Early Statin May Stabilize VP More Rapidly & Effectively: ESCORT Study Using OCT

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VP: Treat or Not to Treat

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# Disclosure Statement of Financial Interest
Takashi Akasaka, MD, PhD, FESC

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support   : Abbott Vascular Japan
                                          Boston Scientific Japan
                                          Goodman Inc.
                                          St. Jude Medical Japan
                                          Terumo Inc.

- Consulting Fees/Honoraria   : Daiichi-Sankyo Pharmaceutical Inc.
                                          Goodman Inc.
                                          St. Jude Medical Japan
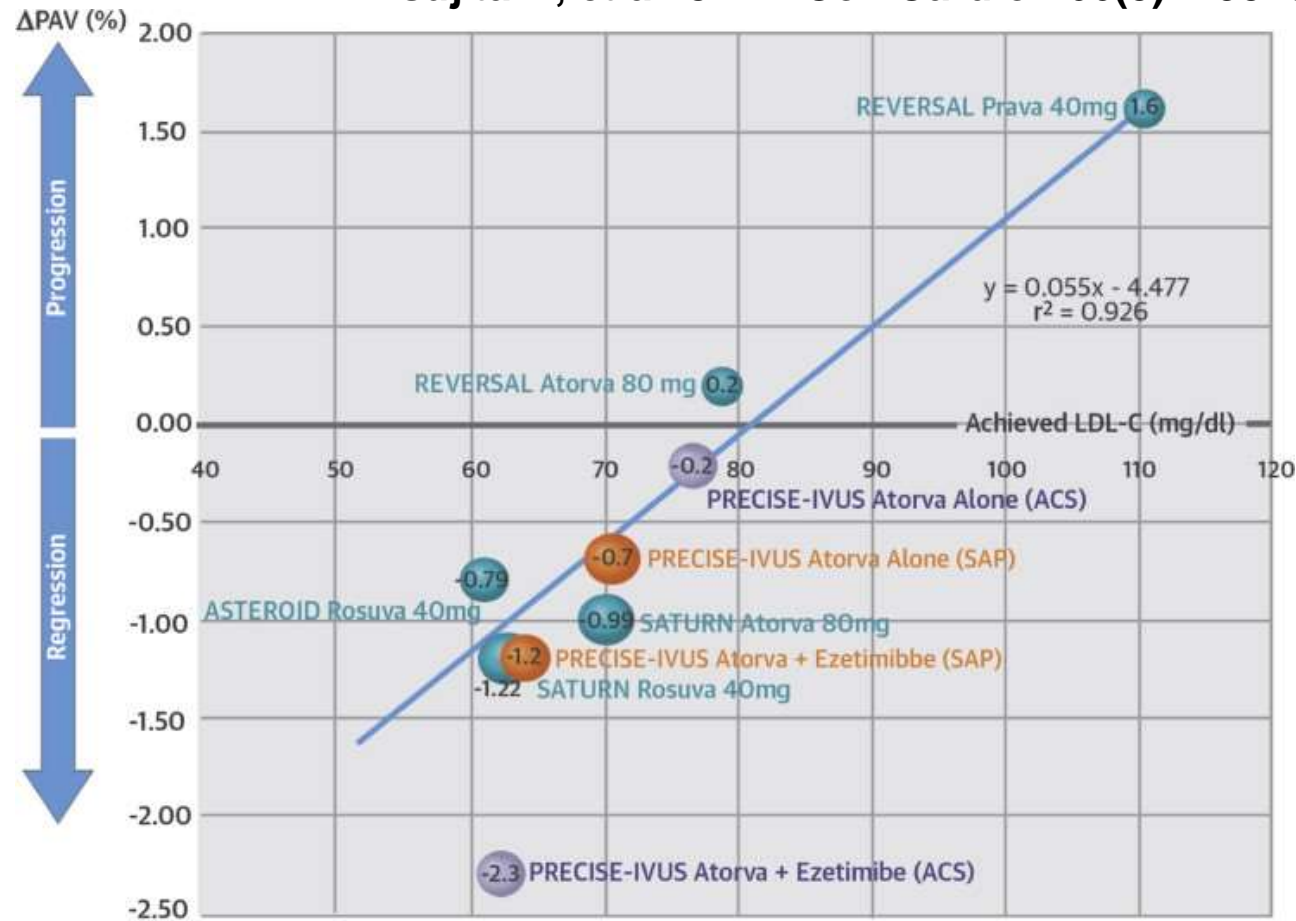   Terumo Inc.

Relation between %change of plaque volume & LDL-C
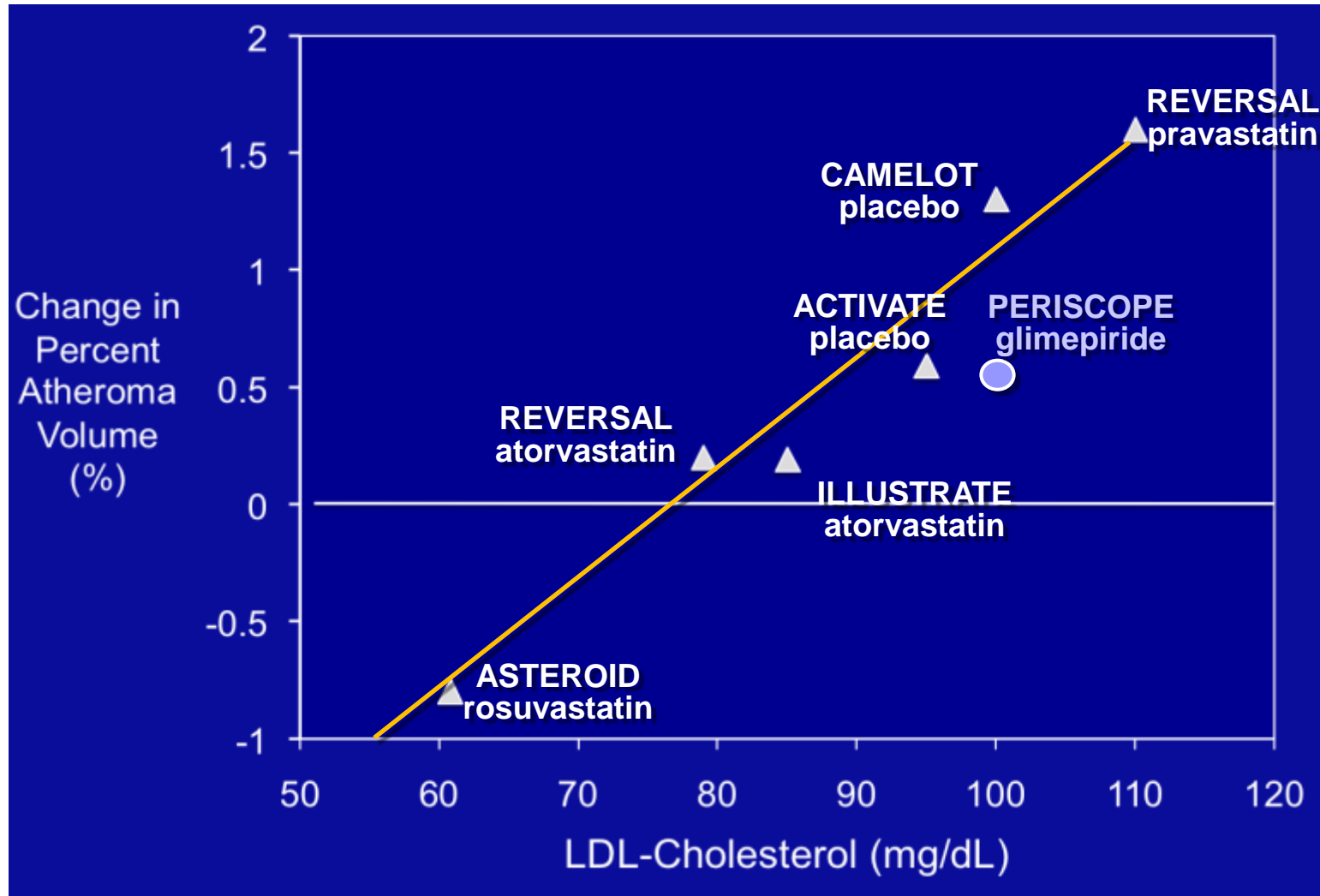
A significant correlation has been demonstrated between % change in atheroma plaque volume and LDL-cholesterol lowering therapy.

Relation between LDL and plaque volume

Tsujita K, et al. J Am Coll Cardiol 66(5): 495–507, 2015

Further regression in % atheroma plaque volume has been demonstrated by LDL lowering therapy using statin and ezetimibe.

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Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients
The GLAGOV Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD;
John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helina Kassahun, MD; Jingyuan Yang, PhD;
Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD, PhD; Jakub Podolec, MD, PhD; Antonius Oude Ophuis, MD, PhD;
Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Danielle M. Brennan, MS; Steven E. Nissen, MD

in cholesterol (LDL-C) with intensive
sclerosis in proportion to achieved
...pe 9 (PCSK9) inhibitors produce
...however, the effects of these drugs on

...on with evolocumab on progression of

...center, double-blind, placebo-controlled,
...nuary 12, 2015) conducted at 197
...Europe, South America, Asia, Australia,
...g for coronary angiography.

...ary disease were randomized to receive

CONCLUSIONS AND RELEVANCE Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.
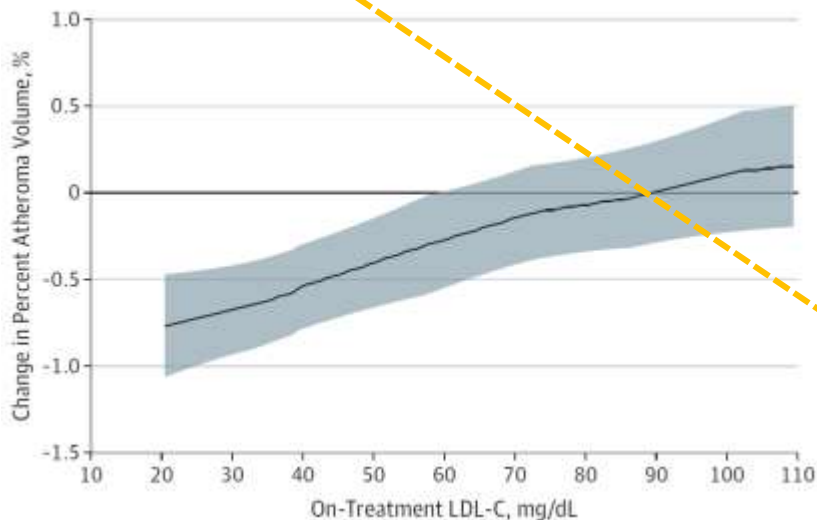
RESULTS Among the 968 treated patients (mean age, 59.8 years [SD, 9.2]; 269 [27.8%] women; mean LDL-C level, 92.5 mg/dL [SD, 27.2]), 846 had evaluable imaging at follow-up. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6 mg/dL; difference, −56.5 mg/dL [95% CI, −59.7 to −53.4]; $P < .001$). The primary efficacy parameter, PAV, increased 0.05% with placebo and decreased 0.95% with evolocumab (difference, −1.0% [95% CI, −1.8% to −0.64%]; $P < .001$). The secondary efficacy parameter, normalized TAV, decreased 0.9 mm^3 with placebo and 5.8 mm^3 with evolocumab (difference, −4.9 mm^3 [95% CI, −7.3 to −2.5]; $P < .001$). Evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; difference, 17.0% [95% CI, 10.4% to 23.6%]; $P < .001$ for PAV and 61.5% vs 48.9%; difference, 12.5% [95% CI, 5.9% to 19.2%]; $P < .001$ for TAV).

CONCLUSIONS AND RELEVANCE Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.
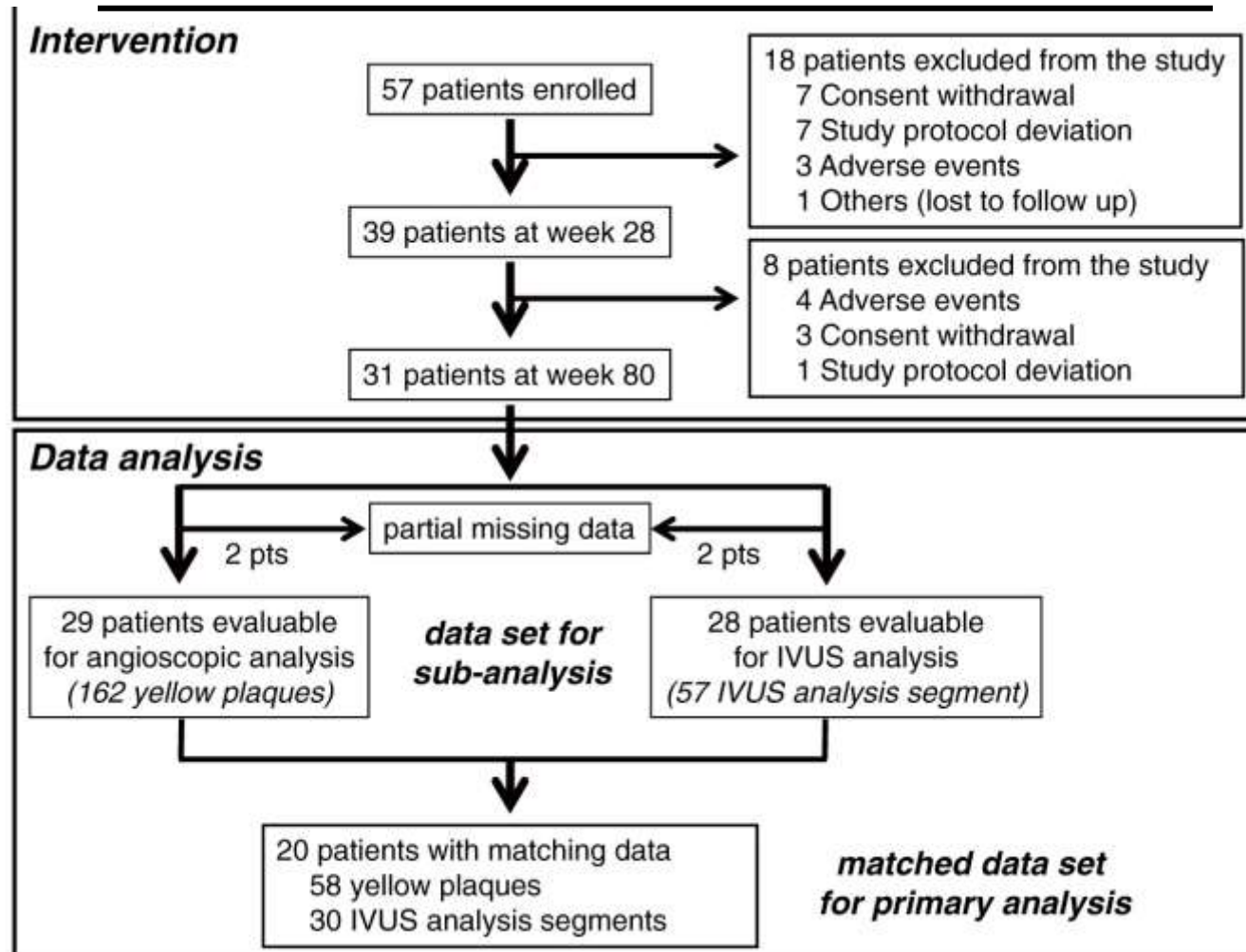
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Qualitative & Quantitative Changes in Coronary Plaque Associated with Atrovastatin Therapy: Evaluation with simultaneous angioscopy & intaravascular ultrasound (TWINS) study

Qualitative & Quantitative Changes in Plaque by Atrovastatin
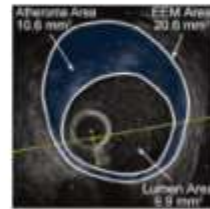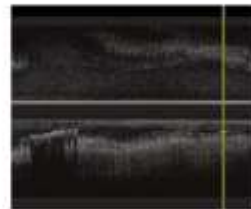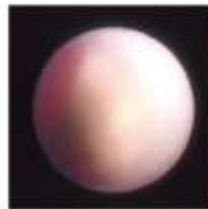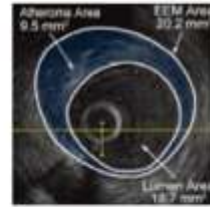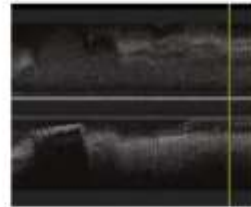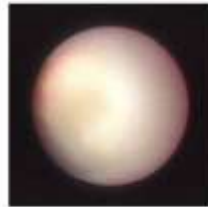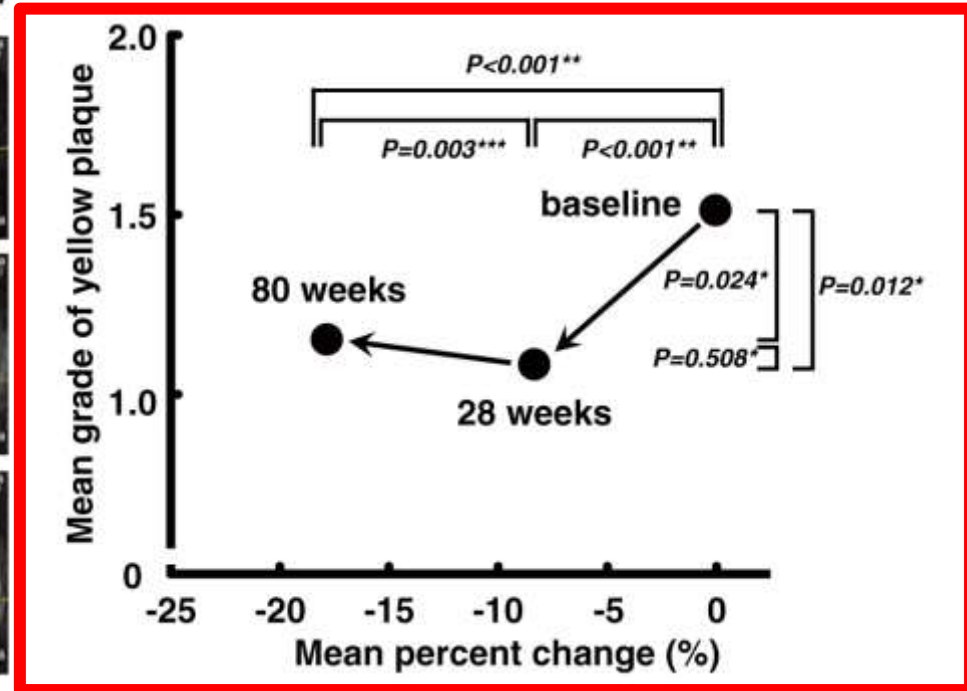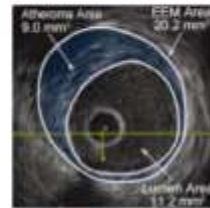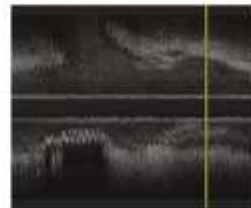
Effect of Atorvastatin Therapy on the Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by OCT (EASY-FIT)

National Clinical Trial Identifier Number: 00700037

102 Patients screened

32 Excluded (Did not meet inclusion criteria or met exclusion criteria)

70 Enrolled

70 Underwent OCT examination at baseline

70 Randomized

35 Assigned to 20 mg/day of atorvastatin

5 Excluded
1 Withdrew consent
2 Had fibrous or fibrocalcific plaques
1 Received study drug <50% of total amount
1 Had an adverse event (Itching)

30 Underwent OCT examination at 12-month follow-up

35 Assigned to 5 mg/day of atorvastatin

5 Excluded
1 Withdrew consent
2 Had fibrous or fibrocalcific plaques
2 Lost to follow-up

30 Underwent OCT examination at 12-month follow-up

Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

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Percent change in laboratory results between baseline and 12-month follow-up

Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

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The EASY-FIT Study

- ✓ **Optical coherence tomography (OCT) allows us to measure fibrous cap thickness (FCT), which is thought to be a major factor in plaque vulnerability.**
- ✓ **The EASY-FIT study demonstrated that intensive LDL-lowering by higher dose of statin therapy leads to greater increase of FCT in non-culprit plaques in 12 months compared to moderate LDL-lowering by lower dose of statin therapy.**

Komukai K, Kubo T, Akasaka T et al. J Am Coll Cardiol. 2014 2;64(21):2207-2217

Decrease of macrophage density during 20mg/day of Atorvastatin
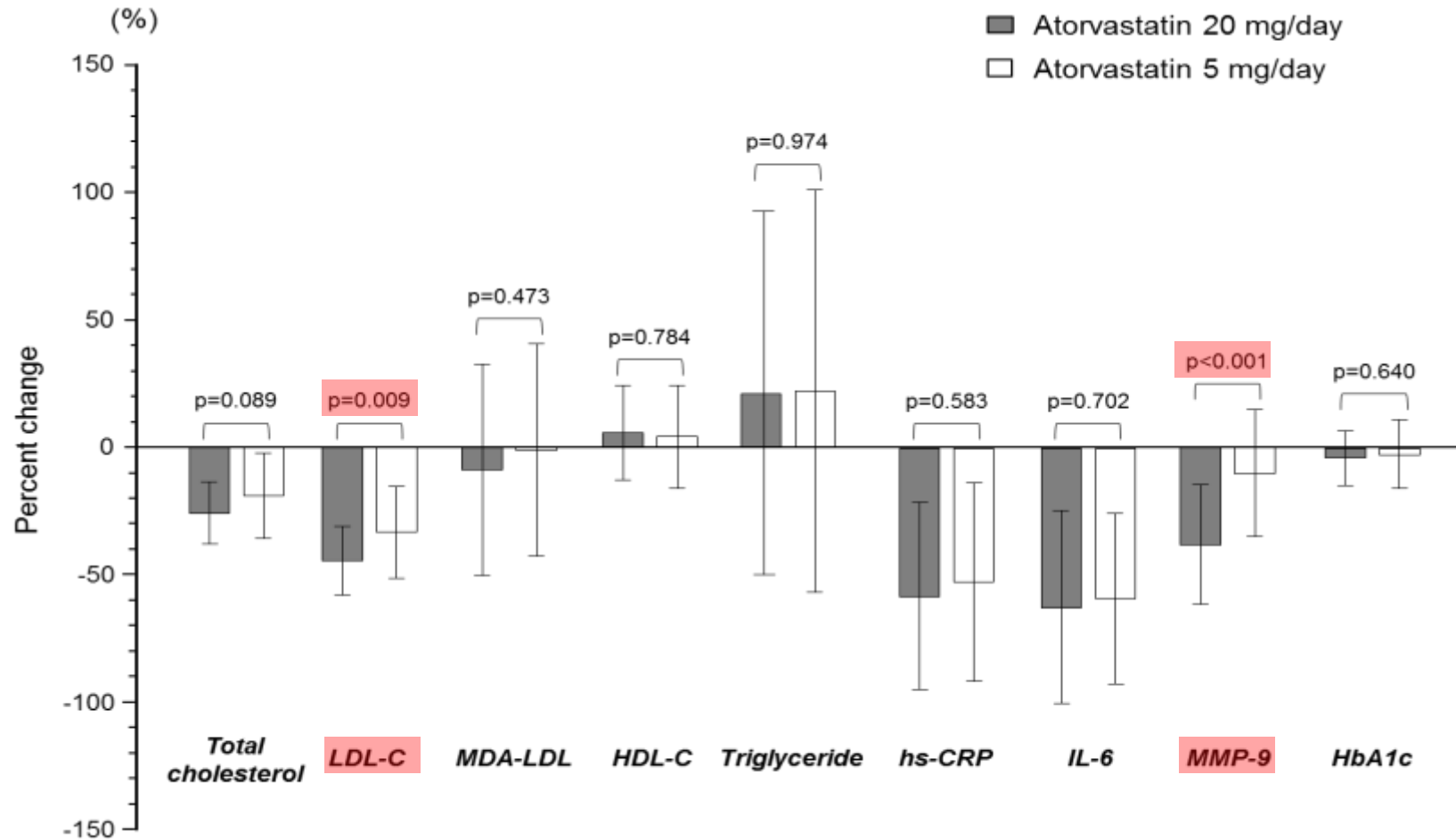
Baseline

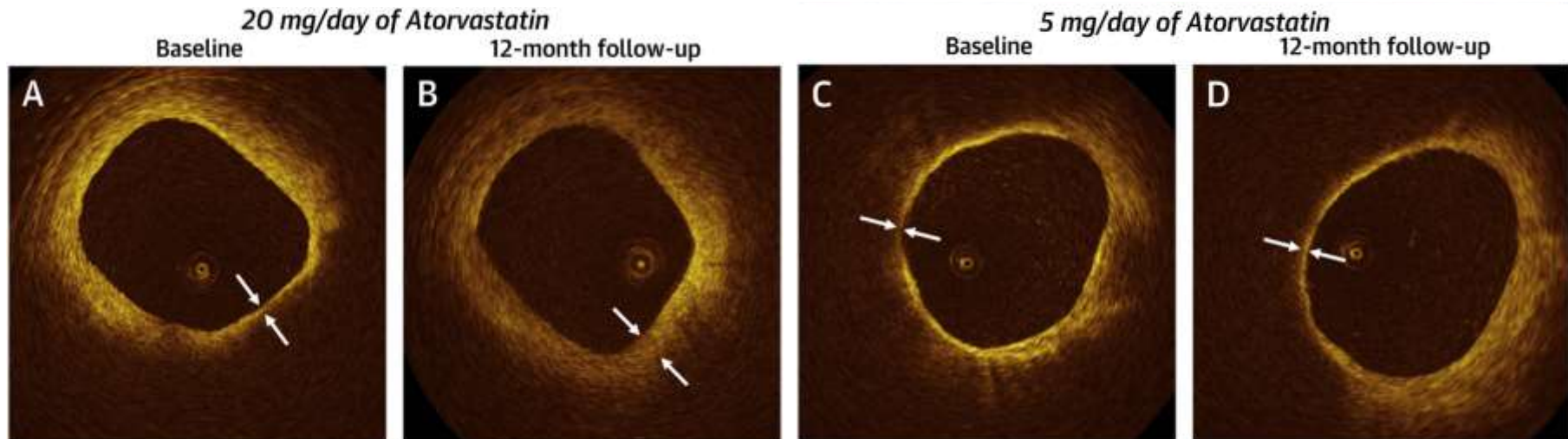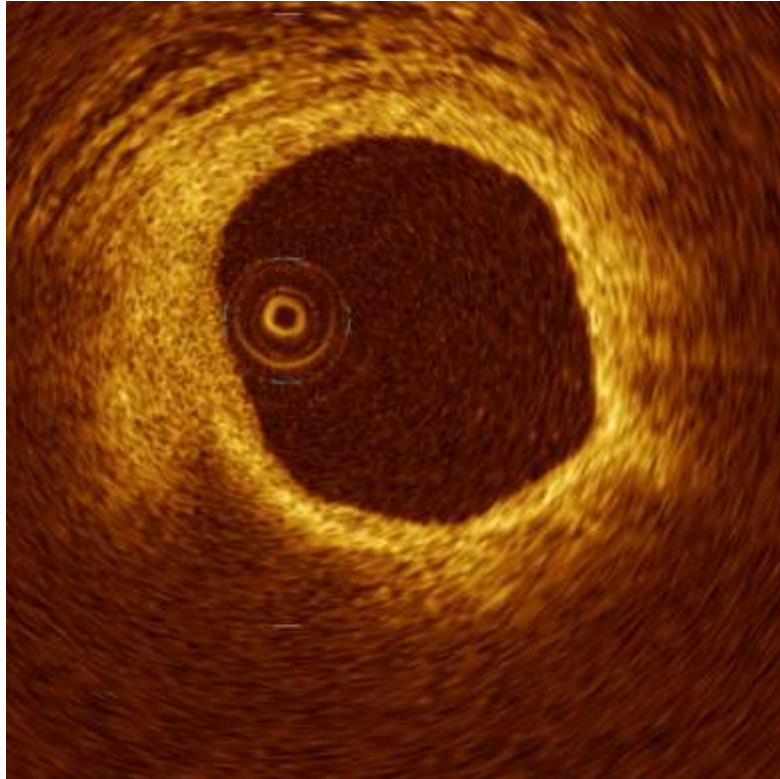**12-month follow-up**
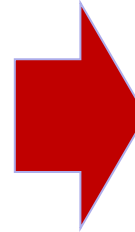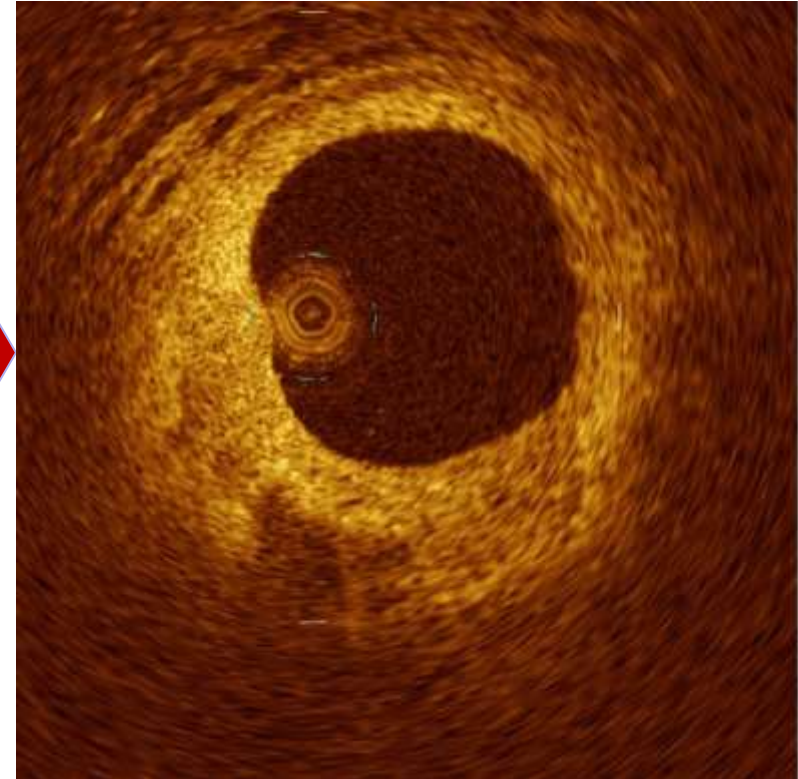
Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Percent change in OCT measurements between baseline and 12-month follow-up
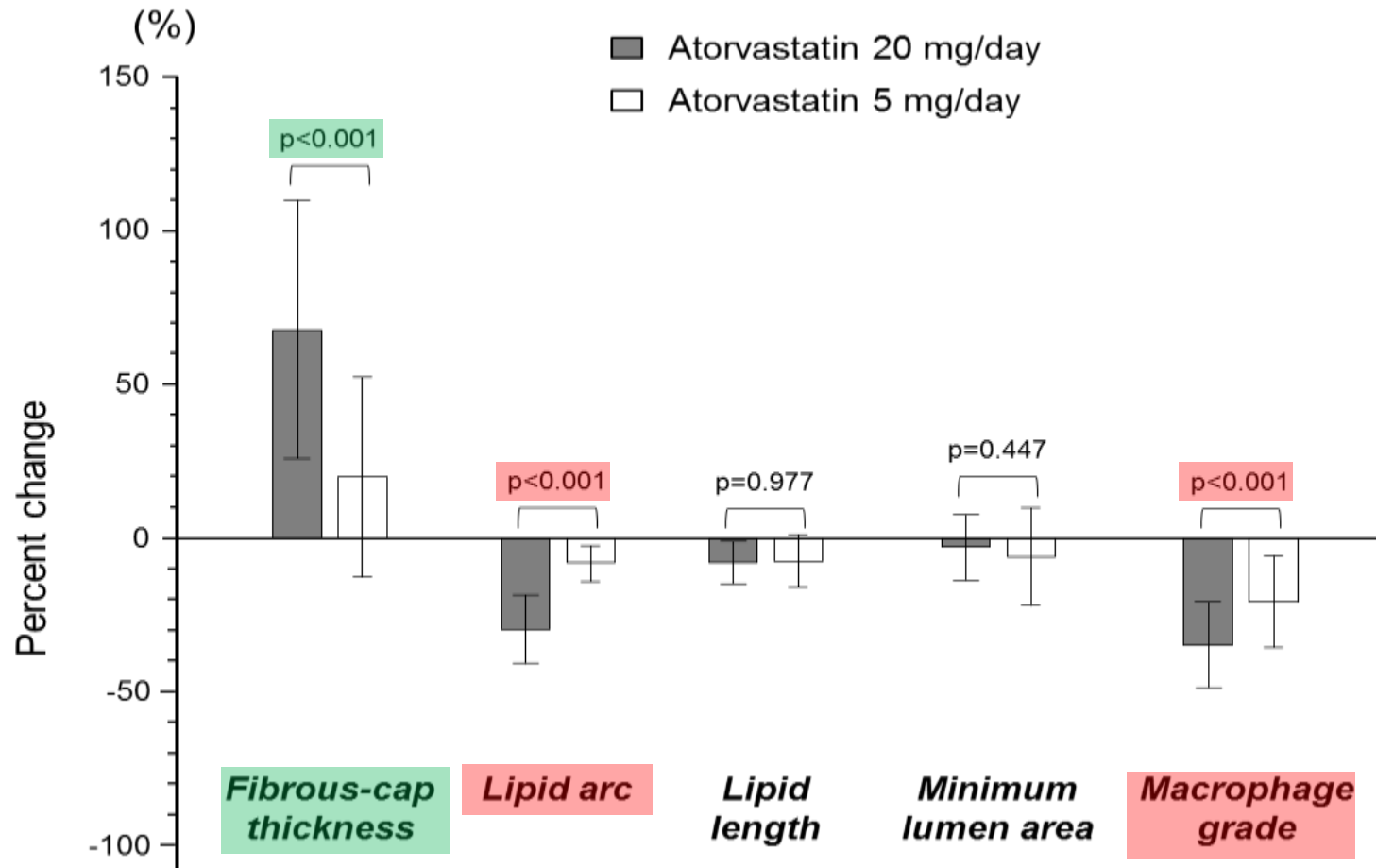
Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

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The MIRACLE Study
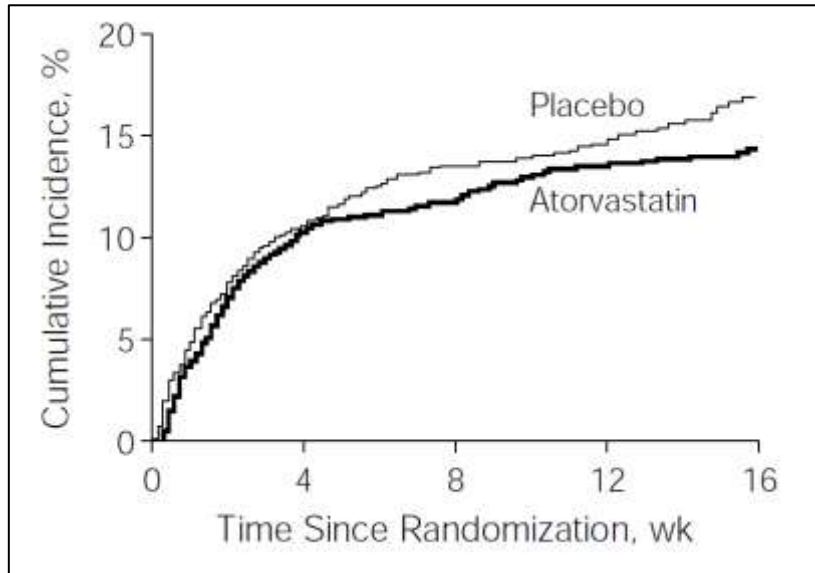
✓ **Patients with acute coronary syndrome (ACS) showed widely spreading vulnerability in pan-coronary artery tree.**

✓ **Recurrent coronary event is strongly associated with increased morbidity and mortality.**

✓ **The MIRACLE Study demonstrated that early statin therapy in ACS patients decrease the event rate within 16 weeks.**

✓ **The incidence rate is especially higher in the first 4 weeks in both groups, however, the incidence rate in placebo group showed greater increase from 1 month compared to atorvastatin group.**

Effect of PitavaStatin on Coronary Fibrous-cap Thickness Assessed by Optical CoheRence Tomography: ESCORT Study

(Effect of Early Statin Therapy on Fibrous-cap Thickness in ACS)

Tsuyoshi Nishiguchi, Takashi Kubo, Yasushi Ino, Takashi Tanimoto, Hiroki Emori, Yosuke Katayama, Akira Taruya, Hiroshi Aoki, Shingo Ota, Makoto Orii, Keishi Okochi, Akio Kuroi, Takeyoshi Kameyama, Takashi Yamano, Tomoyuki Yamaguchi, Yoshiki Matsuo, Atsushi Tanaka, Takeshi Hozumi, and Takashi Akasaka (JACC CV Img submitting)

Aim

The aim of ESCORT study was to assess plaque-stabilizing effects of early statin use compared with late statin use in patients with ACS by using OCT.

Methods

Study design

- ✓ **70 patients with ACS.**
- ✓ **LDL-Cholesterol level >100mg/dl at baseline.**
- ✓ **Patients were 1:1 randomized to early statin group (prescribing 4mg/day of pitavastatin on the day of admission) or late statin group (prescribing 4mg/day of pitavastatin after 3weeks).**
- ✓ **OCT was performed to assess fibrous-cap thickness (FCT) in non-culprit lesions at baseline, 3-week follow-up, and 6-month follow-up.**

ACS patients with successful PCI

Early — Pitavastatin 4mg/day

Late — Pitavastatin 4mg/day

24 hours

Randomization

Baseline
OCT

3 weeks
OCT

6 months
OCT

Patient population

70 patients enrolled

70 underwent OCT examination at baseline

Randomized

Early group:

35 assigned to early group

3 Excluded
 2 Withdrew consent
 1 Had Liver dysfunction

32 underwent OCT examination at 3week

4 Excluded
 1 Withdrew consent
 2 Had cancers
 1 Had canal stenosis

28 underwent OCT examination at 26week

3 Excluded
 3 Unrecognized target plaques

25 analyzed

Late group:

35 assigned to late group

1 Excluded
 1 Withdrew consent

34 underwent OCT examination at 3week

4 Excluded
 2 Withdrew consent
 1 Had cancer
 1 quitted pitavastatin

30 underwent OCT examination at 26week

2 Excluded
 2 Unrecognized target plaques

28 analyzed

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Baseline characteristics

	Early group (n = 25)	Late group (n = 28)	p
Age, year	66.0 [63.0-71.0]	66.0 [61.5-74.0]	0.681
Male	19 (76)	23 (82)	0.582
BMI	23.1 [22.1-26.7]	23.7 [22.1-25.9]	0.887
Diabetes mellitus	10 (40)	9 (32)	0.552
Hypertension	15 (60)	19 (68)	0.552
Current smoking	10 (40)	10 (36)	0.748
Family history of CAD	4 (16)	1 (4)	0.176
Clinical presentation			
AMI	19 (76)	25 (89)	0.279
UAP	6 (24)	3 (11)	

Medications

	Early group (n = 25)			Late group (n = 28)		
	Baseline	**3 weeks**	**6 months**	**Baseline**	**3 weeks**	**6 months**
Aspirin	0 (0)	25 (100)	25 (100)	3 (11)	28 (100)	28 (100)
Tienopilidine	2 (8)	25 (100)	25 (100)	0 (0)	28 (100)	27 (96)
Beta blocker	3 (12)	17 (68)	18 (72)	1 (4)	17 (61)	16 (57)
ACE inhibitor or ARB	7 (28)	23 (92)	22 (88)	7 (25)	25 (89)	22 (79)
Calcium channel blocker	8 (32)	4 (16)	8 (32)	7 (25)	4 (14)	6 (21)
Oral hypoglycemic agents	3 (12)	7 (28)	7 (28)	5 (18)	6 (21)	6 (21)
Insulin	1 (4)	2 (8)	2 (8)	2 (7)	4 (14)	4 (14)

Laboratory data

	Early group (n = 25)			Late group (n = 28)		
	Baseline	3 weeks	6 months	Baseline	3 weeks	6 months
Total cholesterol	184.5 [170.5-198.5]	137.0 [115.0-145.0] *	140.0 [123.0-149.0] *	190 [176.5-213.0]	183.0 [175-205.8]	143.0 [124.3-166.8] *
LDL cholesterol	113.0 [104.5-113.0]	63.0 [58.0-78.0] *	67.0 [63.0-78.0] *	118.0 [108.8-135.0]	119.0 [104.5-137.5]	75.5 [55.8-91.3] *
MDA-LDL	101.0 [78.0-111.0]	78.0 [68.0-101.0]	93.0 [69.0-103.0]	98.0 [78.5-116.5]	109.5 [102.8-142.3] *	84.5 [61.8-112.3]
HDL cholesterol	40.0 [37.8-45.3]	35.5 [33.0-40.3] *	40.5 [37.0-47.8]	42.5 [37.0-48.5]	35.0 [30.0-40.5] *	45.0 [38.3-54.0]
Triglyceride	103.0 [80.0-156.0]	100.5 [76.8-115.8]	122.5 [93.5-186.5]	95.0 [84.0-144.0]	111.0 [91.5-139.3]	91.0 [71.0-116.5]
hs-CRP	0.12 [0.10-0.20]	0.10 [0.07-0.27]	0.06 [0.03-0.16] *	0.10 [0.05-0.23]	0.08 [0.04-0.20]	0.05 [0.02-0.11] *
HbA1c	5.90 [5.60-6.40]	6.00 [5.70-6.40]	5.85 [5.80-6.33]	5.70 [5.60-6.83]	5.80 [5.50-6.75]	5.80 [5.45-6.10]

* indicates $p < 0.05$ vs. baseline.
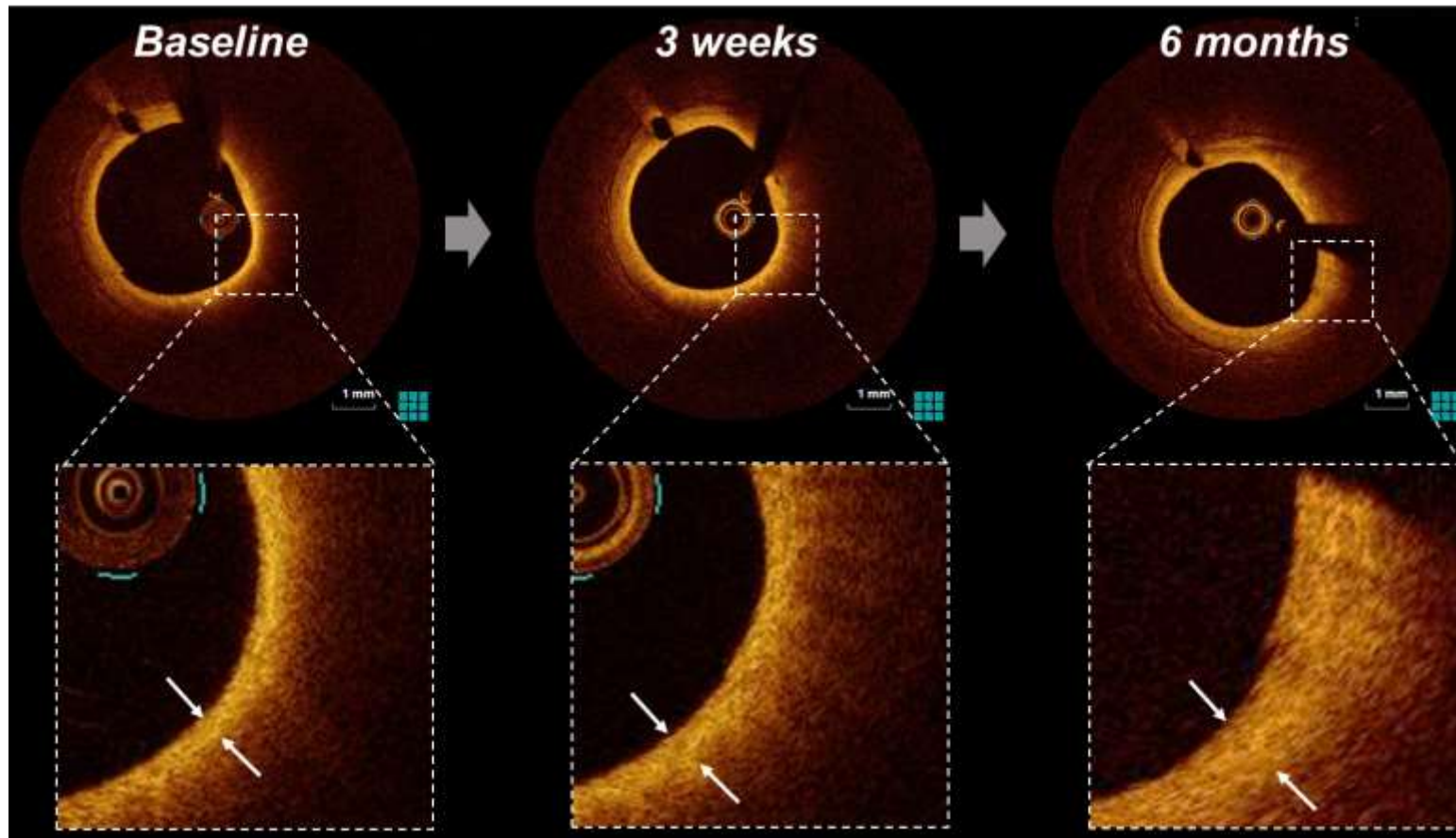
Percent change in Laboratory data

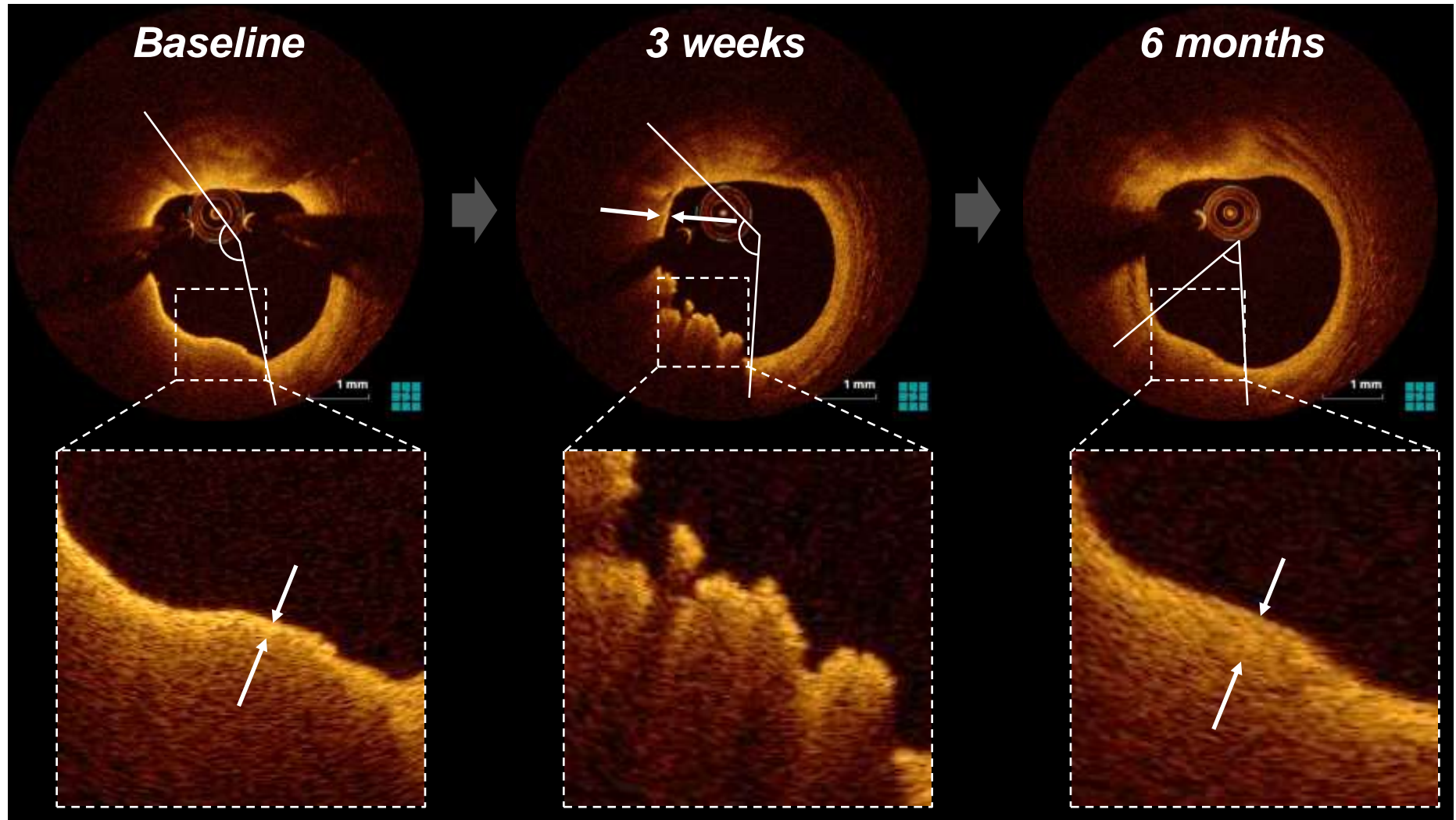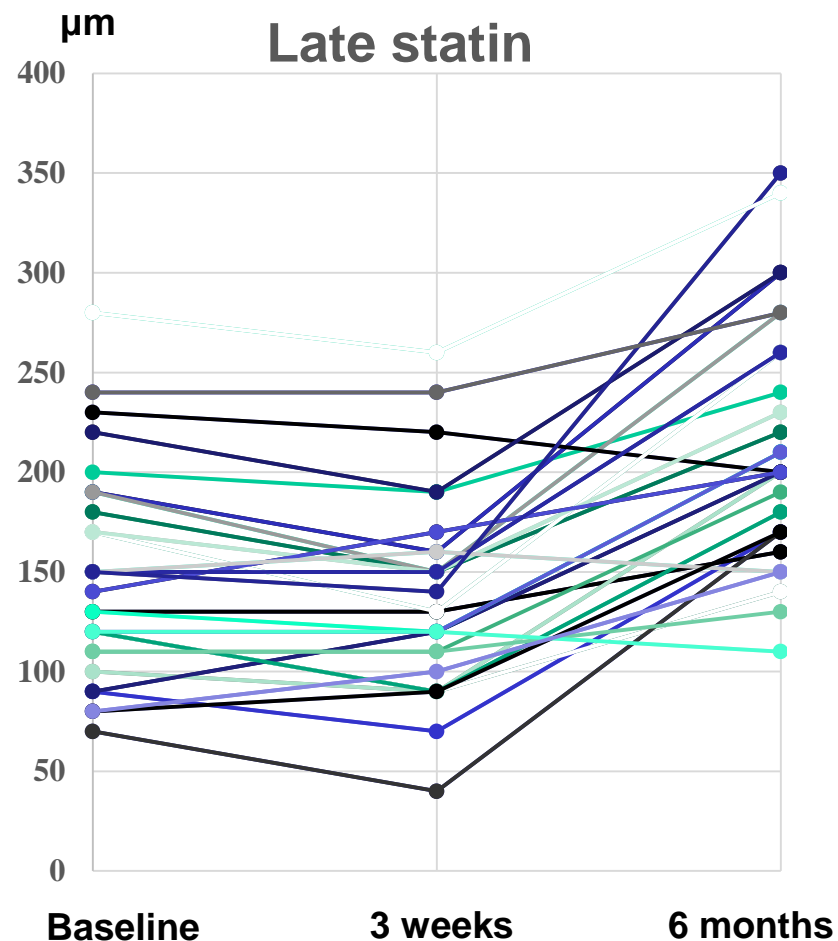|	Early group (n = 25)		Late group (n = 28)	
	Baseline vs. 3 weeks	Baseline vs. 6 months	Baseline vs. 3 weeks	Baseline vs. 6 months
Total cholesterol	70.0 [63.5-79.6]*	79.5 [67.2-82.2]	94.9 [87.8-100.0]	73.9 [67.1-83.4]
LDL cholesterol	57.3 [52.7-63.0]*	60.0 [50.8-65.3]	93.9 [85.0-103.4]	60.6 [48.4-69.9]
MDA-LDL	98.1 [66.0-119.9]*	112.6 [73.2-137.8]	118.1 [97.9-177.9]	90.1 [67.7-113.8]
HDL cholesterol	84.7 [79.4-100.0]	100.0 [90.5-112.9]	79.3 [70.0-93.6]	106.8 [99.3-117.0]
Triglyceride	99.4 [77.5-137.2]	128.2 [67.7-218.9]	122.5 [96.8-176.0]	109.7 [71.4-184.5]
MMP-9	84.2 [65.9-158.0]	95.0 [55.4-111.3]	95.7 [70.6-168.8]	103.1 [66.1-169.7]
hs-CRP	100.0 [46.2-166.7]	40.0 [30.2-125.0]	71.4 [53.3-120.0]	53.7 [20.0-100.0]
HbA1c	100.0 [98.4-100.0]	101.6 [98.3-102.5]	100.0 [98.2-100.4]	98.1 [93.7-101.8]

* indicates $p < 0.05$ vs. late group.

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Early statin

Late statin

Baseline   3 weeks   6 months

Change in fibrous cap thickness

Early statin

Late statin

Baseline   3 weeks   6 months

Baseline   3 weeks   6 months

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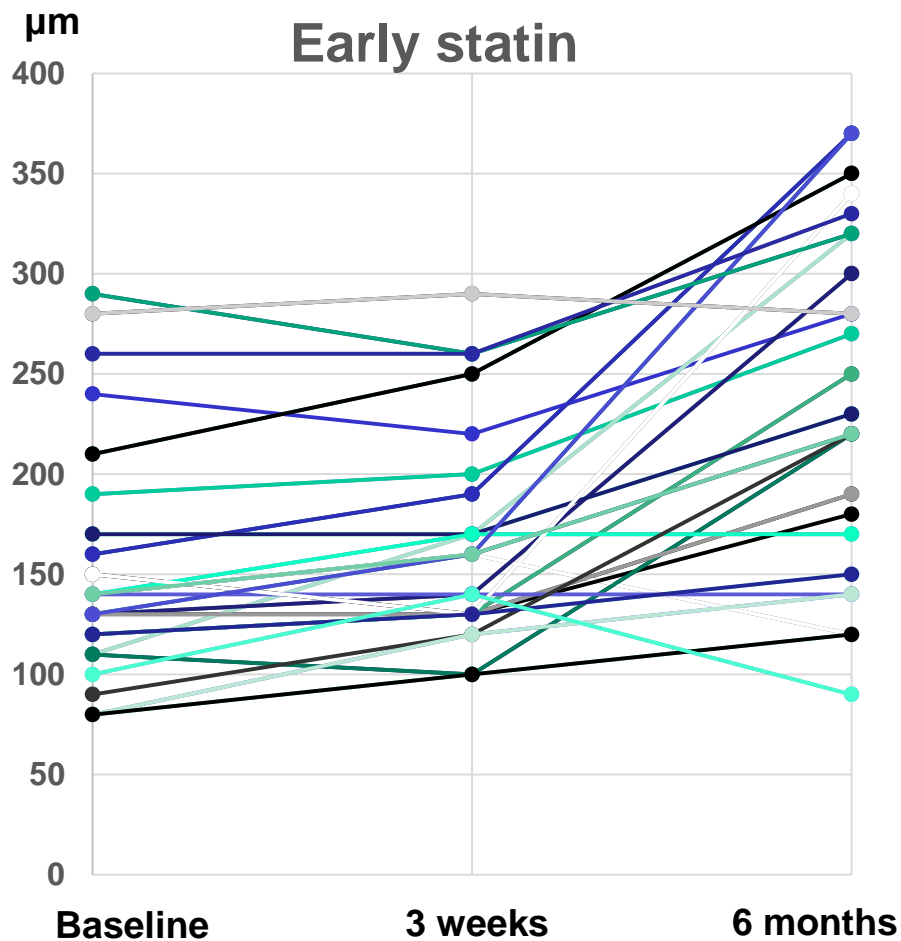
Changes in fibrous cap thickness
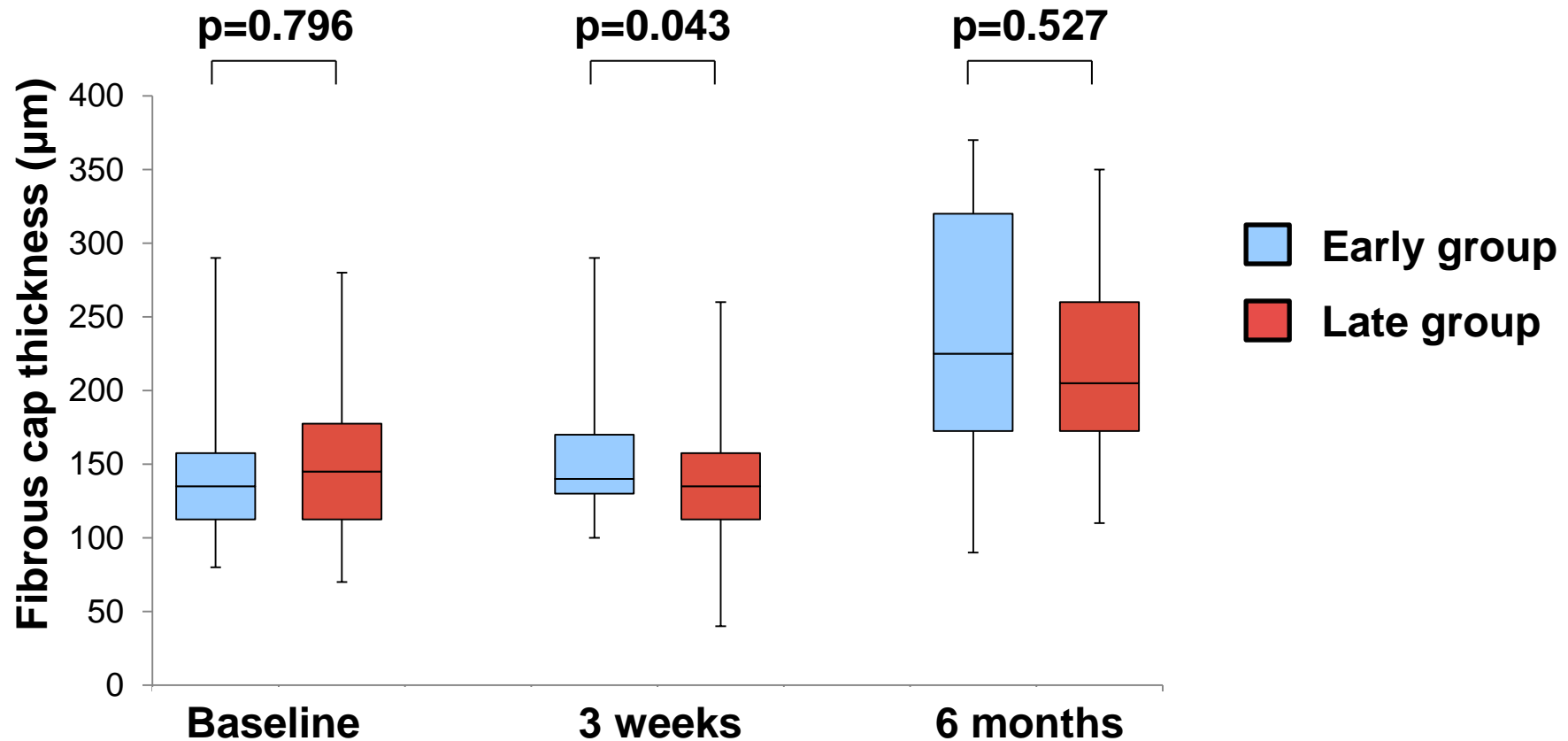
Percent change in OCT measurement

	Early group (n = 25)		Late group (n = 28)	
	Baseline vs. 3 weeks	Baseline vs. 6 months	Baseline vs. 3 weeks	Baseline vs. 6 months
Minimum fibrous cap thickness, μm	108.3 [100.0-121.4]*	135.3 [116.7-188.2]	94.2 [84.0-100.0]	162.3 [125.5-187.8]
Maximum lipid arc, degree	100.0 [96.7-103.9]	89.5 [80.3-98.3]	98.9 [92.6-101.6]	92.8 [81.6-98.9]
Lipid length, mm	97.6 [94.7-101.8]	92.4 [81.1-100.8]	100.0 [96.2-102.8]	94.2 [73.3-101.9]
Minimum lumen area, mm^2	97.7 [94.1-108.4]	97.1 [85.6-100.0]	100.4 [96.8-110.7]	95.3 [86.8-106.9]

* indicates $p < 0.05$ vs. late group.

Percent change in FCT & LDL and MDA-LAD 3 weeks after admission in ACS

Left plot: x-axis "LDL-C 3 weeks after admission" (0–180), y-axis "% change in FCT during 3 weeks" (0–180). r=-0.351, p=0.009. Legend: Early group (green), Late group (blue).

Right plot: x-axis "MDA-LDL 3 weeks after admission" (0–350), y-axis "% change in FCT during 3 weeks" (0–180). r=-0.281, p=0.041. Legend: Early group (green), Late group (blue).
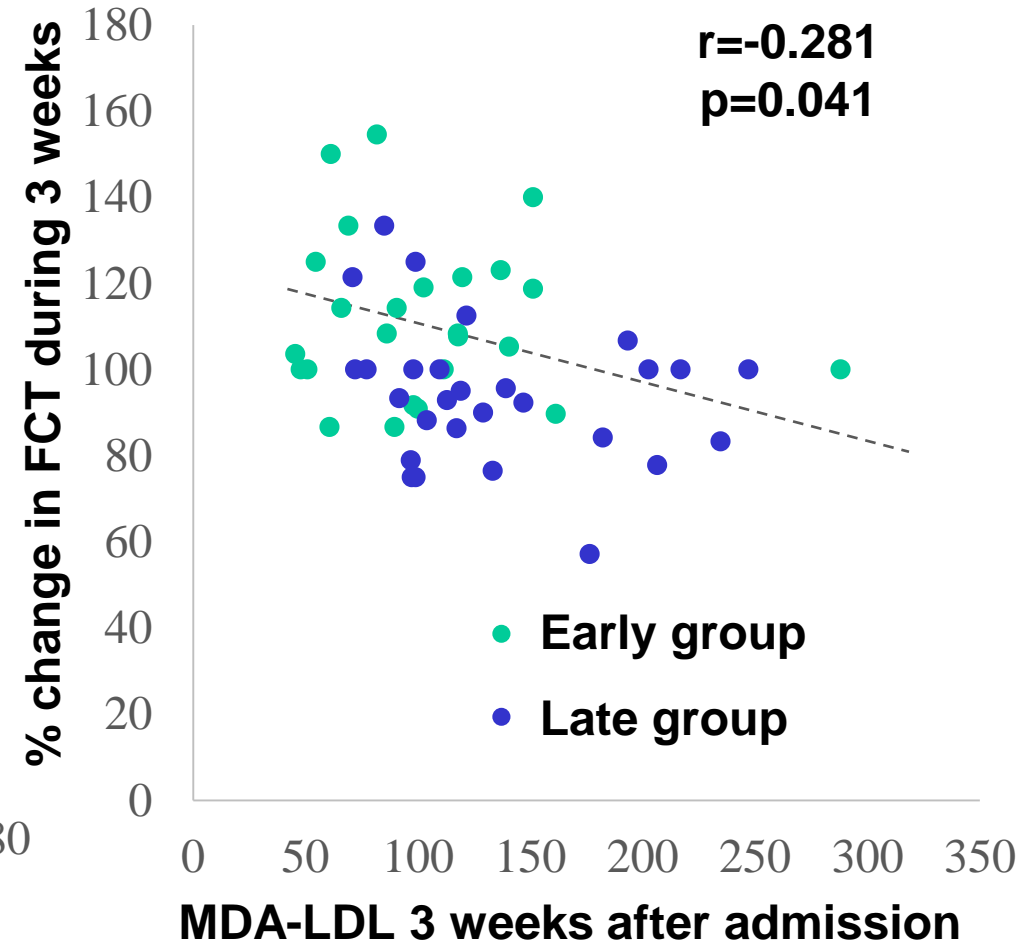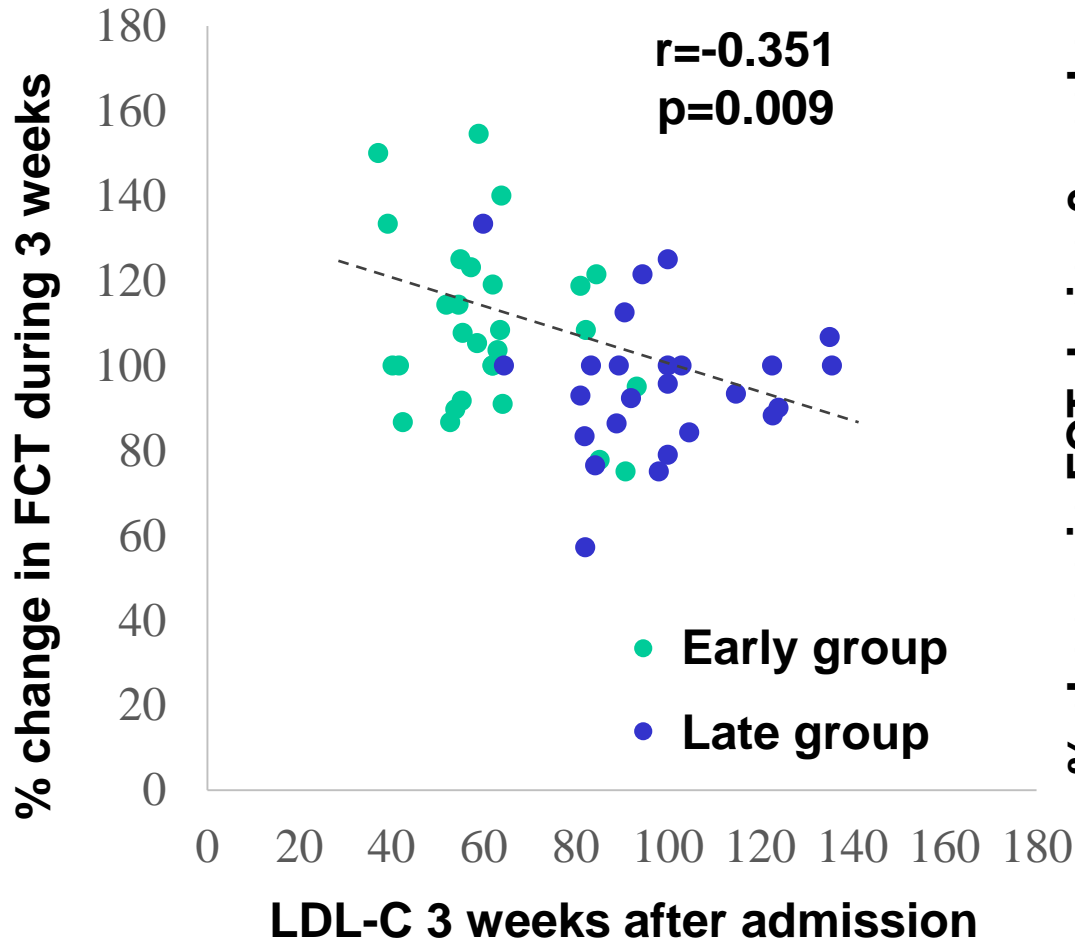
Summary

- ➢ **Increase of FCT in coronary plaque was demonstrated at 3 weeks with earlier statin therapy.**

- ➢ **Decrease of FCT was observed in non-culprit lesion in the first 3 weeks without statin therapy, suggesting that pan-coronary destabilization was ongoing in patients with ACS.**

- ➢ **Percent change in LDL-C was negatively correlated with percent change in FCT at 3 weeks.**

- ➢ **Similar increase in FCT was identified at 6-month follow-up in early and late statin group.**

Take home message

➤ Decrease of FCT observed in non-culprit lesion in ACS without statin therapy during first 3 weeks after admission may demonstrate that progression of plaque vulnerability may continue in ACS.

➤ Plaque stabilization by statin administration may allow us to increase of FCT even in non-culprit coronary plaque in ACS, and statin should be administered as earliest as possible in ACS for stabilizing plaque vulnerability.

➤ Plaque stabilization could be expected much more effectively and rapidly by further aggressive LDL-lowering using PCSK-9 inhibitor in addition to statin, and further prospective study should be planned to demonstrate stabilization of plaque vulnerability.