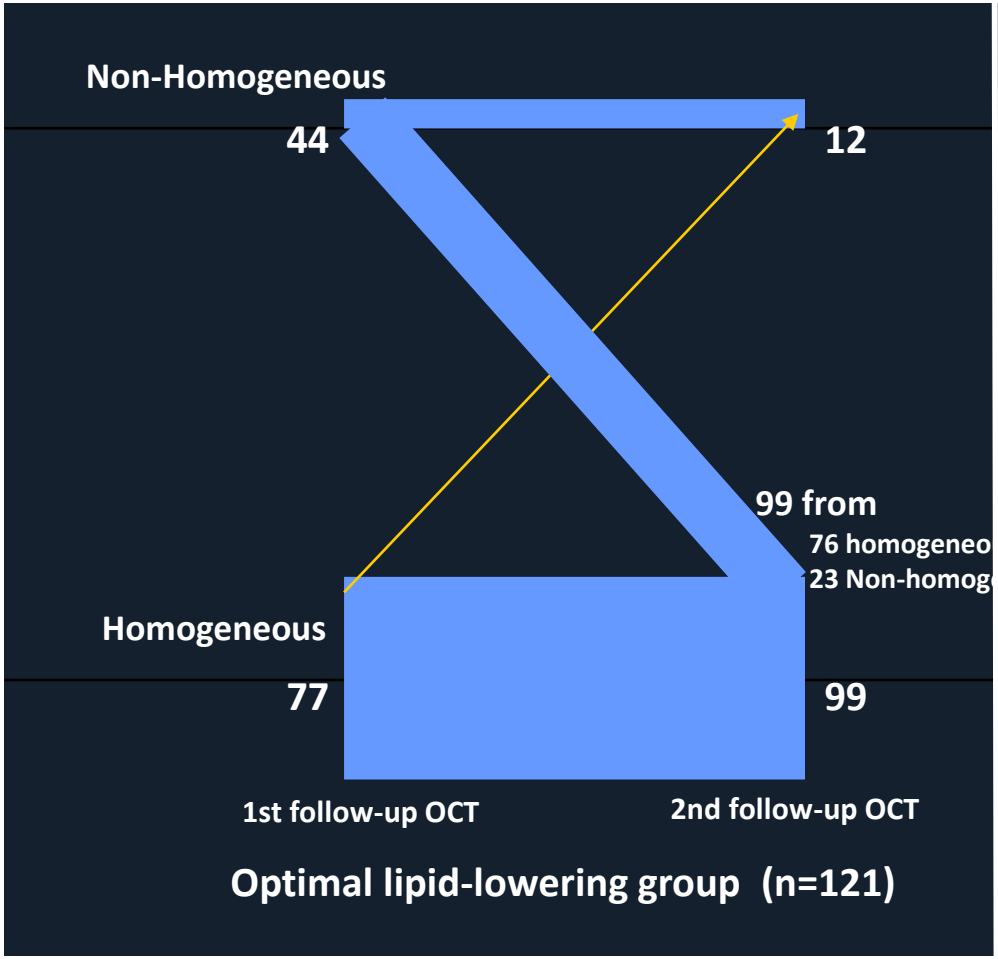
Serial changes in representative images

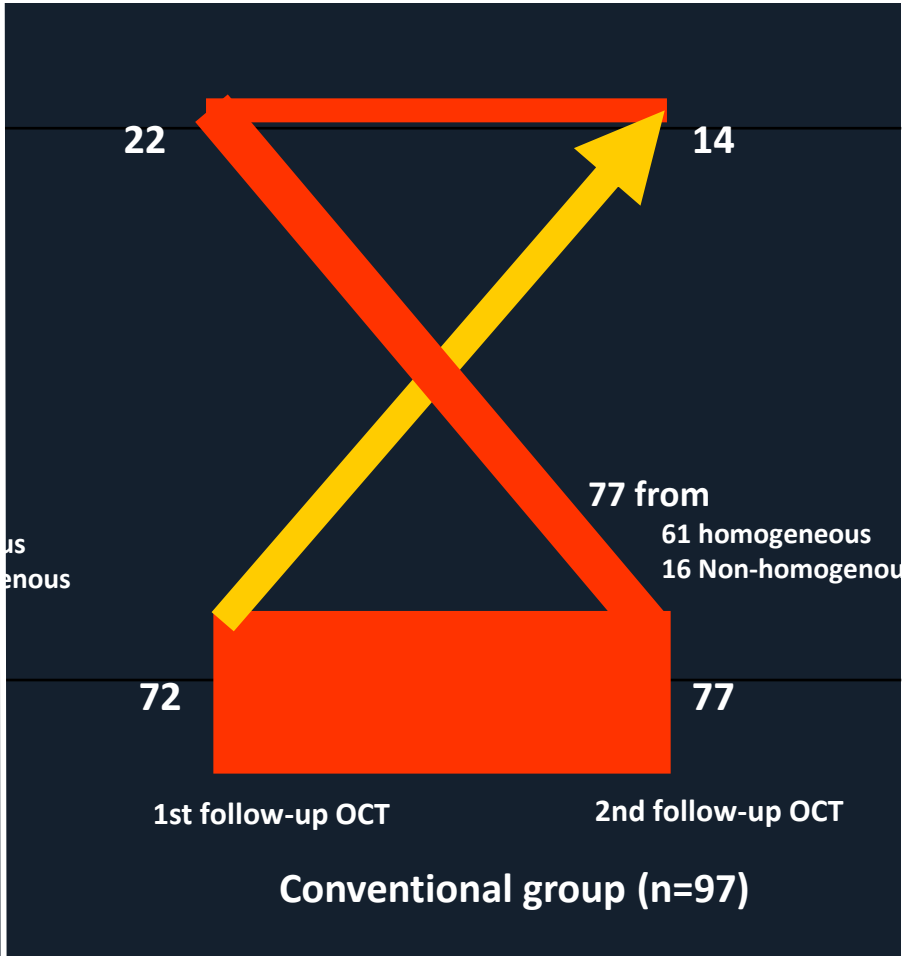


(A) There were **no changes in homogeneous** neointimal characteristics in the optimal lipid-lowering group. **(B) Changes from the non-homogeneous to homogeneous** neointima were observed in the optimal lipid-lowering group. **(C)** Changes from the **homogeneous to non-homogeneous** neointima were observed in the conventional group. **(D)** There were **no changes in non-homogeneous** neointimal characteristics in the conventional group

Jang JY, Kim JS, Hong MK, et al. Atherosclerosis 2015

intensive reduction in LDL-C levels can prevent *non-homogeneous change*

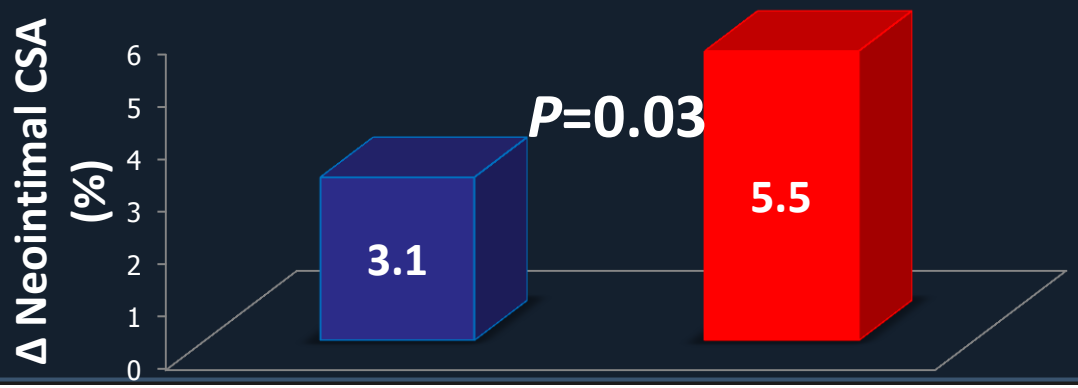




Jang JY, Kim JS, Hong MK, et al. Atherosclerosis 2015

Serial qualitative changes in neointima

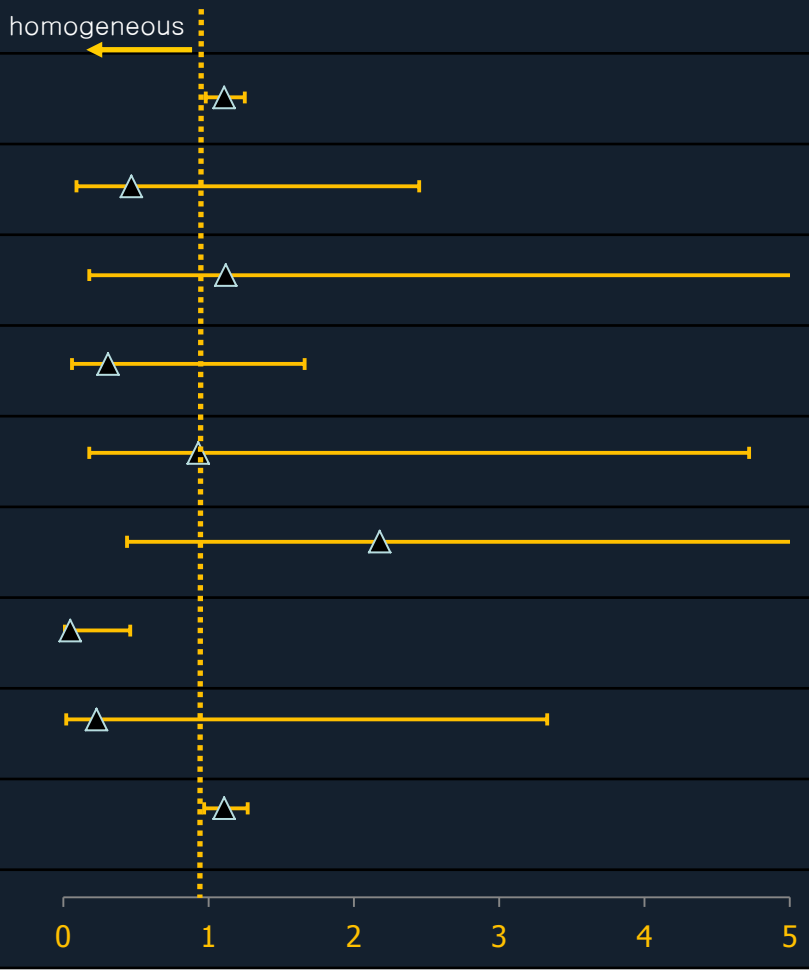
Difference between first and second follow-up OCT	Optimal group	Conventional group	p
Δ Neointimal thickness (μm)	28.6 (4.4–57.1)	31.9 (12.0–74.8)	0.09
Δ Lumen CSA (mm^2)	-0.5±0.8	-0.6±0.9	0.32
Δ Stent CSA (mm^2)	-0.2±0.7	-0.1±0.7	0.56
Δ Neointimal CSA (mm^2)	**0.2±0.4**	**0.4±0.5**	**0.01**
Δ Percent neointimal CSA (%)	**3.1±5.5**	**5.5±6.4**	**0.03**



Jang JY, Kim JS, Hong MK, et al. Atherosclerosis 2015

Multivariate logistic analysis

	OR	95% CI	P value
Age	1.11	(0.98~1.25)	0.08
Male	0.47	(0.09~2.45)	0.37
Diabetes mellitus	1.12	(0.18~6.79)	0.90
Hypertension	0.31	(0.06~1.66)	0.17
ACS	0.93	(0.18~4.72)	0.93
1st-generation DES	2.18	(0.44~10.82)	0.34
Optimal LDL-C control	*0.05*	*(0.01~0.46)*	**0.008**
Stent diameter (mm)	0.23	(0.02~3.33)	0.23
Stent length (mm)	1.11	(0.97~1.27)	0.12



Clinical Implication of Neointimal Characteristics

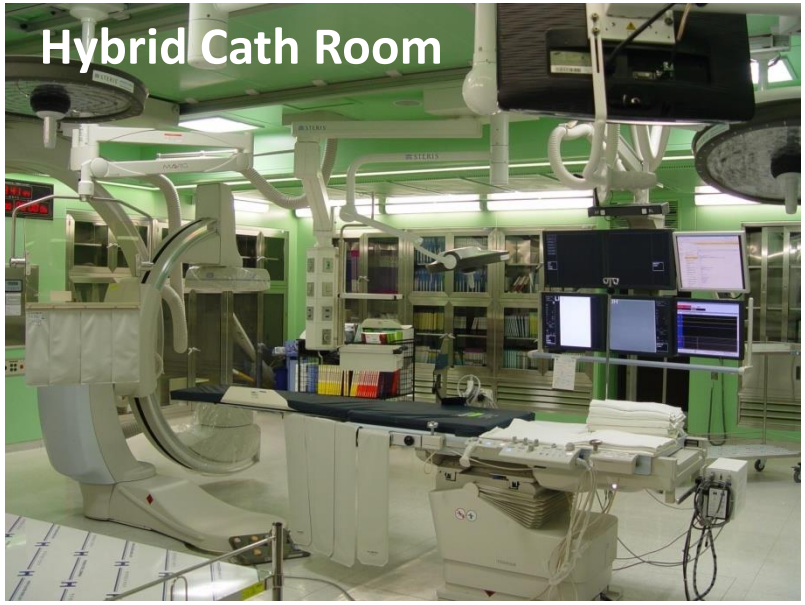
- This findings implied that although the quantitative growth of neointimal tissue were important factors for the occurrence of MACEs after stent implantation, the qualitative pattern of neointimal characteristics might be also a possible prognostic parameter.

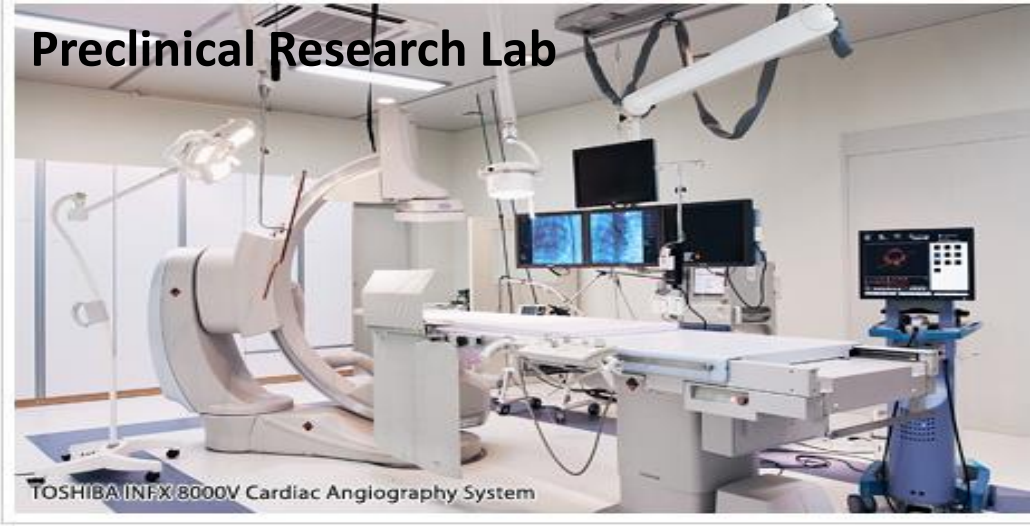
- Optimal statin treatment may have a protective effect to progression of abnormal pattern of neointima and reverse to normal pattern of neointima.

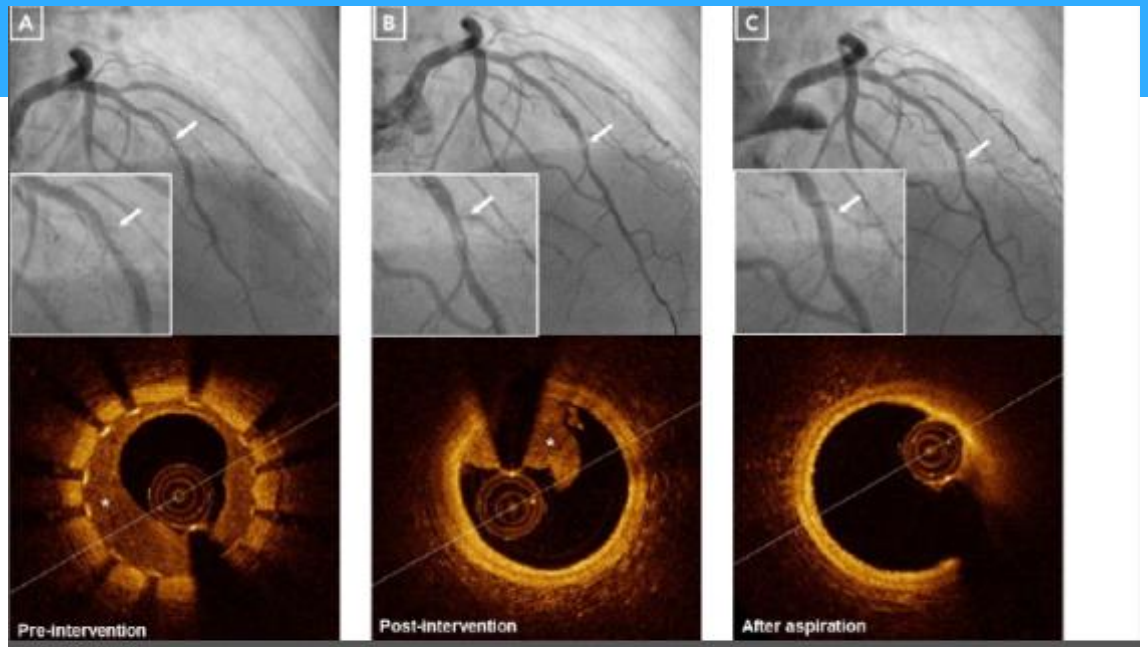
SUMMARY

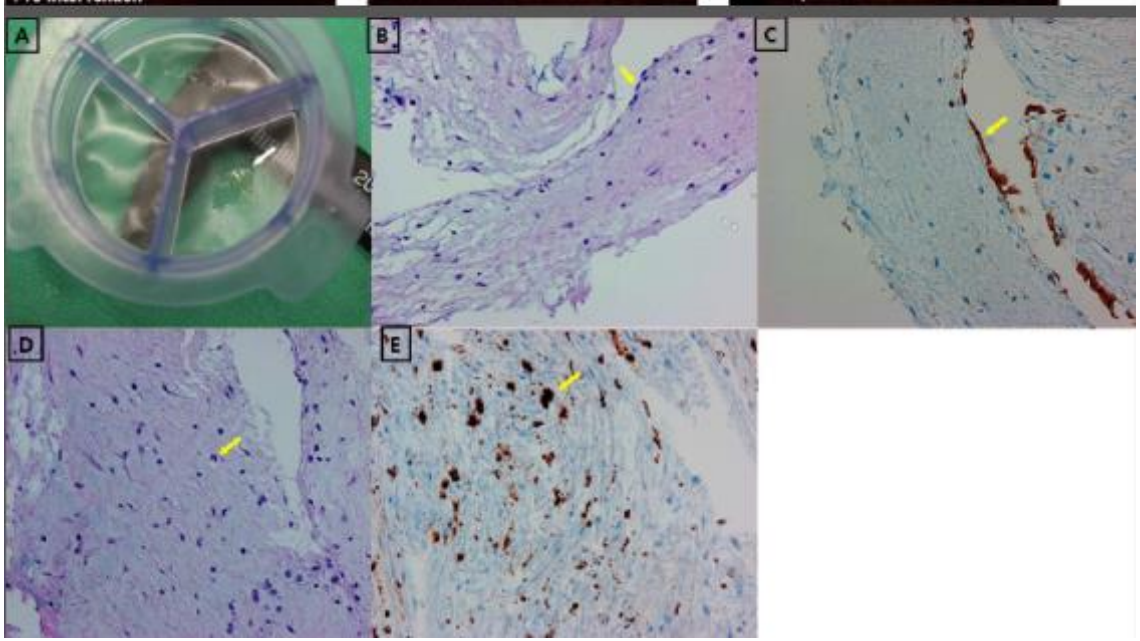
Intensive reduction in LDL- C by high intensity statin may improve a stent healing process and prevent the abnormal degeneration of neointimal tissue.

Thanks for your Attention







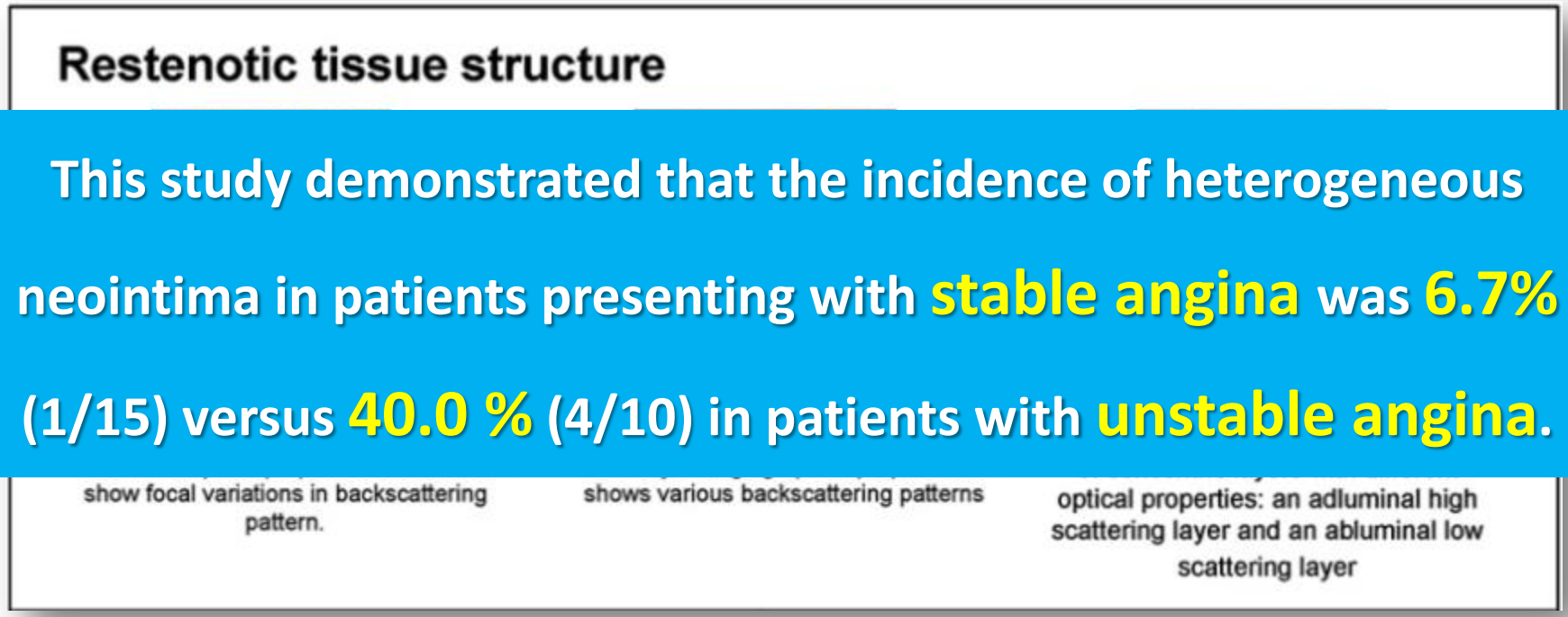


Heterogeneous Pattern of Neointima

- loose tissue containing scattered short spindle cells in the myxoid stroma on pathologic examination

Cho SS, et al Circulation 2015

Neointimal tissue of In-stent Restenosis

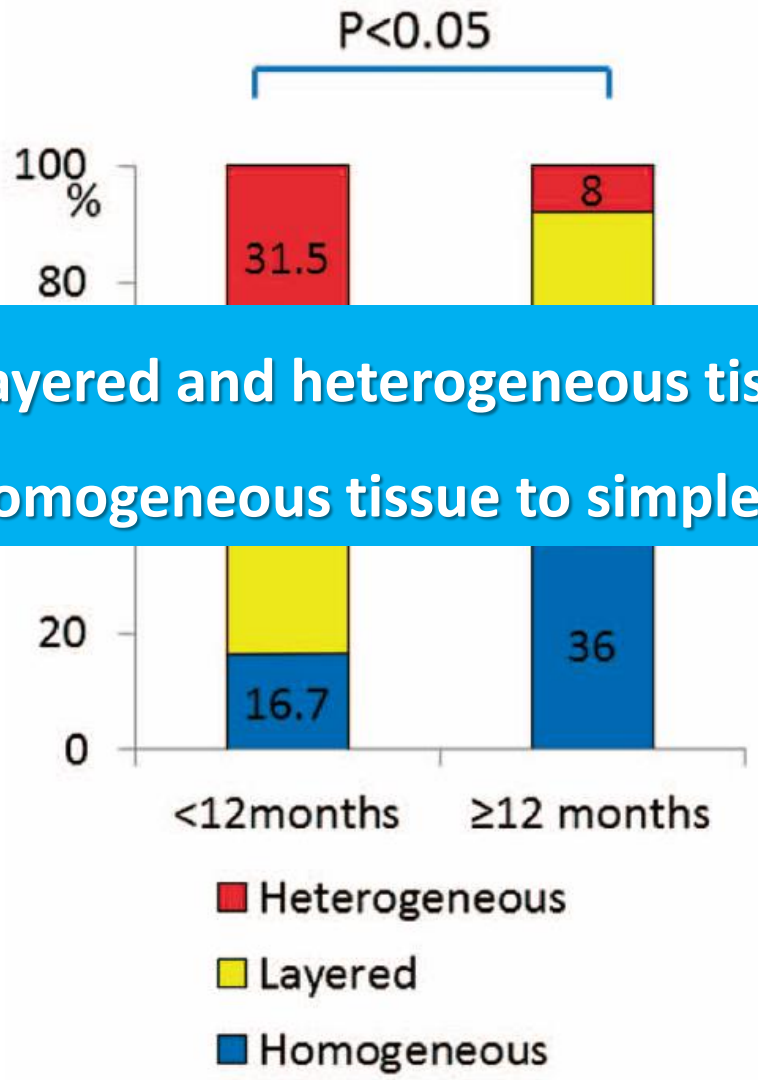


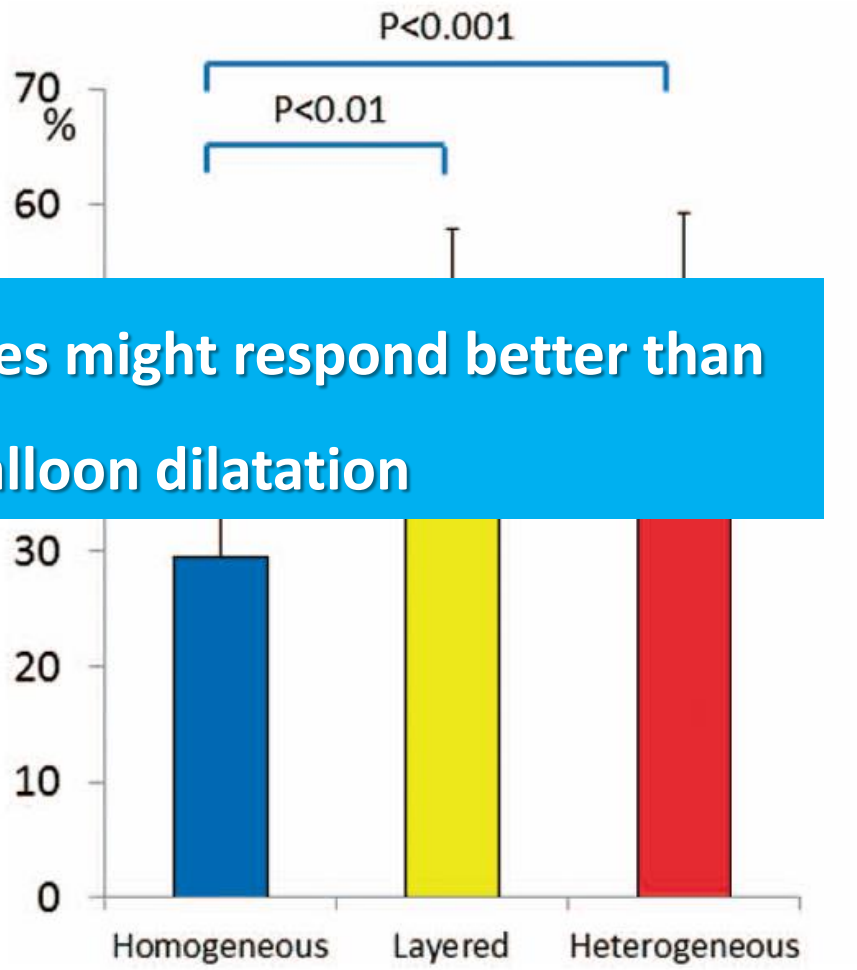
This study demonstrated that the incidence of heterogeneous neointima in patients presenting with stable angina was 6.7% (1/15) versus 40.0 % (4/10) in patients with unstable angina.

	Angiographic classification			
	Diffuse (n = 9)	Focal (n = 11)	Margin (n = 5)	p
Layered	7 (77.8%)	5 (45.5%)	1 (20%)	0.005
Homogeneous	2 (22.2%)	1 (9.1%)	4 (80%)	
Heterogeneous	0	5 (45.5%)	0	

Gonzalo N, et al. Am Heart J 2009;158:284-93

Possible direction for OCT-based ISR treatment strategies



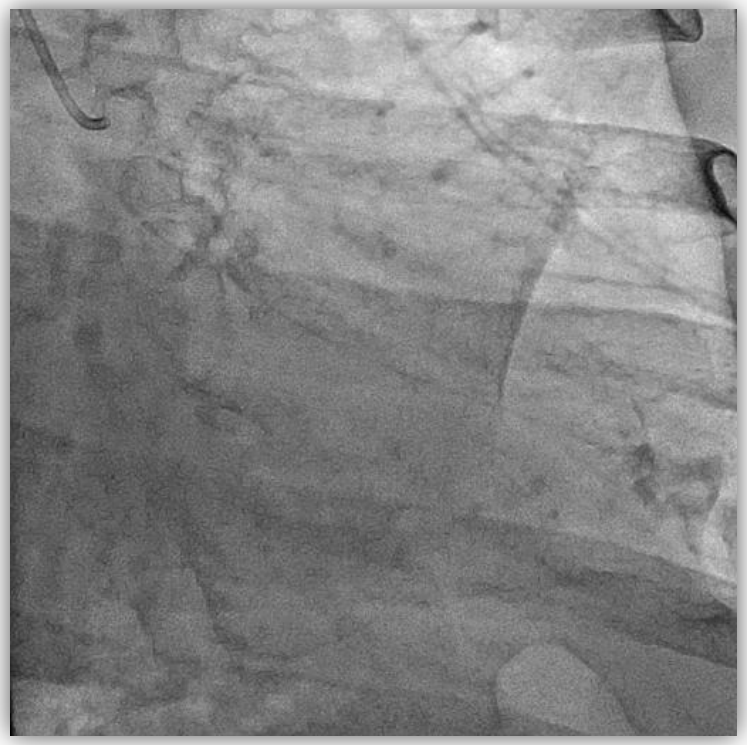


Layered and heterogeneous tissues might respond better than homogeneous tissue to simple balloon dilatation

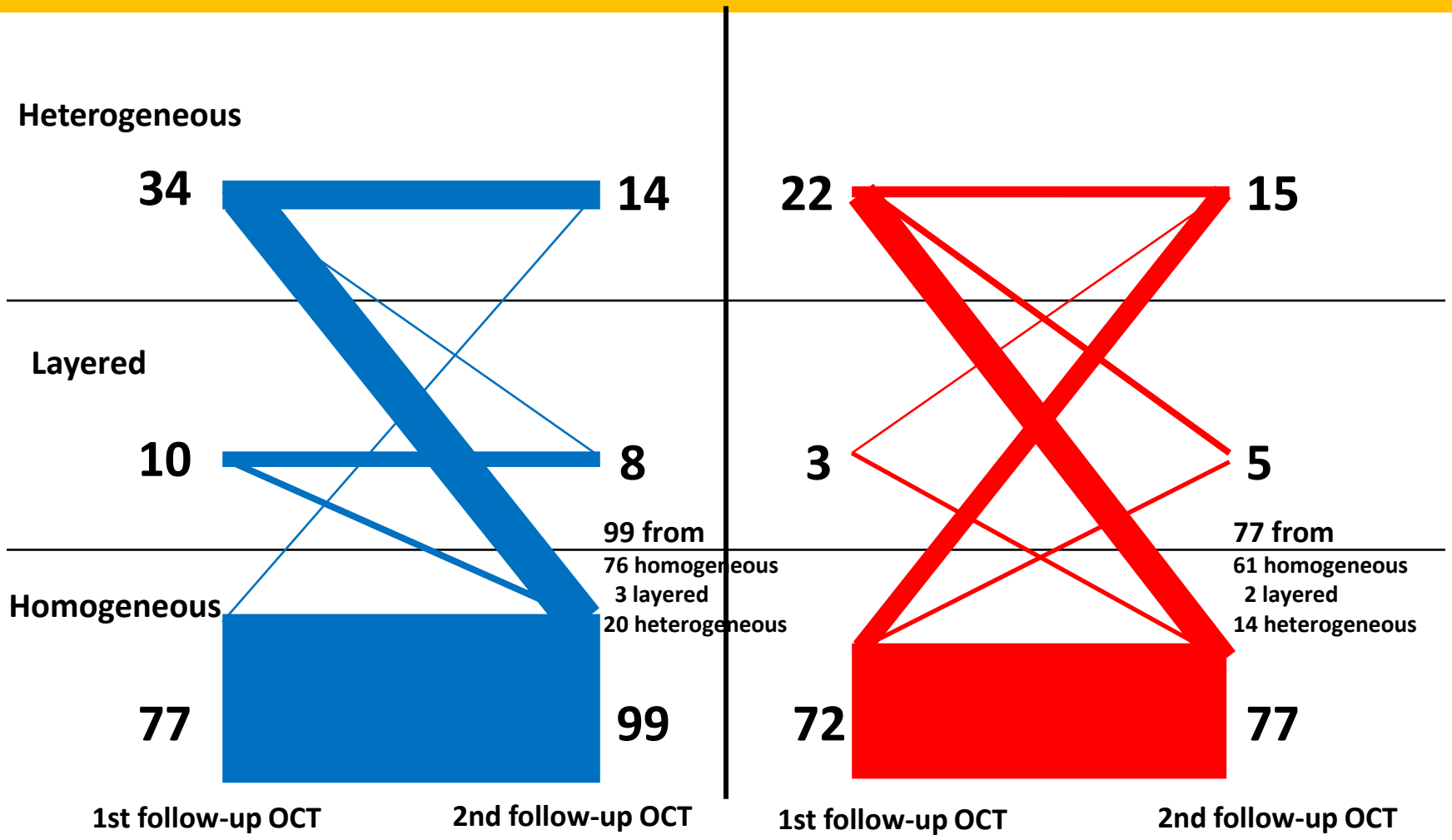
Nagoshi R, et al. Cir J 2012

CASE: F/59

- CC: Unstable angina
- P/Hx : HTN, DM



Matched Analysis of Serial Change



Jang JY, Kim JS, Hong MK, et al . Atherosclerosis 2015 In Press

Difference between first and second follow-up OCT

Variable	Optimal group (N=121)	Conventional group (n=97)	*p*
Δ Neointimal thickness (μm)	**28.6 (4.4 - 57.1)**	**31.9 (12.0 – 74.8)**	**0.09**
Δ Lumen CSA (mm^2)	-0.5±0.8	-0.6±0.9	0.32
Δ Stent CSA (mm^2)	-0.2±0.7	-0.1±0.7	0.56
Δ Neointimal CSA (mm^2)	**0.2±0.4**	**0.4±0.5**	**0.01**
Δ Percent neointimal CSA (%)	**3.7±6.3**	**6.2±7.6**	**0.01**

CSA=cross section area, OCT=optical coherence tomography. Δ indicates the difference between values from the first and second follow-up OCT

Jang JY, Kim JS, Hong MK, et al . Atherosclerosis 2015 In Press

Independent predictors of neointimal change

	Univariate Analysis		Multivariate Analysis	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Baseline LDL-C>100mg/dL	0.89 (0.25~3.19)	0.85		
Optimal LDL-C control	**0.07 (0.01~0.58)**	**0.01**	**0.04 (0.01~0.41)**	**0.006**
Male	0.38 (0.12~1.26)	0.12	0.67 (0.14~3.11)	0.61
Age	**1.07 (0.99~1.15)**	**0.08**	**1.13 (1.01~1.27)**	**0.03**
Diabetes mellitus	0.87 (0.22~3.38)	0.84	1.43 (0.27~7.48)	0.68
Hypertension	0.78 (0.24~2.59)	0.68	0.24 (0.05~1.29)	0.10
1st-generation drug-eluting stents	2.44 (0.73~8.08)	0.15	1.67 (0.39~7.13)	0.49
Acute coronary syndrome as Initial presentation	0.99 (0.30~3.30)	0.99	0.55 (0.11~2.80)	0.47

Jang JY, Kim JS, Hong MK, et al . Atherosclerosis 2015 In Press

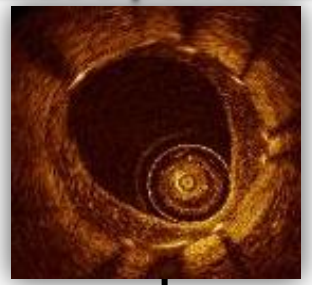
COMPASS trial

1. Patients received DES between 1 and 2 year before OCT evaluation
2. Patients received OCT related to clinical needs or end point of other study

Divide by two arms according to neointimal pattern

Homogenous
504 patients

Heterogenous
258 patients

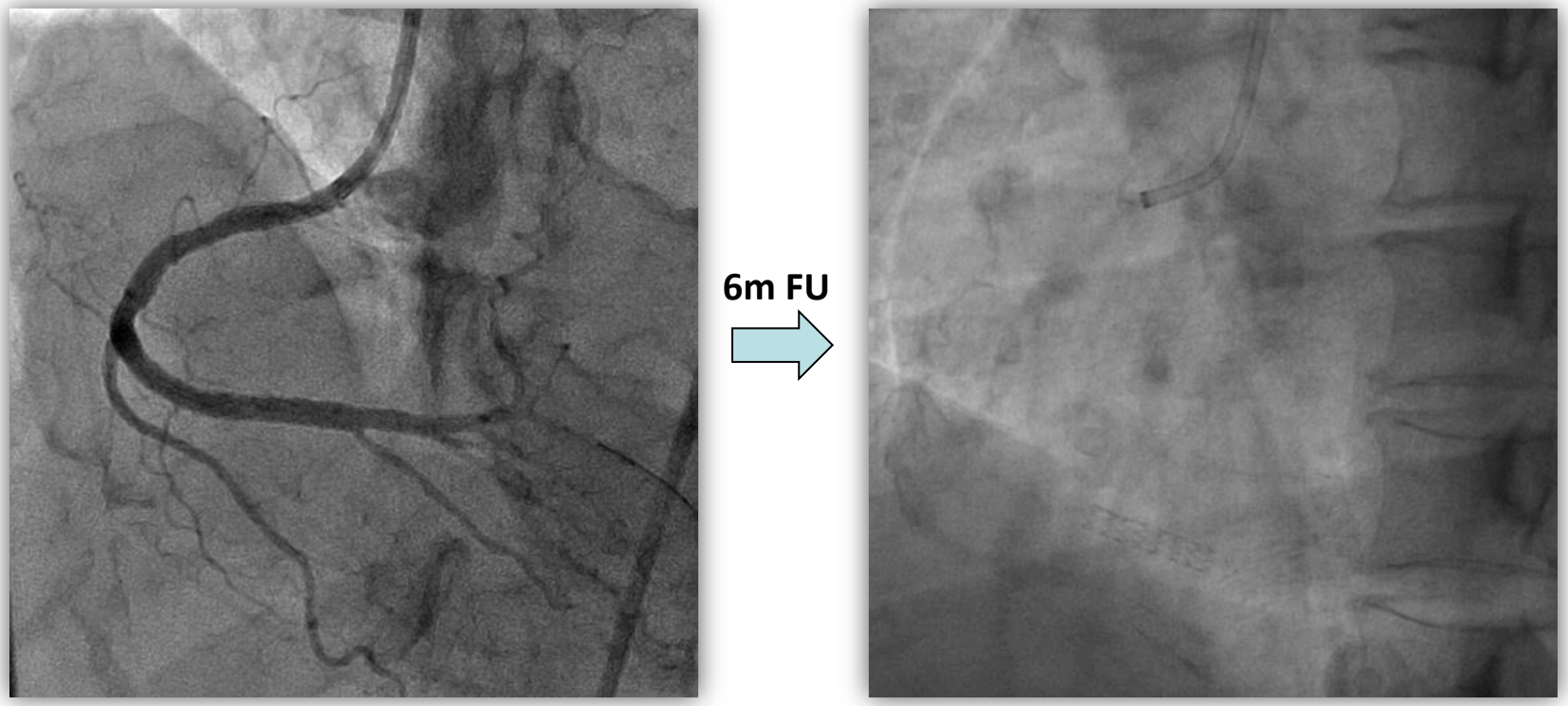


ClinicalTrials.gov Identifier:
NCT02155530

- Atorvastatin 40mg 252 patients
- Pravastatin 20mg 252 patients
- Atorvastatin 40mg 129 patients
- Pravastatin 20mg 129 patients

CASE: F/59

- PCI at dRCA (Cypher 3.5 x 18mm) & 6month F/U angiography

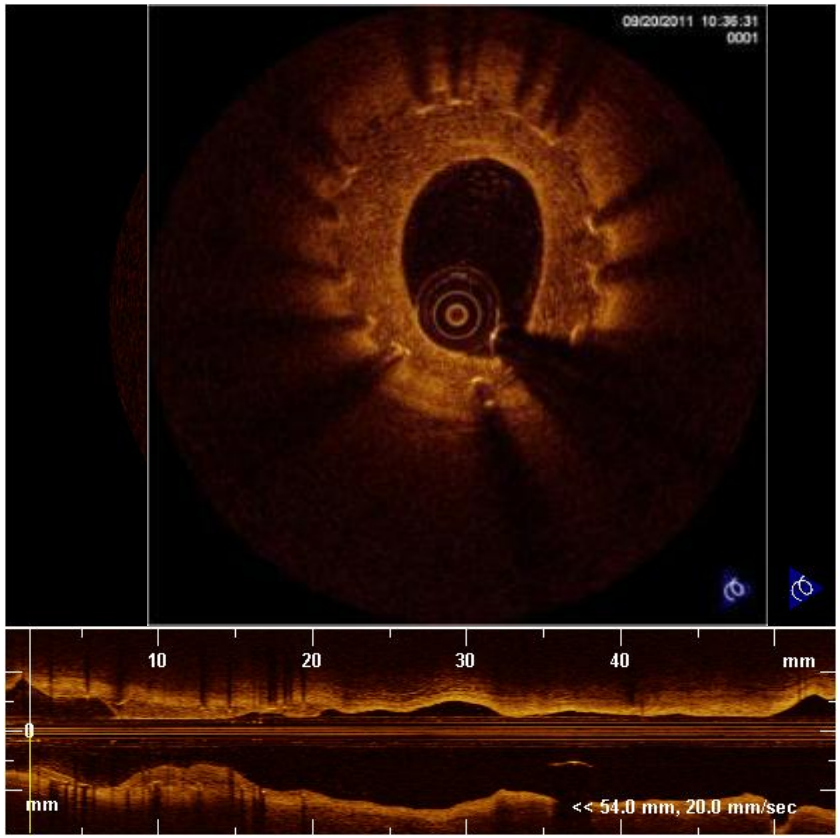


After 2 years

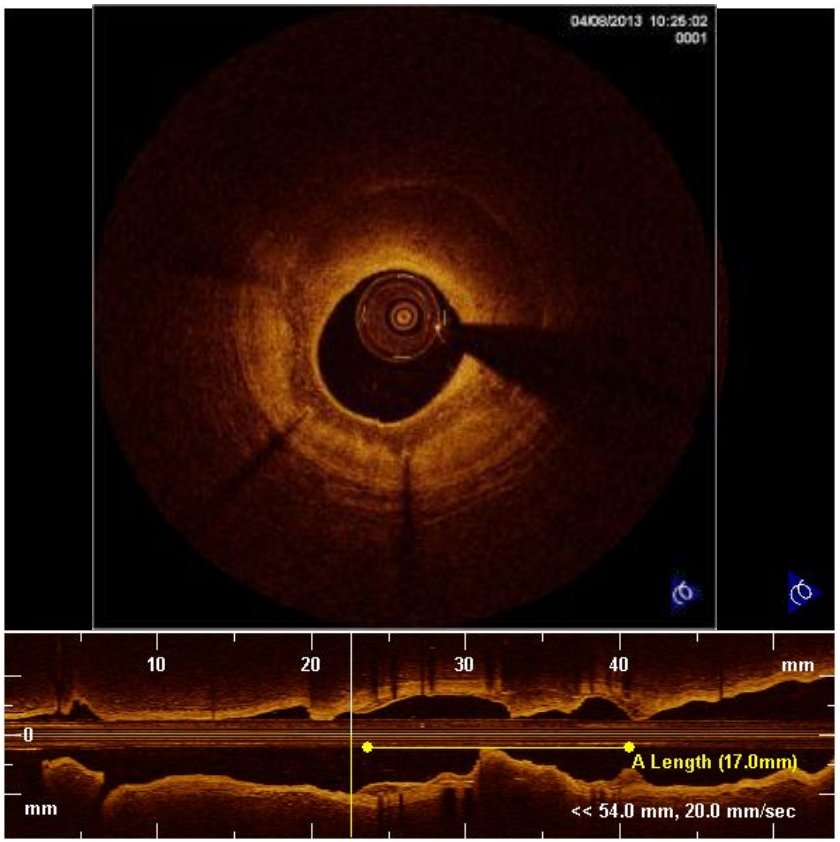
- **Follow up angiogram d/t chest discomfort**
  →PTCA c DEB at dRCA (Sequent please 3.5 x 15)



OCT findings



18 Months
F/U

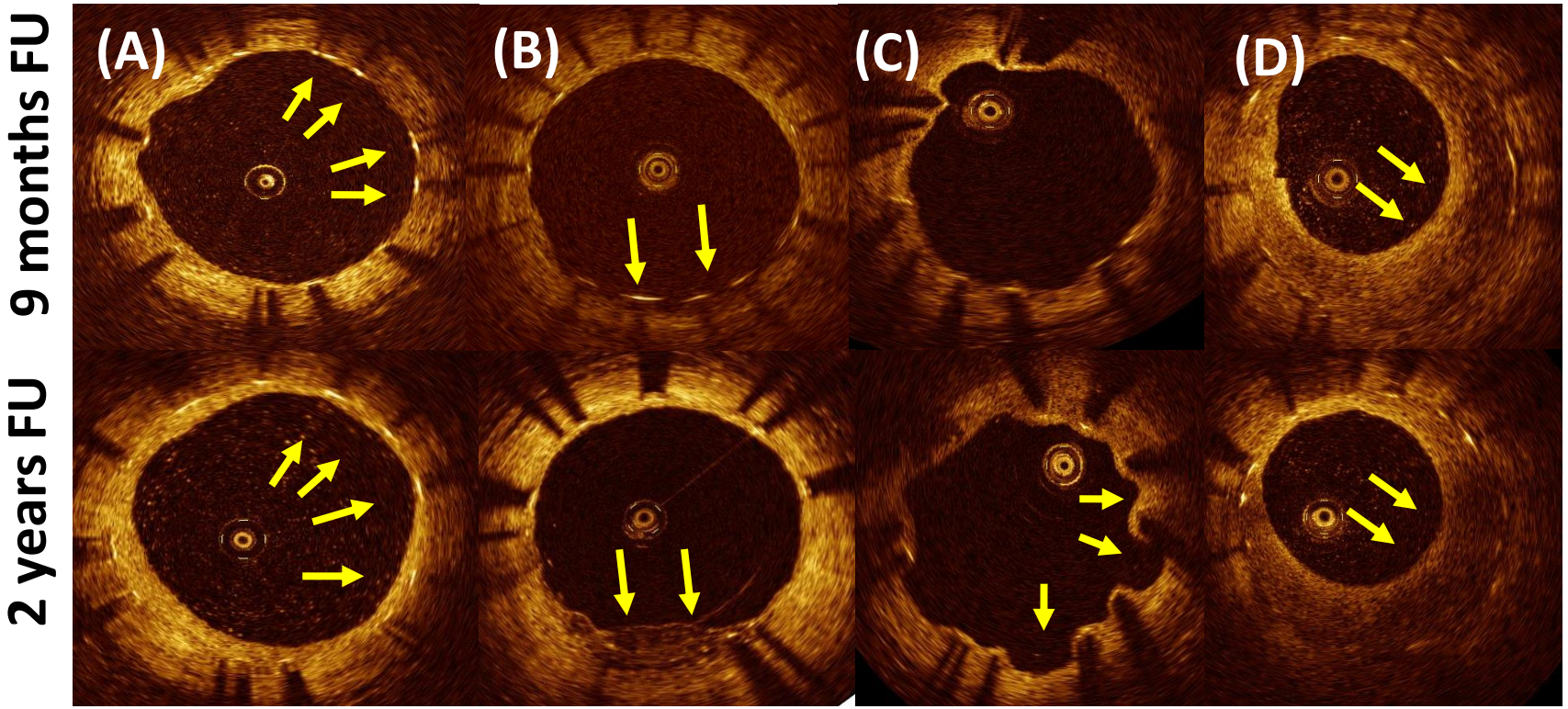


Background

- However, the relationship between different OCT-based neointimal characteristics and clinical outcomes has not been well investigated.

- Therefore, we tried to find out the correlation between in-stent neointimal characteristics as assessed by OCT and clinical outcomes.

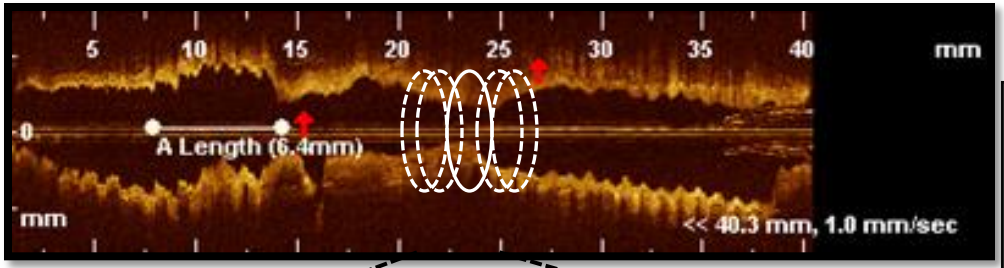
Serial Change of Neointimal Tissue



(A) Uncovered struts at 9 months were covered with neointima on 2 yr FU (white arrow).
(B) Appearance of a low density abnormal tissue structure over uncovered struts during serial follow-up (white arrow), (C) Extrastent lumen not present at 9 months was noted at 2 yr FU (yellow arrow),
(D) Increase in the low density within heterogeneous neointima between 9 months (white arrow) and 2 yr (yellow arrow).

Kim JS, MK Hong, et al. J Am Coll Cardiol Img 2012

Methods



368 stented lesions with a neointimal thickness of **at least 100 μm in 5 consecutive CS** around MLA were assessed.

(A) Homogeneous pattern : an uniform signal-rich band without focal variation or attenuation.

(B) Heterogeneous pattern : focally changing optical properties and various backscattering patterns.

(C) Layered pattern : layers with different optical properties, namely an adluminal high scattering layer and abluminal low scattering layer.

Predictors for MACEs

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age (per years)	1.006 (0.959-1.055)	0.814	0.970 (0.915-1.029)	0.314
Gender (male)	0.931 (0.371-2.333)	0.879	0.885 (0.309-2.421)	0.865
Hypertension	0.688 (0.286-1.652)	0.402		
Diabetes mellitus	1.881 (0.779-4.539)	0.160	1.262 (0.479-3.326)	0.638
Initial ACS dx	1.586 (0.648-3.884)	0.312	1.008 (0.384-2.648)	0.987
1st gen. DES	2.440 (0.980-6.075)	0.055	2.447 (0.792-7.560)	0.120
Time interval to OCT (months)	1.018 (1.003-1.033)	0.017	0.988 (0.958-1.020)	0.457
Minimal lumen CSA (per mm^2)	0.319 (0.206-0.495)	<0.001	0.421 (0.267-0.664)	<0.001
Stent length (per mm)	1.024 (0.954-1.098)	0.513		
Heterogeneous pattern*	5.638 (2.044-15.549)	0.001	4.524 (1.293-15.825)	0.018
Layered group*	2.632 (0.743-9.332)	0.134	1.880 (0.478-7.394)	0.366

Baseline characteristics

	Homogeneous (n=208)	Heterogeneous (n=73)	Layered (n=55)	p
Age (years)	60.8 ± 9.6	64.0 ± 7.9	63.5 ± 7.9	0.014
Male, n (%)	134 (64.4)	52 (71.2)	39 (70.9)	0.450
Diabetes mellitus, n (%)	58 (27.9)	24 (32.9)	22 (40.0)	0.207
Hypertension, n (%)	125 (60.1)	40 (54.8)	36 (65.5)	0.472
Dyslipidemia, n (%)	95 (45.7)	25 (34.2)	25 (45.5)	0.221
Current smoker, n (%)	39 (18.8)	19 (26.0)	15 (27.3)	0.238
Chronic renal failure, n (%)	3 (1.4)	1 (1.4)	0 (0.0)	0.672
Clinical presentation, n (%)				0.096
Stable angina	117 (56.3)	31 (42.5)	32 (58.2)	
Acute coronary syndrome	91 (43.8)	42 (57.5)	23 (41.8)	

OCT analysis

	Homogeneous (n=227)	Heterogeneous (n=79)	Layered (n=62)	p
Total frames	5380	1649	1386	
Median time interval (m), IQR	9.0 (6.0-10.0)	8.0 (5.0-10.0)	9.0 (6.0-11.0)	0.637
Mean stent CSA (mm^2)	7.1 ± 1.9	7.1 ± 2.1	7.3 ± 1.8	0.599
Mean neointimal CSA (mm^2)	1.2 ± 0.7	1.4 ± 0.9	1.9 ± 1.2	<0.001
Mean lumen CSA (mm^2)	5.9 ± 1.7	5.7 ± 1.9	5.5 ± 1.7	0.193
Minimal lumen area (mm^2)	4.5 ± 1.6	4.0 ± 1.9	3.7 ± 1.8	0.001
Mean neointimal thickness (μm)	138 ± 68	168 ± 119	217 ± 133	<0.001
Neointimal CSA (%)	16.5 ± 8.1	20.1 ± 12.9	25.4 ± 13.7	<0.001
Uncovered strut (%)	3.4 ± 5.4	4.7 ± 8.0	4.1 ± 7.3	0.293

Predictors for Heterogeneous Pattern

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age (per years)	1.032 (1.003-1.062)	0.029	1.039 (1.008-1.070)	0.013
Gender (male)	1.046 (0.616-1.775)	0.868	0.852 (0.484-1.498)	0.578
1st gen. DES	1.125 (0.662-1.912)	0.663		
Initial ACS dx	1.874 (1.130-3.107)	0.015	2.010 (1.182-3.418)	0.010
Diabetes mellitus	1.289 (0.758-2.190)	0.348	1.396 (0.797-2.443)	0.243
Hypertension	0.831 (0.503-1.373)	0.470		
Dyslipidemia	0.662 (0.395-1.109)	0.117	0.723 (0.419-1.248)	0.244
Chronic renal failure	0.913 (0.101-8.290)	0.936		
Time interval to OCT (m)	1.015 (1.002-1.028)	<0.001	1.014 (0.999-1.025)	0.079
Uncovered struts (%)	1.024 (0.989-1.061)	0.179	1.022 (0.986-1.060)	0.230
Stent length (per mm)	0.975 (0.938-1.014)	0.206		

MACE during follow up after OCT

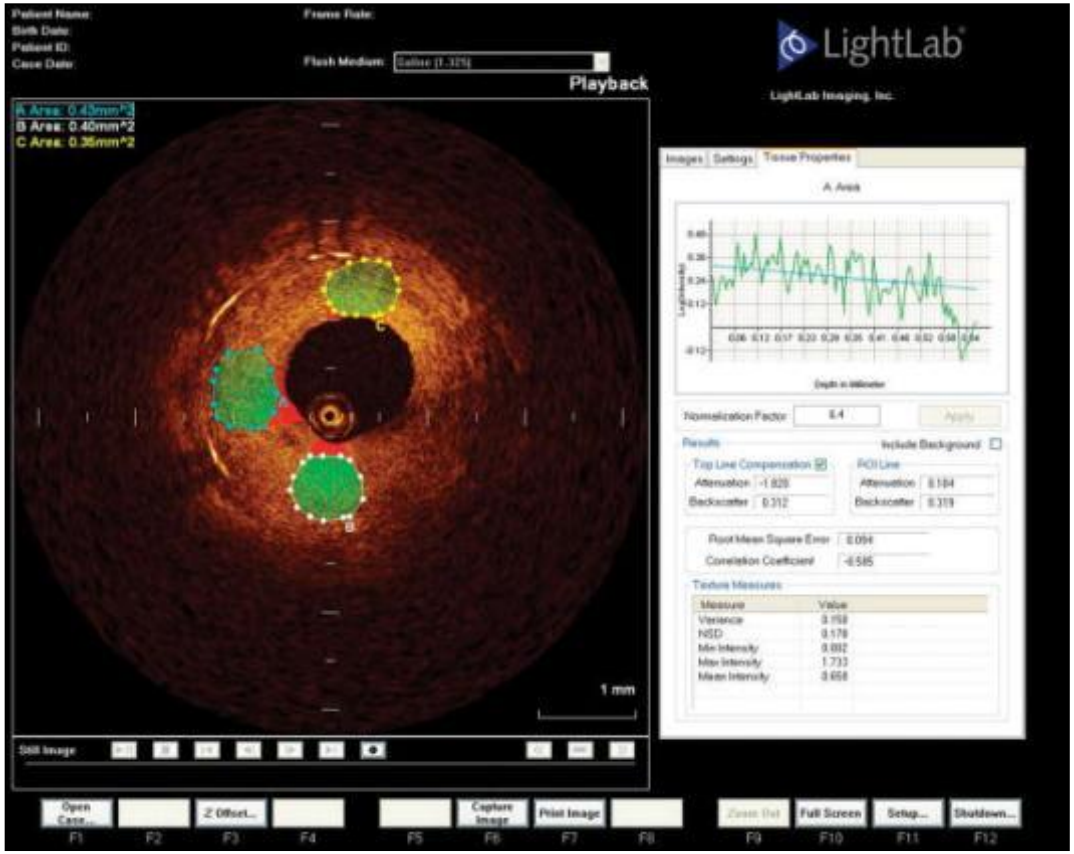
	Homogeneous (n=208)	Heterogeneous (n=73)	Layered (n=55)	p
A composite of cardiac death, non-fatal MI, or TLR	6 (2.9%)	10 (13.7%)	4 (7.3%)	0.001
Cardiac death	1 (0.5%)	0 (0.0%)	0 (0.0%)	0.780
Non-fatal MI	0 (0.0%)	3 (4.1%)	0 (0.0%)	<0.001
TLR	5 (2.4%)	7 (9.6%)	4 (7.3%)	0.020
Stent thrombosis	1 (0.5%)	3 (4.1%)	0 (0.0%)	0.006

TLR and Stent Thrombosis

152 ISR lesions with intimal hyperplasia > 50% of stent area

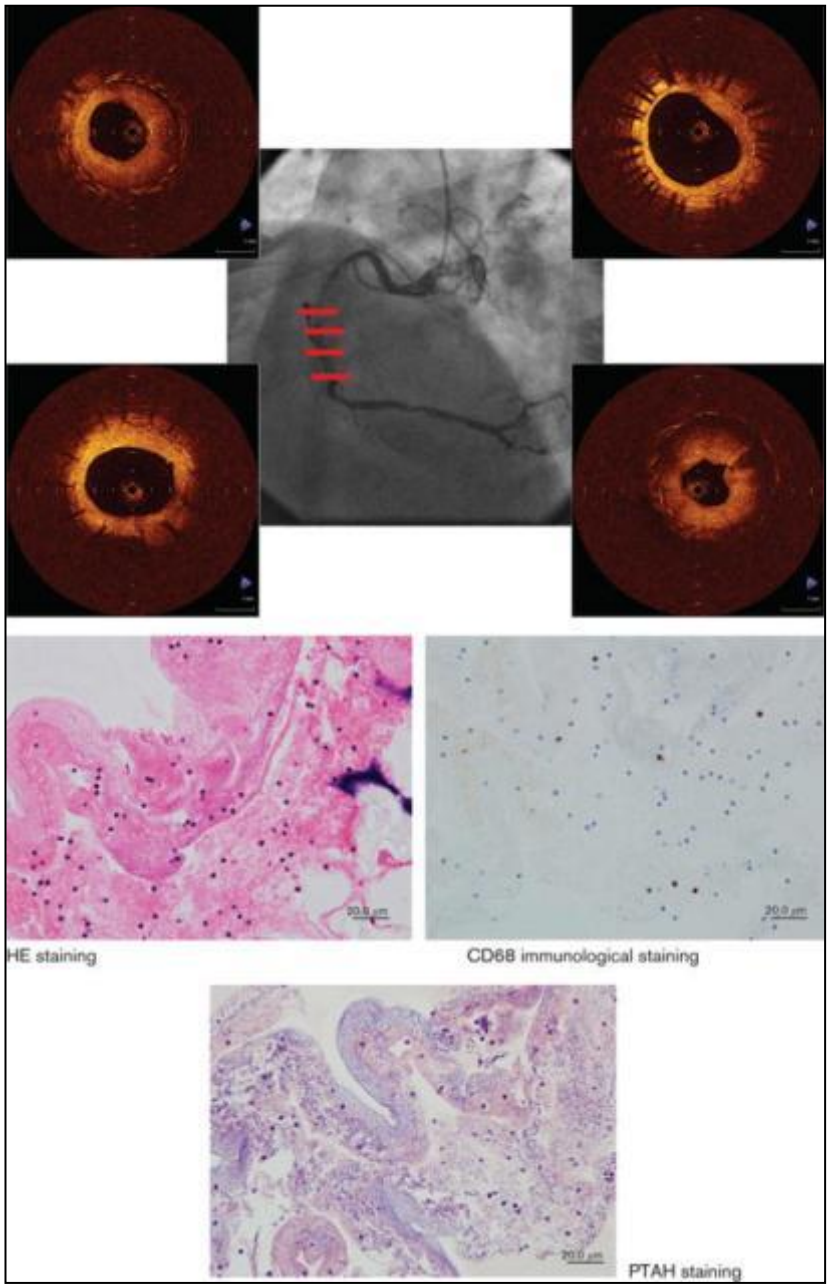
	Presence of neoatherosclerosis (n = 54)	Absence of neoatherosclerosis (n = 98)	p
Time interval to follow-up OCT (months)	70.7 (54.4 – 120.4)	13.4 (10.6 – 39.6)	< 0.001
Clinical variables			
Clinical presentation at follow-up OCT, # (%)			< 0.001
Asymptomatic	4 (7.4)	22 (22.4)	
Stable angina	33 (61.1)	72 (73.5)	
Acute coronary syndrome	17 (31.5)	4 (4.1)	
Target lesion revascularization, # (%)	50 (92.6)	76 (77.6)	0.018
Stent thrombosis, # (%)	8 (14.8)	0 (0)	< 0.001

Lee SY, Hong MK, et al, Eurointervention 2014



Clinical and pathological characteristics of homogeneous and nonhomogeneous tissue of in-stent restenosis visualized by optical coherence tomography.
Tomonori I, et al; Coronary Artery Disease. 26(3):201-211, May 2015.

Fig. 1 . Representative case of OCT-NSD value analysis. OCT signal-intensity normalized standard deviation (OCT-NSD) in NIH tissue at the minimal lumen area evaluated by Tissue Properties (LightLab Imaging, Westford, Massachusetts, USA). The region of interest (ROI) was defined in the frame at the minimal lumen area near the surface of the ISR lesion using three points to randomly designate the ROI. Moreover, ROI at a control site was defined in the phantom model to determine the normalization factor. ROI in ISR was set up as a circle with a diameter of 0.127 mm in each case (as near as possible to 0.4 mm2). The homogeneous image case shows that the OCT-NSD value was 0.178. ISR, in-stent restenosis; NIH, neo-intimal hyperplasia; OCT, optical coherence tomography.



Clinical and pathological characteristics of homogeneous and nonhomogeneous tissue of in-stent restenosis visualized by optical coherence tomography.
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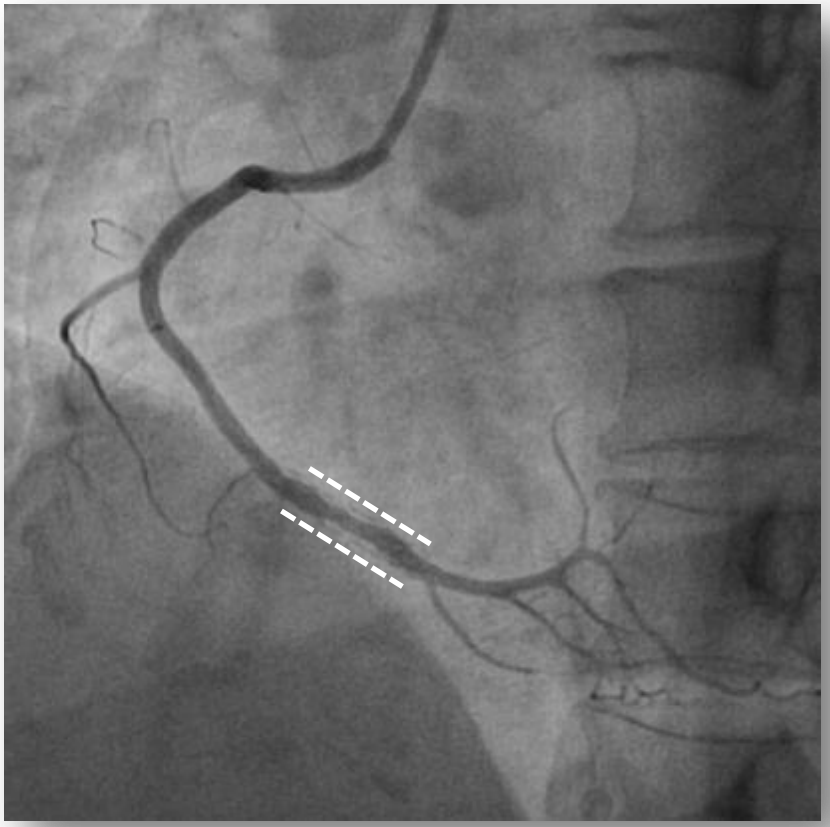
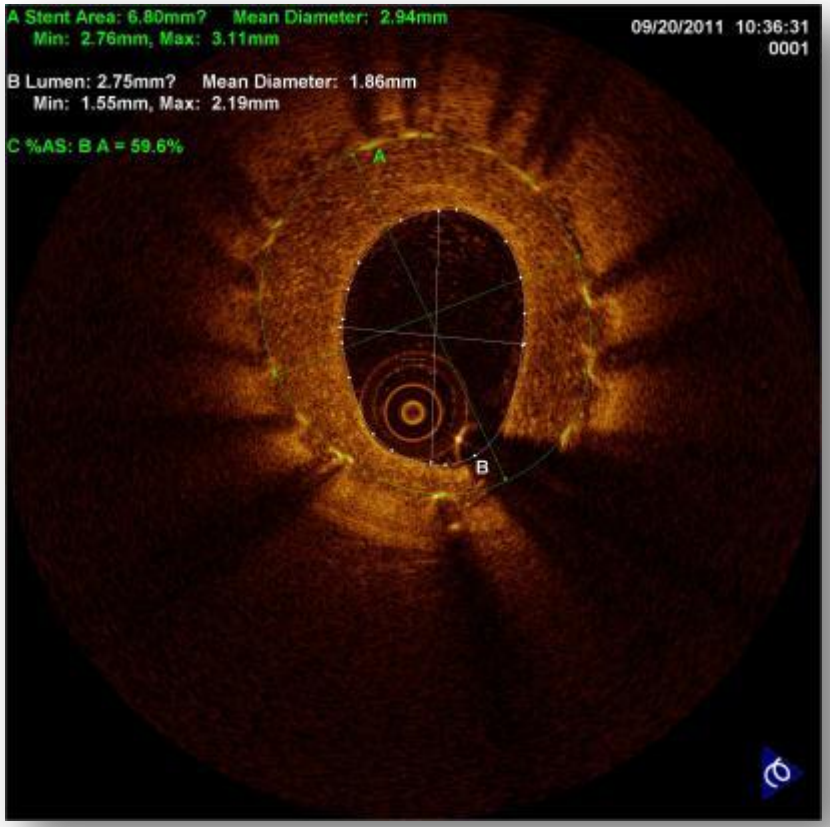
Representative case (case 11) in the nonhomogeneous image group without neolipidic tissue. This case was implanted with two zotarolimus-eluting stents (3.0/18 and 2.75/18 mm) previously at the right coronary artery and showed ISR after 8 months. OCT showed a layered ISR image (upper panel). OCT-NSD values were 0.241 at the ISR site. Collected pathological tissues showed fibrin thrombus (PTAH-positive) with CD68-positive cells (lower panel). ISR, in-stent restenosis; NSD, normalized standard deviation; OCT, optical coherence tomography.

6 months follow angiography





QCA analysis

Diameter stenosis = 29.4%

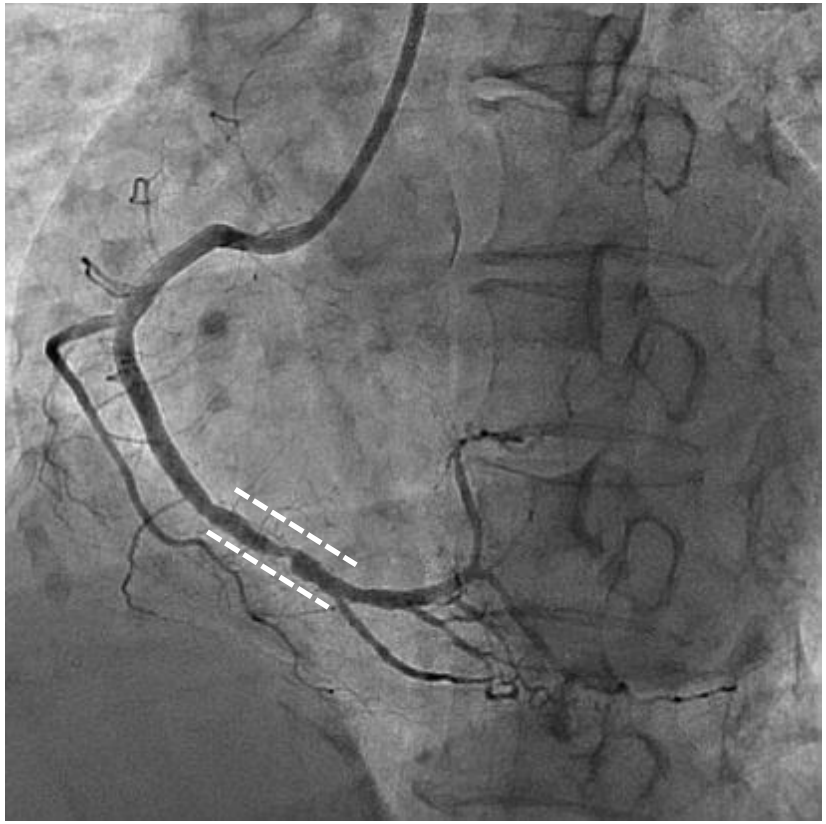
OCT analysis

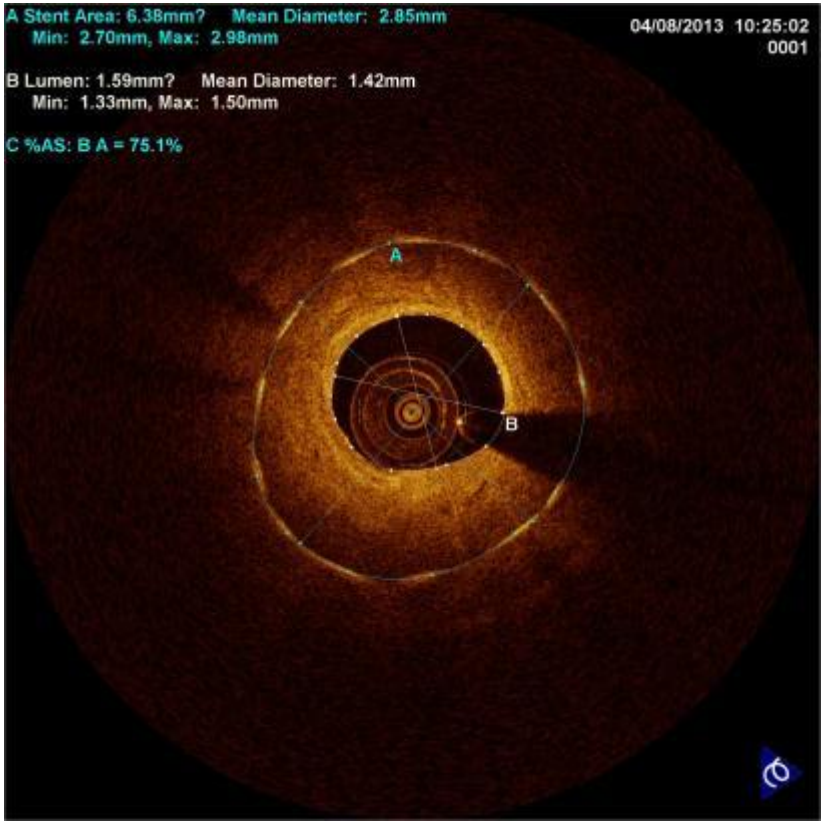
Stent area= 6.80 mm2

Lumen area= 2.75mm2

NIH = 59.6%

2 years follow angiography





QCA analysis

Diameter stenosis = 72.8%

OCT analysis

Stent area= 6.38 mm2

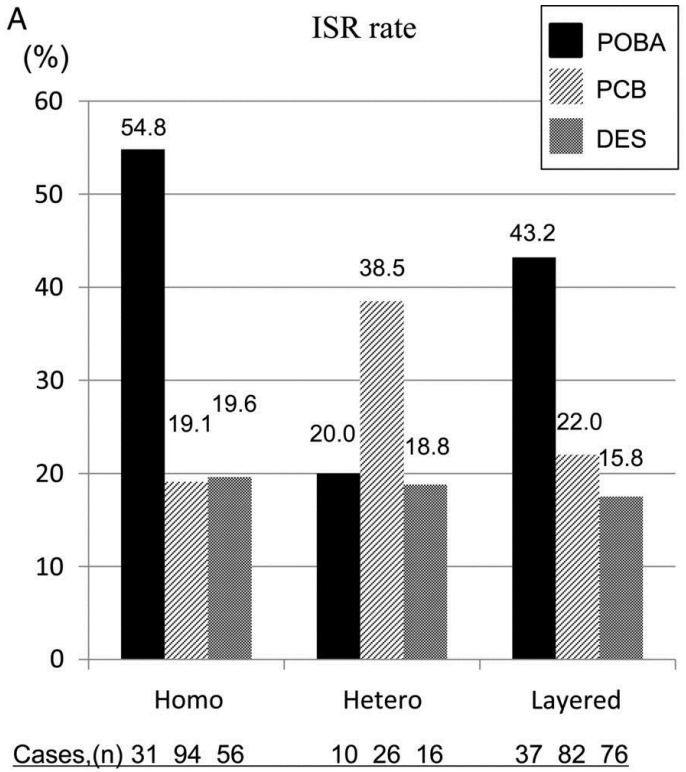
Lumen area= 1.59 mm2

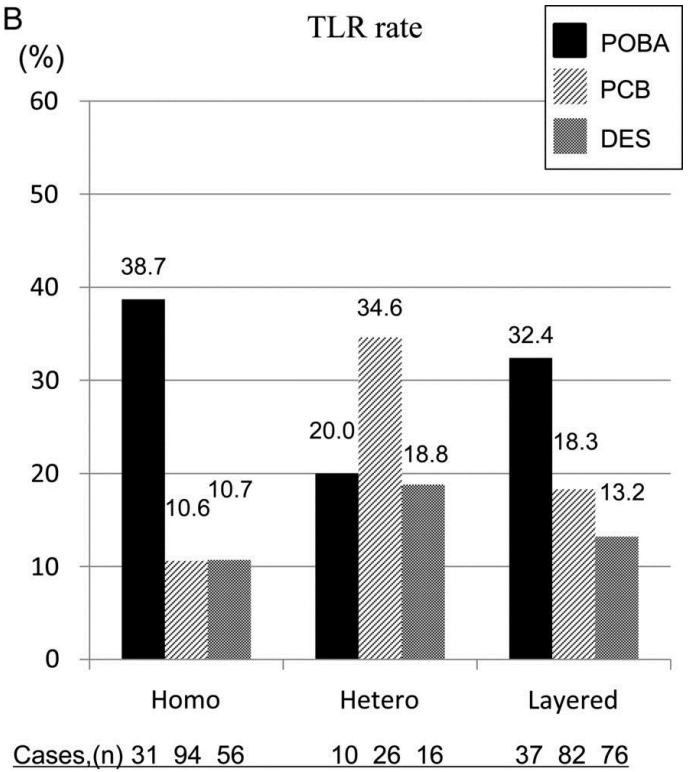
NIH = 75.1 %

Angiographic characteristics

	Homogeneous (n=227)	Heterogeneous (n=79)	Layered (n=62)	p
Target coronary artery				0.033
Left anterior descending	117 (51.5)	46 (58.2)	28 (45.2)	
Left circumflex	58 (25.6)	14 (17.7)	9 (14.5)	
Right	52 (22.9)	19 (24.1)	25 (40.3)	
Stent types, n (%)				
Bare-metal stent	0 (0.0)	3 (3.8)	0 (0.0)	0.004
Drug-eluting stent	227 (100.0)	76 (96.2)	289 (100.0)	
1st generation DES	74 (32.6)	27 (35.5)	21 (33.9)	0.893
Stent diameter (mm)	3.0 ± 0.3	3.1 ± 0.4	3.0 ± 0.4	0.125
Total stent length (mm)	24.1 ± 6.2	21.4 ± 6.4	23.6 ± 6.6	0.006

Associations between restenotic tissue structure and mid-term results





p value	Homo	Hetero	Layered
POBA vs. PCB	<0.001	0.438	0.027
POBA vs. DES	0.002	1.000	0.002
PCB vs. DES	1.000	0.303	0.417

p value	Homo	Hetero	Layered
POBA vs. PCB	<0.001	0.688	0.102
POBA vs. DES	0.005	1.000	0.022
PCB vs. DES	1.000	0.316	0.394

Tada T, et al. Eur Hear J Cardiovasc Img 2015;16:1101-11