Statin Benefit in Atherosclerosis : Focus on Asian Population

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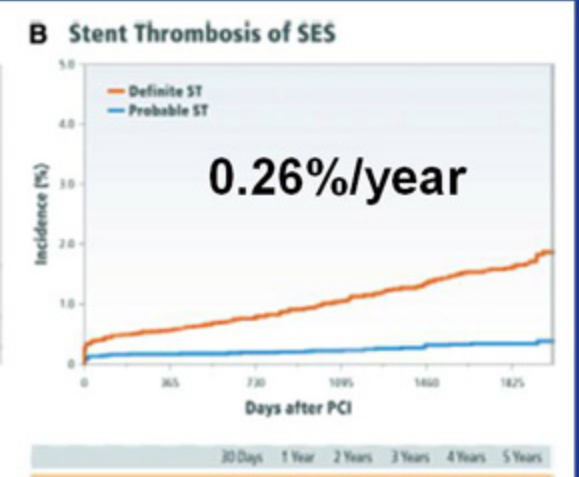
Interventional Cardiology

Very Late Stent Thrombosis and Late Target Lesion Revascularization After Sirolimus-Eluting Stent Implantation

Five-Year Outcome of the j-Cypher Registry

Takeshi Kimura, MD; Takeshi Morimoto, MD; Yoshihisa Nakagawa, MD; Kazuya Kawai, MD; Shunichi Miyazaki, MD; Toshiya Muramatsu, MD; Nobuo Shiode, MD; Masanobu Namura, MD; Takahito Sone, MD; Shigeru Oshima, MD; Hideo Nishikawa, MD; Yoshikazu Hiasa, MD; Yasuhiko Hayashi, MD; Masakiyo Nobuyoshi, MD; Kazuaki Mitudo, MD; on Behalf of the j-Cypher Registry Investigators

Circulation 2012. 125:584-591:



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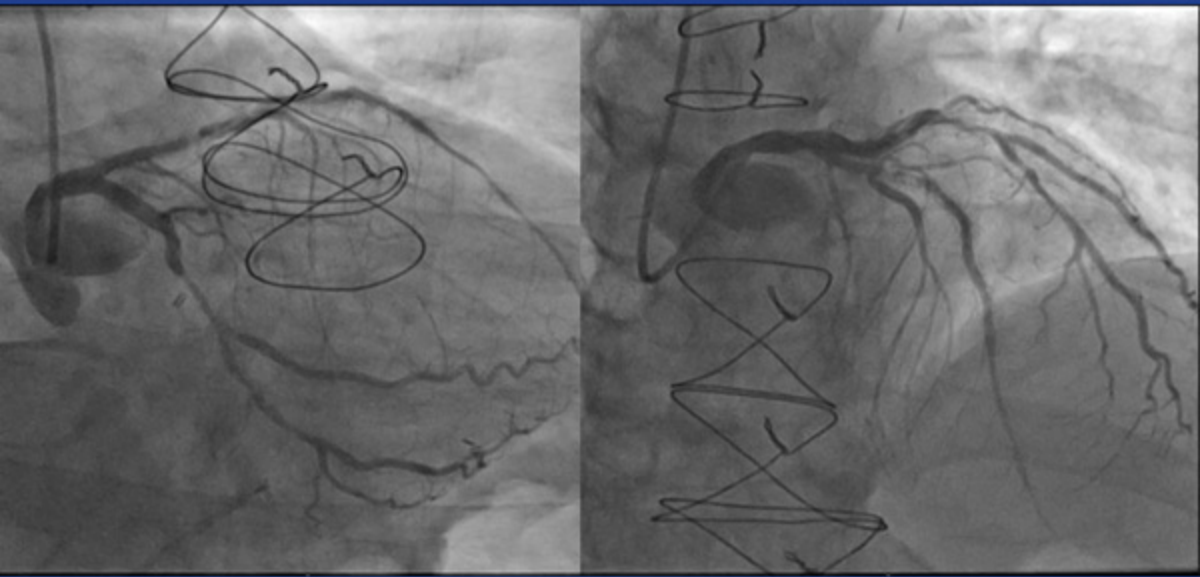
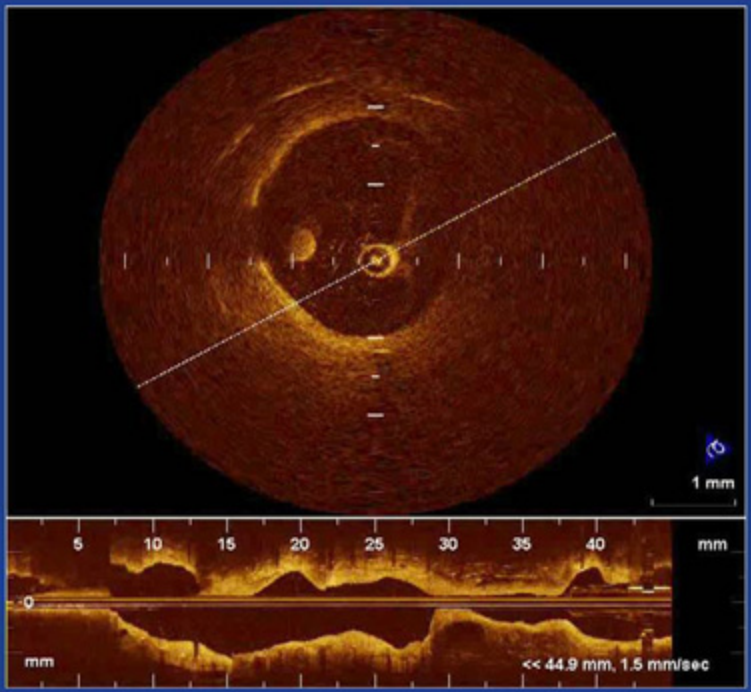
Circulation 2012, 125:584-591

Late TLR

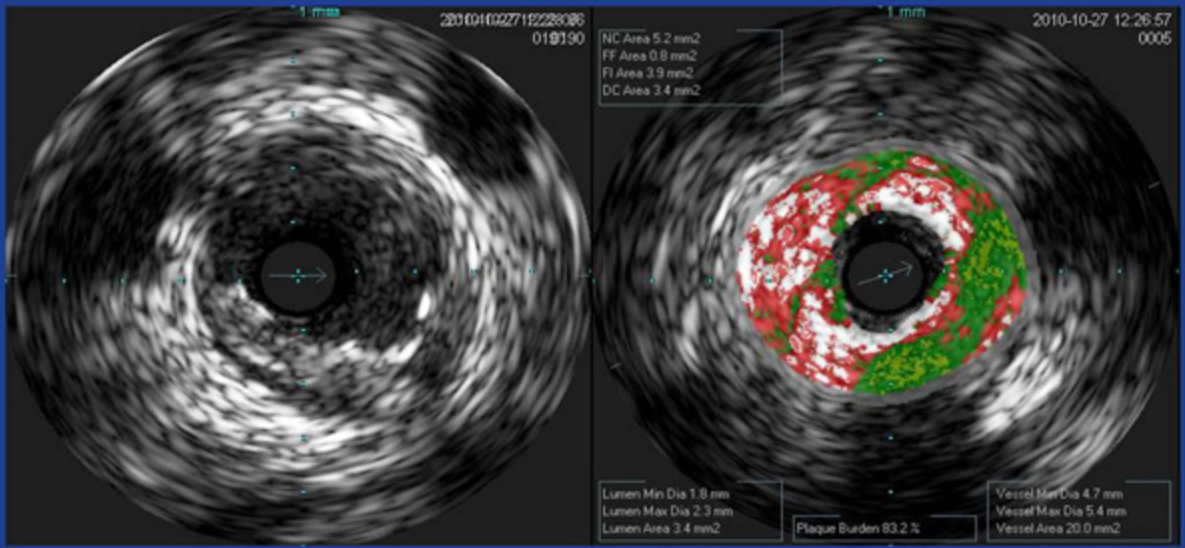
2010.10 (CYPHER 5Y)
LAD Late Catch-up



Pre-OCT



IVUS(VH)


1 mm
2010-10-27 12:26:57
0005
NC Area 5.2 mm2
FF Area 0.8 mm2
FI Area 3.9 mm2
DC Area 3.4 mm2
Lumen Min Dia 1.8 mm
Lumen Max Dia 2.3 mm
Lumen Area 3.4 mm2
Plaque Burden 83.2 %
Vessel Min Dia 4.7 mm
Vessel Max Dia 5.4 mm
Vessel Area 20.0 mm2

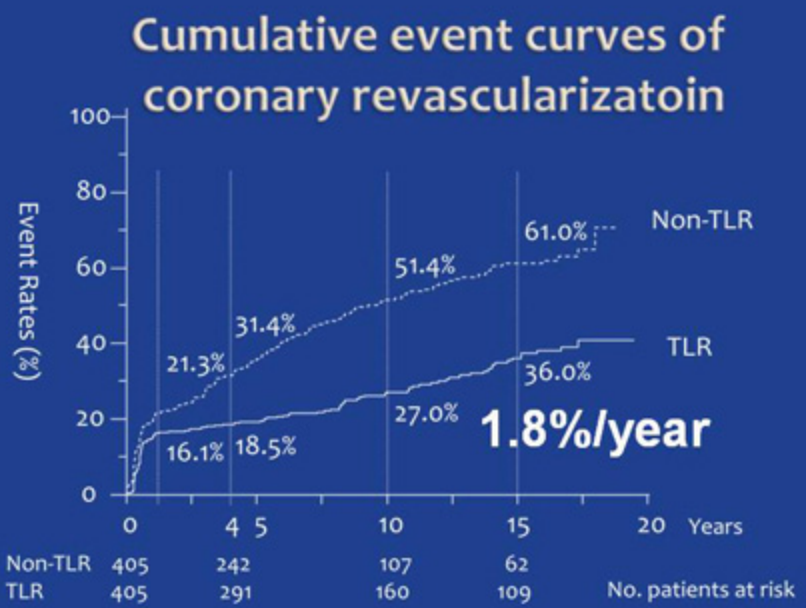
Very long-term (15 to 20 years) clinical and angiographic outcome after BMS implantation

Patients characteristics

Number of patients	405
Age (years) (range)	64±9 (34-89)
Male gender	320 (79%)
Extent of coronary artery disease	
Single vessel disease	179 (44%)
Multi-vessel disease	200 (49%)
Prior coronary artery bypass grafting	26 (6%)
Prior myocardial infarction	221 (55%)
Left ventricular dysfunction	47 (12%)
Class 3 or 4 angina	192 (47%)
Hypertension	180 (44%)
Hyperchlesterolemia	130 (32%)
Diabetes mellitus	117 (29%)
Chronic renal failure	51 (13%)
Smokers	105 (26%)
Use of statins	69 (17%)
Use of angiotensin-converting enzyme inhibitors	34 (8%)

Circulation CI. 2010;3(5):468-75

Very long-term (15 to 20 years) clinical and angiographic outcome after BMS implantation

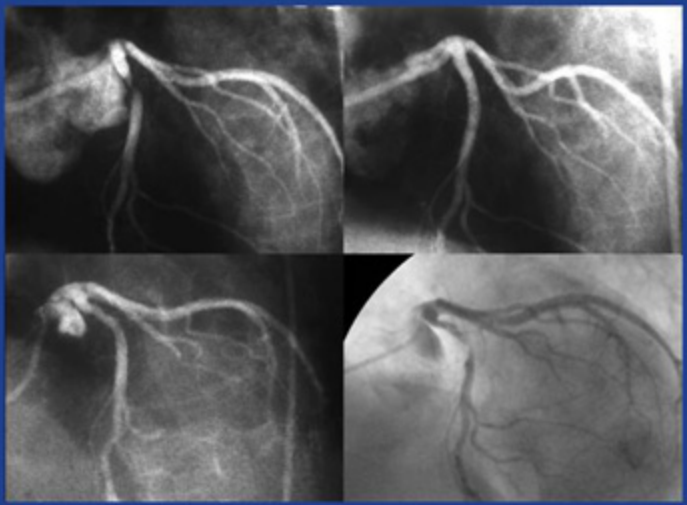


Circulation CI. 2010;3(5):468-75

Representative case of late progression

Pre

Post



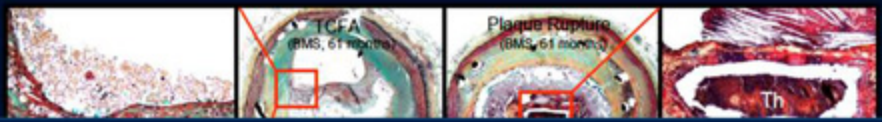
5 years

15 years

Circulation CI. 2010;3(5):468-75

Neoatherosclerosis within the Neointima

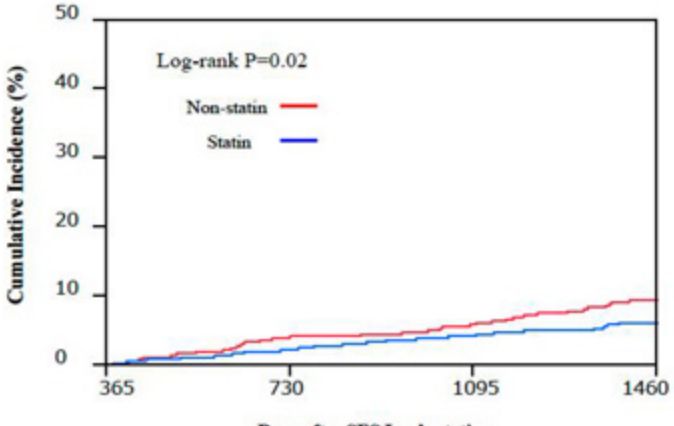
BMS



There was no significant difference on histology of instent neoatherosclerosis between DES and BMS.

Late TLR

SES Stratum



Adjusted HR 0.73
95%CI (0.54-0.98)
P=0.04

Interval	1 year	2 years	3 years	4 years
Non-statin				
N of events		74	95	115
N of patients at risk	1966	1576	818	182
Incidence		4.0%	5.9%	9.6%
Statin				
N of events		52	82	94
N of patients at risk	2439	1924	999	225
Incidence		2.3%	4.2%	6.1%

- Regression or attenuation of the progression of plaque volume might be associated with beneficial outcome in terms of cardiovascular events.
- Several previous studies have suggested that cardio-vascular morbidity and mortality in patients with hyper-cholesterolemia with or without coronary arterydisease (CAD) can be significantly reduced by lipid-lowering therapy with statin.

- Among the statin class of medications, Rosuvastatin is considered to have robust effects, including highly effective LDL-C lowering, significantly raising HDL-C, lowering hs-CRP, and stabilizing risk factors and biomarkers of atherosclerosis.
- Recently, some trials have shown that intensive lipid-lowering therapy with Rosuvastatin slows the progression or induces regression of atherosclerosis in Japanese patients.

COSMOS

***CO**ronary atherosclerosis **S**tudy **M**easuring effects **O**f rosuvastatin using intravascular ultrasound in Japanese **S**ubjects*

Tadateru Takayama et al. Japanese Circulation Journal 2009;doi:10.1253/circj.CJ-09-0358

Objective

- COSMOS was a multicenter study to investigate the effect of rosuvastatin on plaque regression by IVUS imaging in hypercholesterolemic Japanese patients with chronic CHD for whom percutaneous coronary intervention (PCI) was clinically indicated.

Takayama T *et al. Circ. J* 2007;71 (2) :271-275

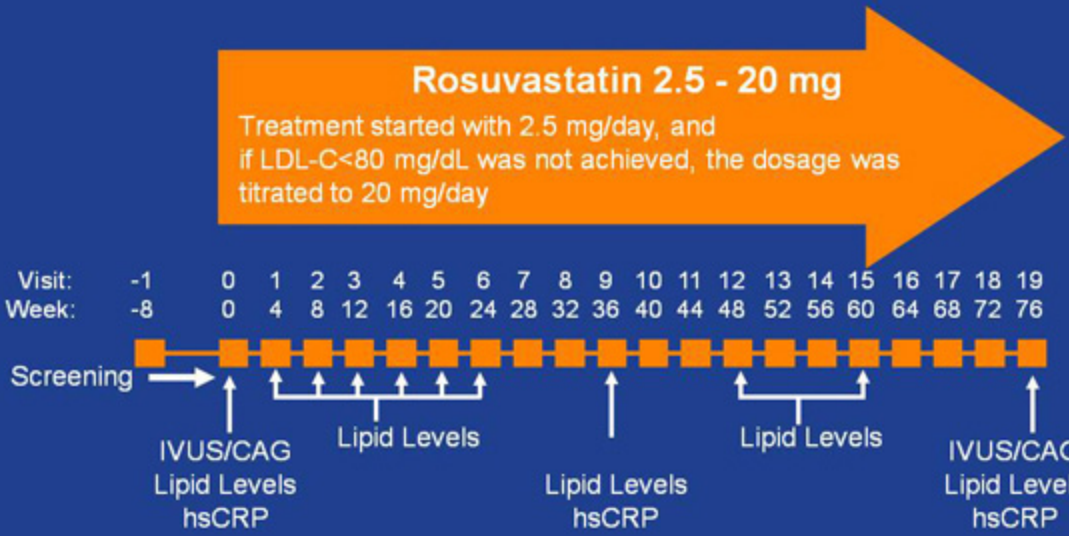
Study Design (1)

Inclusion Criteria

1) 20-75 years old
2) Patients with CHD who required PCI
3) Hypercholesterolemia
   A) Untreated patients:
      LDL-C≥140mg/dL or TC≥220mg/dL
   B) Prior use patients:
      LDL-C≥100mg/dL or TC≥180mg/dL
4) PCI lesion: ≥75%, target lesion: ≤50% stenosis

Takayama T *et al. Circ. J* 2007;71 (2) :271-275

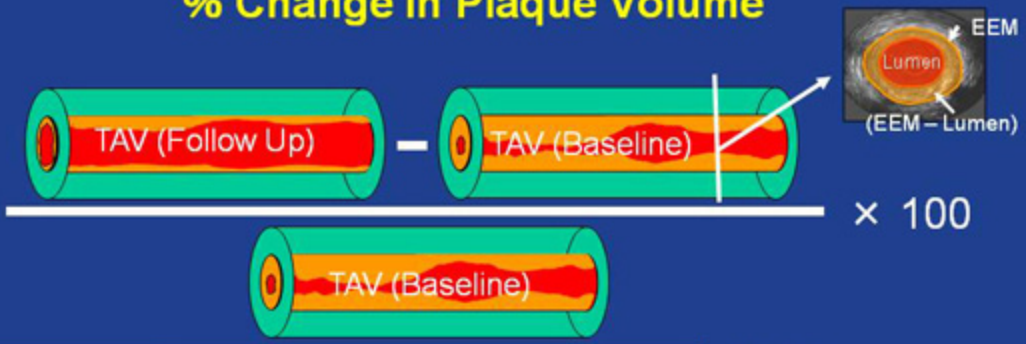
Study Design (2)



Takayama T *et al. Circ. J* 2007;71 (2) :271-275

Primary Endpoint

% Change in Plaque Volume



$$TAV\ *(mm^3) = \sum_{i=0}^{n} (EEM_i - Lumen_i)_{CSA} \times 0.09\ mm$$

× 0.09 mm

*TAV: Total Atheroma Volume

- IVUS : Clearview™, Galaxy™ or Galaxy2™ (Boston Scientific, USA)
- Auto pullback : 0.5 mm/sec
- Target lesions were selected >5 mm away from PCI site
- Calculation : echoPlaque™ (Indec, USA)
- Evaluated lesion length : ≥6 mm

Baseline Patient Characteristics

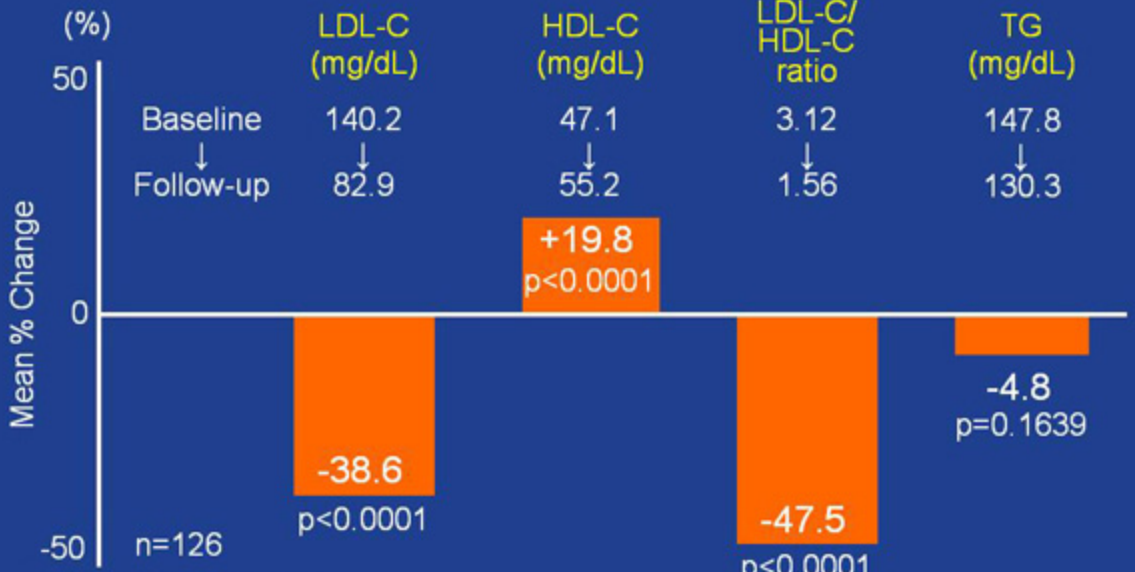
	Mean (±S.D.)
Age (years old)	62.6(±7.7)
Male (%)	76.2
BMI (kg/m^2)	25.0(±3.3)
Hypertension (%)	76.2
Smoking (%)	28.6
Diabetes (%)	37.3
Family History of CHD (%)	20.6
Low HDL-C (%)	25.4
Unstable angina (%)	7.9
Prior use of lipid-lowering drugs (%)	73.0
Dosage at follow-up IVUS (mg/day)	16.9(±5.3)

		Mean
Analyzed coronary artery Vessel (%)		
	RCA	40.5
	LAD	30.2
	LCX	28.6
	LMT	0.7
Segment (%)		
	Proximal	26.2
	Distal	31.7
	Others	42.1

n=126

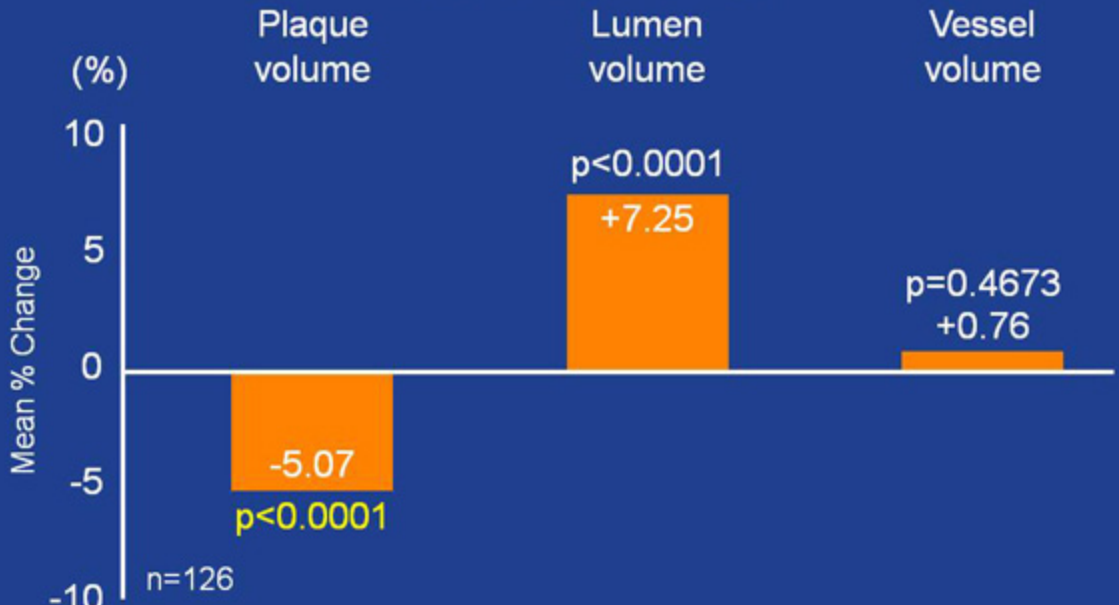
Tadateru Takayama et al. Japanese Circulation Journal 2009;doi:10.1253/circj.CJ-09-0358

<Results>
% Change in Lipid Parameters



Tadateru Takayama et al. Japanese Circulation Journal 2009;doi:10.1253/circj.CJ-09-0358

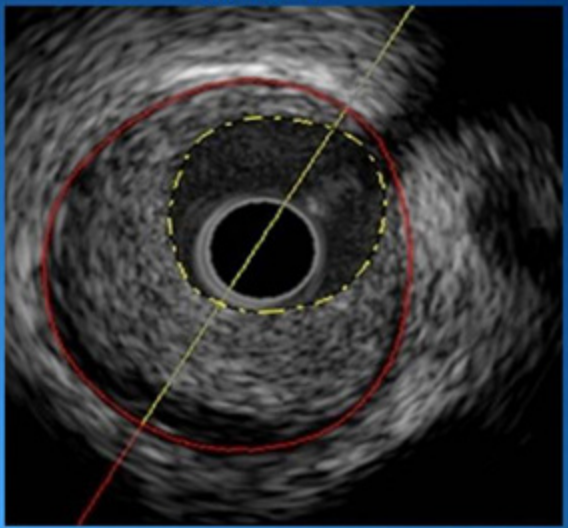
% Change in Coronary Artery Volume Parameters



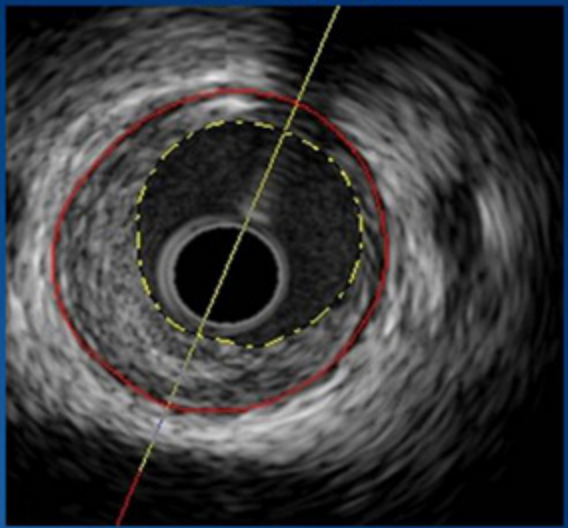
p value : follow-up vs. baseline

COSMOS：症例紹介

開始時



終了時（76週）



症例：53歳　女性
右冠動脈

〔Takayama T et al. Circ J, 73, 2110-2117, 2009〕

Factor Affecting Plaque Regression

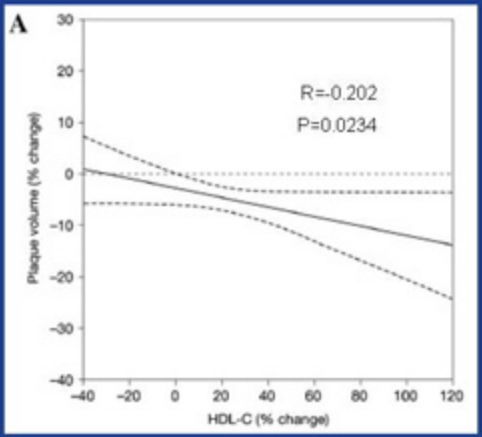
Univariate analyses

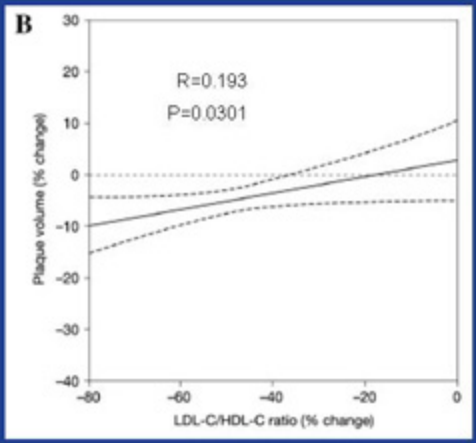
Factors	Estimate	95% CI	p value
BMI	0.766	0.017, 1.514	0.0450
ACE inhibitor usage	-6.655	-12.604, -0.706	0.0286
Sulfonylurea usage	6.672	0.100, 13.244	0.0467
HbA1c	2.941	0.452, 5.429	0.0209
Evaluated plaque length	-0.997	-1.698, -0.296	0.0057
Plaque volume	-0.112	-0.174, -0.049	0.0006
Vessel volume	-0.047	-0.080, -0.013	0.0067
Plaque area	-0.918	-1.598, -0.238	0.0086
Diabetes	3.630	-1.476, 8.736	0.1618

Multivariate analyses

Factors	Estimate	95% CI	p value
HbA1c	2.683	0.292, 5.074	0.0282
Plaque volume	-0.107	-0.169, -0.046	0.0008

Relationship Between change in HDL-C and LDL-C /HDL-C ratio and change of plaque volume





Relationship between change in HDL-C level or LDL-C/HDL-C ratio and change in plaque volume (Solid line).
Upper and lower limits for 95% confidence interval of mean values (Dotted lines)

Tadateru Takayama et al. Japanese Circulation Journal 2009;doi:10.1253/circj.CJ-09-0358

Summary

- Plaque volume was significantly regressed by 5.1% with rosuvastatin treatment that accompanied LDL-C reduction, HDL-C elevation and LDL-C/HDL-C ratio improvement in Japanese patients with stable CAD
- Rosuvastatin treatment for 76 weeks significantly reduced LDL-C by 39% to 82.9 mg/dL, increased HDL-C by 20% to 55.2 mg/dL and lowered LDL-C/HDL-C ratio by 48% to 1.56.
- Treatment with rosuvastatin 2.5 to 20 mg for 76 weeks was generally well tolerated.

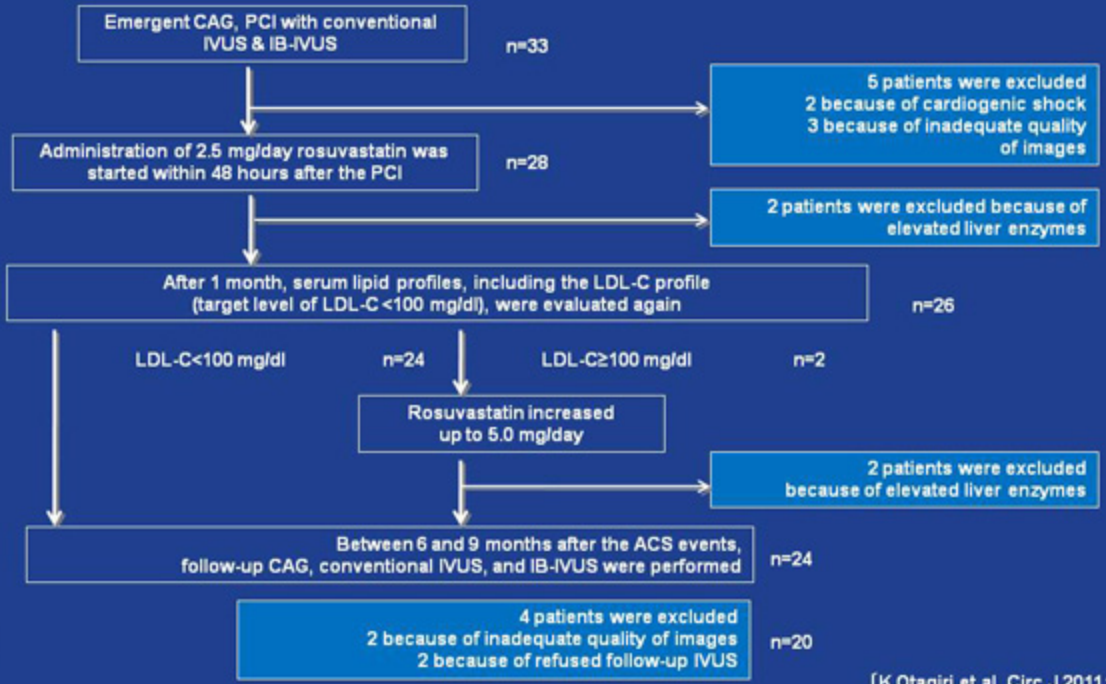
Tadateru Takayama et al. Japanese Circulation Journal 2009;doi:10.1253/circj.CJ-09-0358

Early Intervention With Rosuvastatin Decreases the Lipid Components of the Plaque in Acute Coronary Syndrome

– Analysis Using Integrated Backscatter IVUS (ELAN Study) –

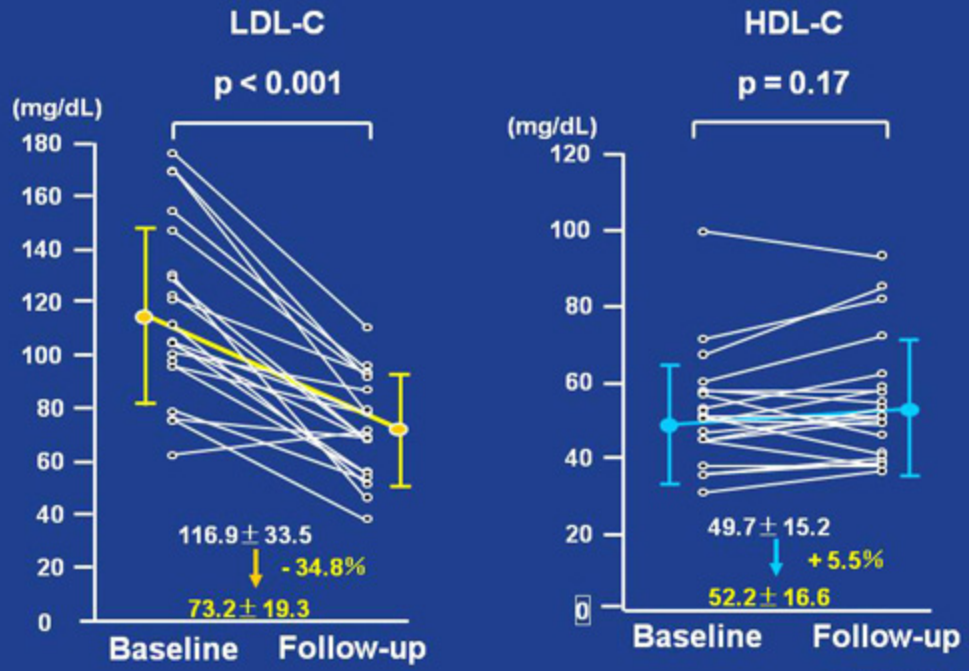
Kyuhachi Otagiri, MD; Hiroshi Tsutsui, MD, PhD;
Setsuo Kumazaki, MD; Yusuke Miyashita, MD;
Kazunori Aizawa, MD, PhD; Megumi Koshikawa, MD, PhD;
Hiroki Kasai, MD, PhD; Atsushi Izawa, MD, PhD;
Takeshi Tomita, MD, PhD; Jun Koyama, MD, PhD;
Uichi Ikeda, MD, PhD

Overview of the study protocol



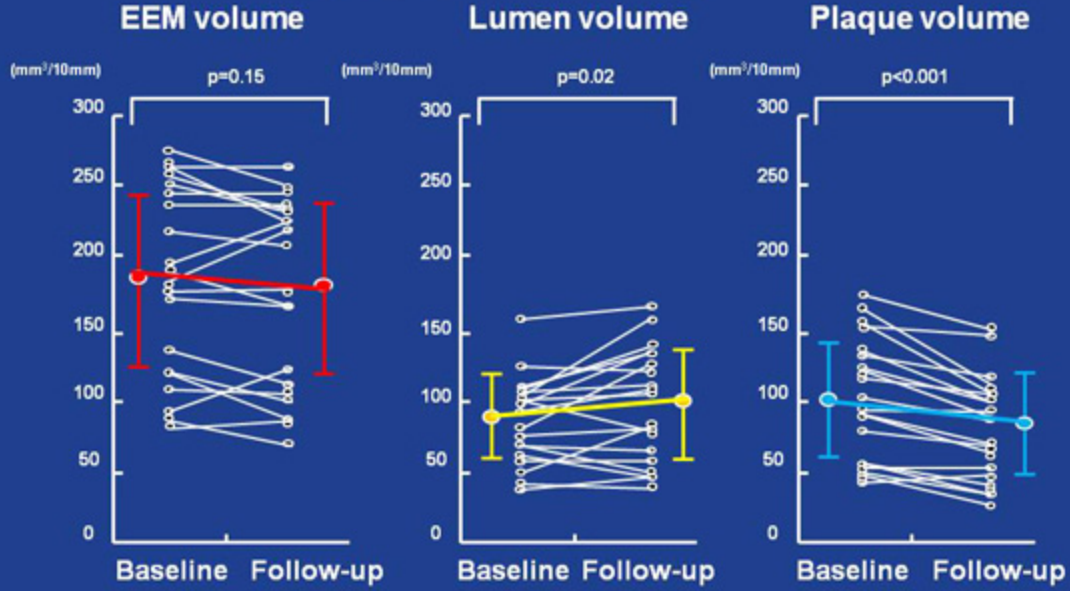
[K Otagiri et al. Circ J 2011;]

Change in LDL-C and HDL-C levels in each case



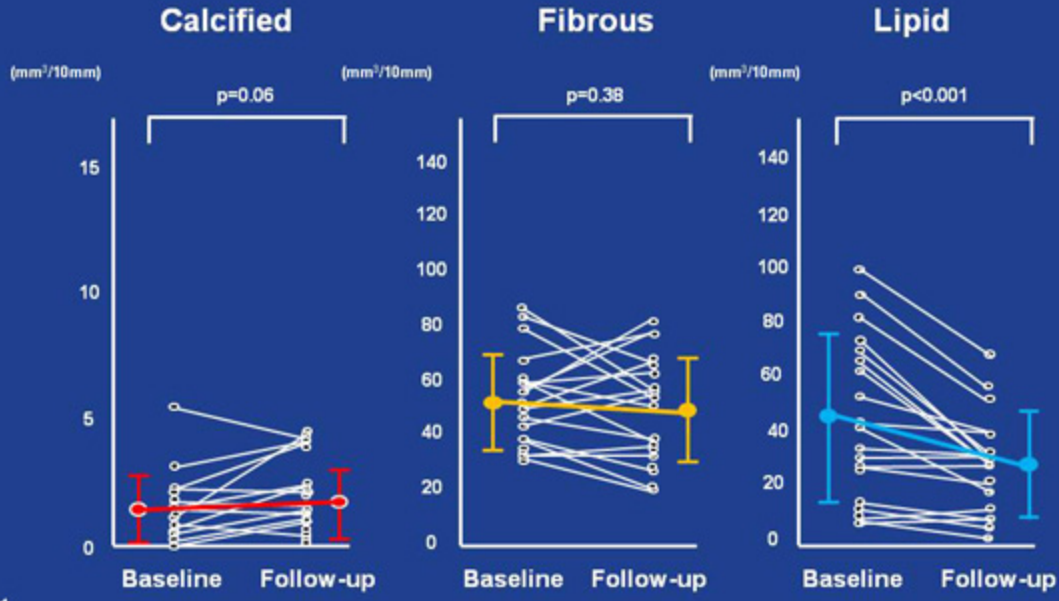
[K Otagiri et al. Circ J 2011;]

Changes in external elastic membrane (EEM), lumen, and plaque volume derived from conventional intravascular ultrasound in each case



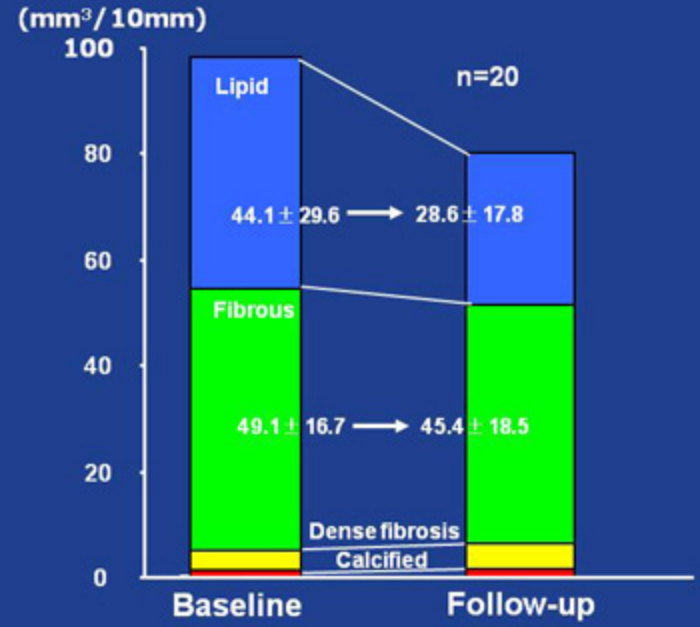
〔K Otagiri et al. Circ J 2011; 〕

Volumetric changes in the calcified, fibrous, and lipid components of plaque in each case



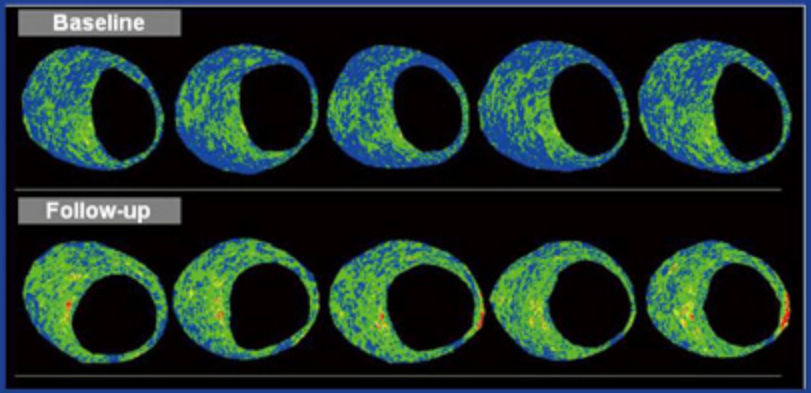
〔K Otagiri et al. Circ J 2011; 〕

Volumetric changes in plaque components with stacked column at baseline and follow-up



〔K Otagiri et al. Circ J 2011; 〕

Serial integrated backscatter intravascular ultrasound images at 0.5 mm intervals from baseline (Upper) and follow-up (Lower)



		Baseline		Follow-up
LDL-C (mg/dl)		105	→	56
Plaque Volume (mm^3/10mm)		128.5	→	112.5
% Volume				
■	Calcified	0.1%	→	0.5%
■ ■	Fibrous	45.1%	→	69.5%
■	Lipid	54.8%	→	30.0%

[K Otagiri et al. Circ J 2011;]

Summary

- Plaque regression can be achieved by adopting a strategy of aggressive LDL reduction with high dose statin therapy and HDL elevation.
- Plaque regression was mainly due to the decrease in the lipid component of the plaque.

Justification for Atherosclerosis Regression Treatment (JART Study)

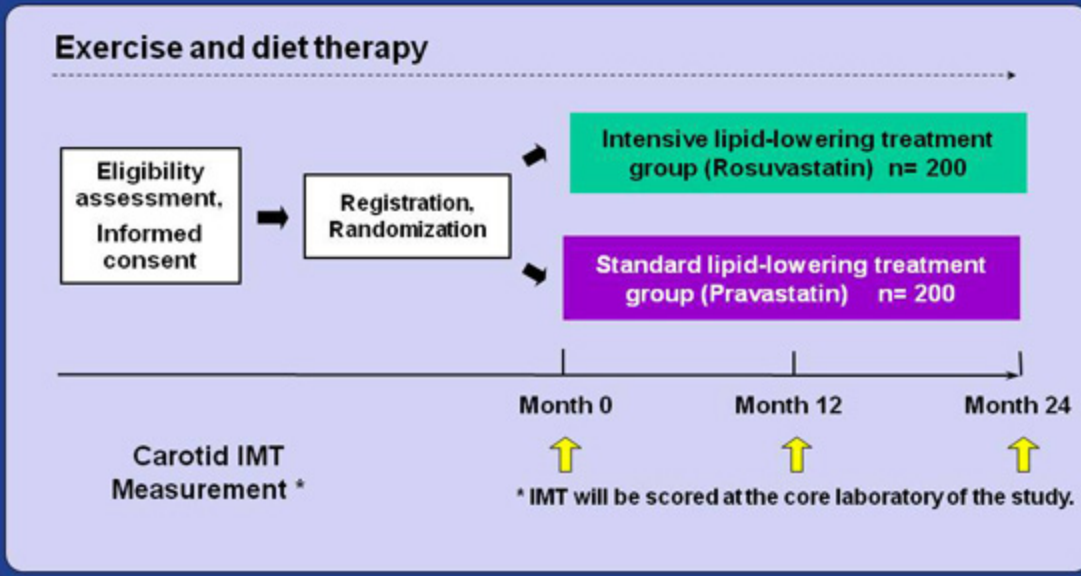
Methods

- A multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) trial was conducted between June 2008 and April 2011 in Japan.
- Eligible patients were those with elevated LDL-C (serum level≥140 mg/dL) aged 20 years or older who had a maximum IMT≥1.1 mm measured at the carotid artery.
- Exclusion criteria included:
  - required lipid-lowering agents other than trial treatments and prespecified ones (i.e., anion-exchange resin, probucol, or ethyl icosapentate)
  - statin therapy within 1 month before starting the trial
  - carotid artery stenosis (≥80%) or calcification
  - familial hypercholesterolemia or secondary hypercholesterolemia
  - fasting serum TG level≥400 mg/dL
  - hypersensitivity to statins
  - uncontrolled hypertension
  - type 1 diabetes or uncontrolled type 2 diabetes

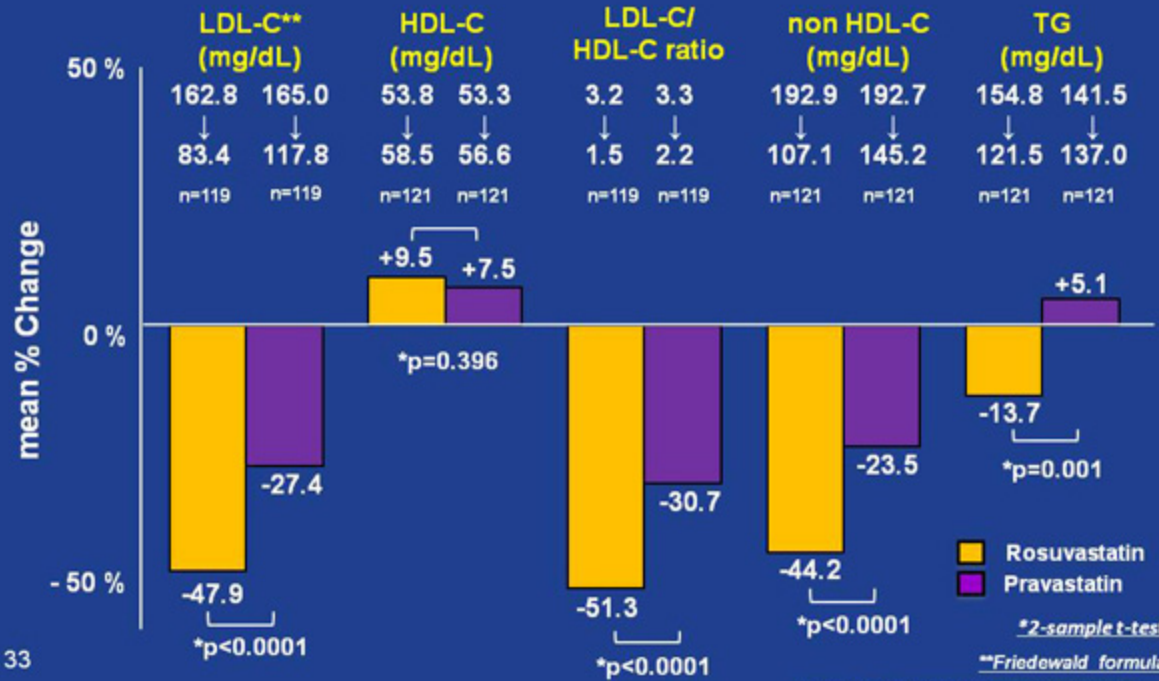
Methods

- Exclusion criteria, continued:
  - myocardial infarction or stroke within 3 months
  - heart failure (New York Heart Association class III–IV)
  - confirmed or suspected of malignant tumor.
- Patients were randomly assigned to receive rosuvastatin 5 mg (intensive therapy) or pravastatin 10 mg (conventional therapy) in a 1:1 ratio.
- In the rosuvastatin group, the LDL-C goal was defined as <80 mg/dL for primary prevention. In the pravastatin group, the LDL-C goal was defined according to the Japan Atherosclerosis Society (JAS) guideline. In this guideline, the LDL-C goal was defined according to the risk category . In primary prevention, the goal was <160 mg/dL for the low-risk group, <140 mg/dL for the intermediate-risk group, and <120 mg/dL for the high-risk group.

Methods: Design of the trial



Results: % Changes in lipid profile (at 12 months, in high risk patients ***)

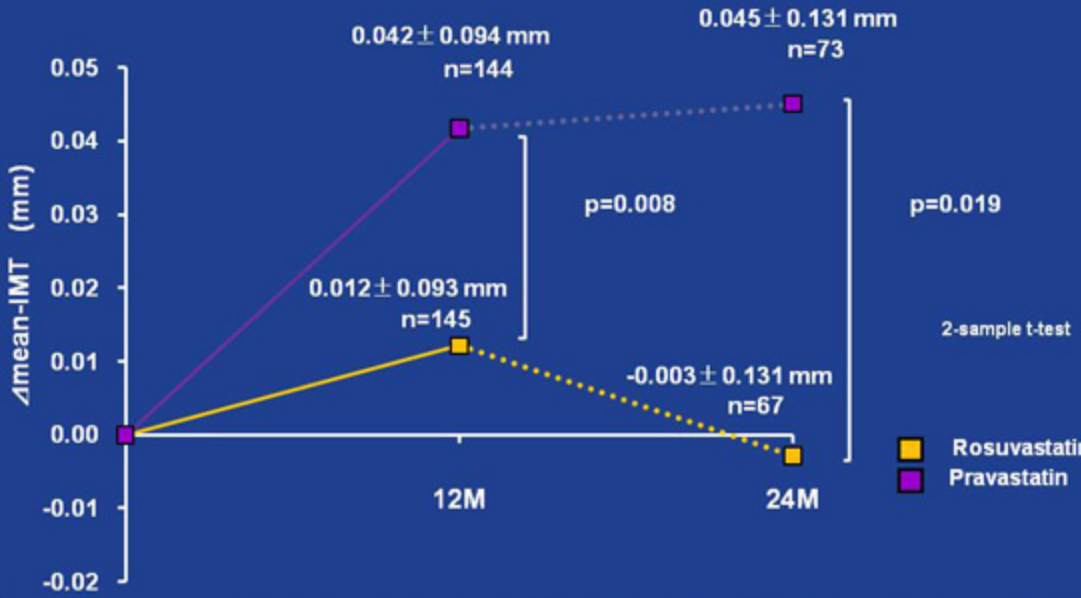


*2-sample t-test

**Friedewald formula

***JSAGL2007 category III or secondary prevention

Results: Change in the mean-IMT* (at 12 and 24 months)



*Data from patients who measured the mean-IMT at 12 and 24 months in each efficacy population.

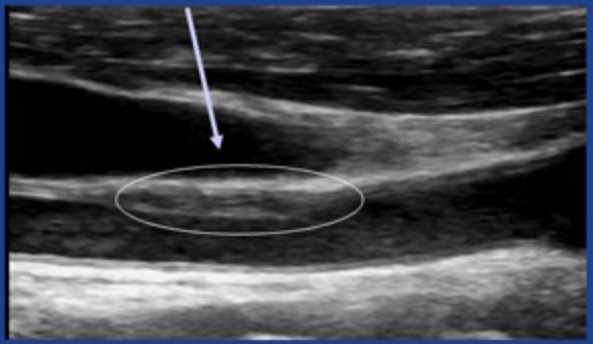
Results: A case with obvious regression of carotid IMT and plaque

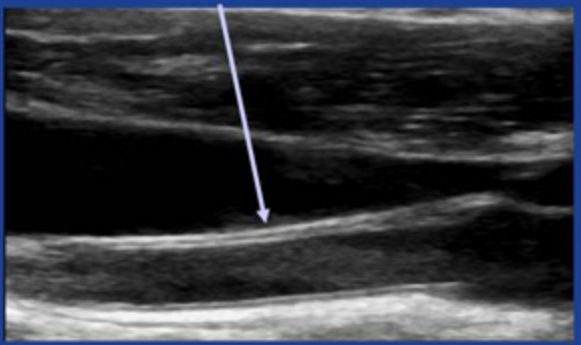
Before treatment

After 24 months

Soft plaque

Plaque regresssion/ disappearance





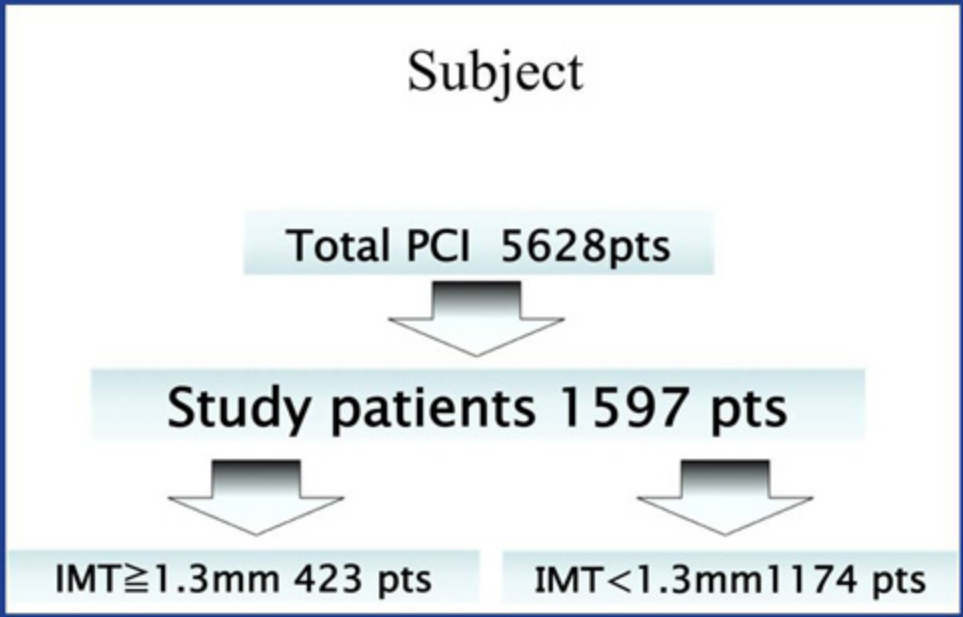
LDL-C 158/ HDL-C 33 = 4.79

LDL-C 54/ HDL-C 41 = 1.32

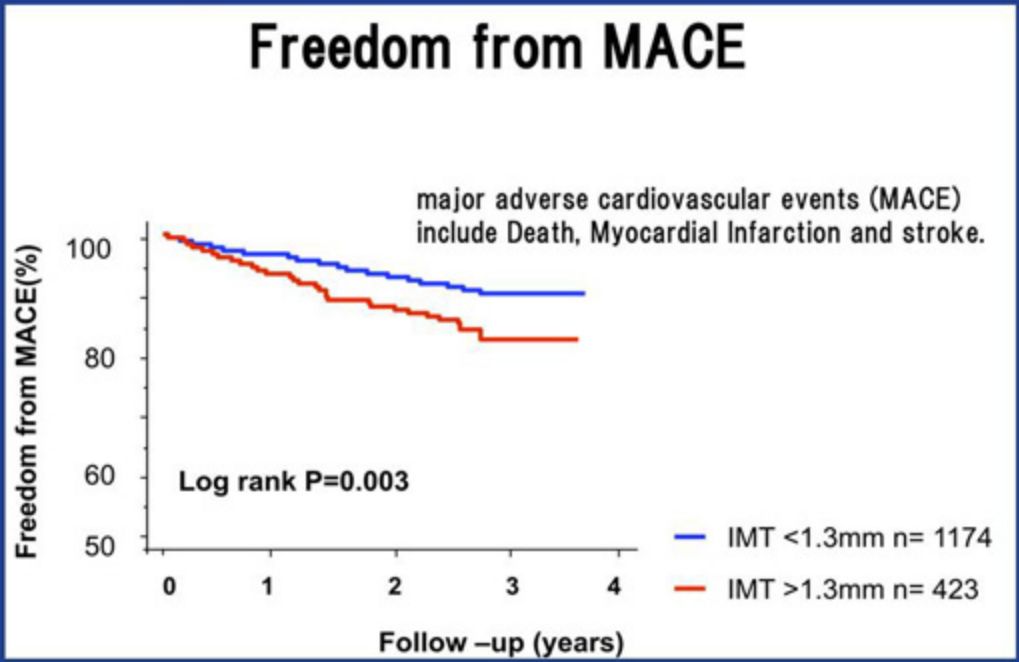
Summary

- In the rosuvastatin group, LDL-C decreased to 83.4 mg/dL, HDL-C increased to 58.5 mg/dL and LDL-C/HDL-C ratio decreased to 1.5 at 12 months.
- It is suggested that rosuvastatin's effect on the lipid profile resulted in slowing the progression of the carotid IMT.

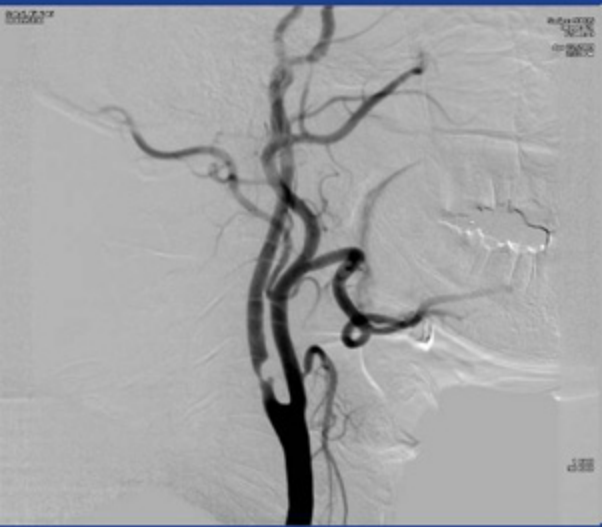
Impact of carotid IMT on long-term outcome in patients with CAD after PCI



Impact of carotid IMT on long-term outcome in patients with CAD after PCI



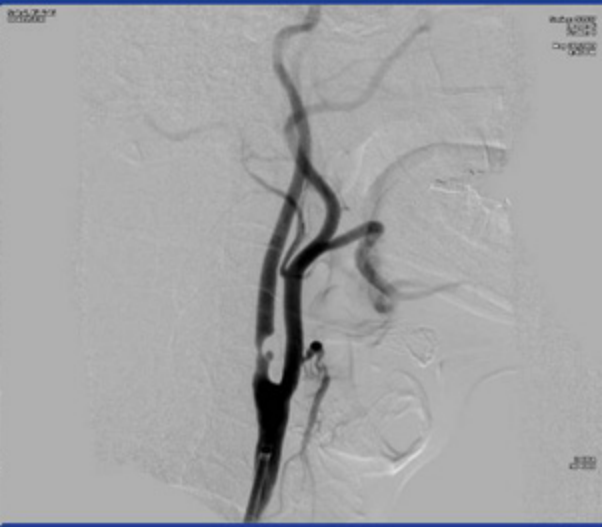
EPA pre (4/20/09)



LDL 144mg/dl
HDL 57mg/dl
TG 91mg/dl
L/H ratio 2.5

Rosuvastatin 5mg
EPA 1800mg

EPA post (5/30/09)



LDL 68mg/dl
HDL 52mg/dl
TG 79mg/dl
L/H ratio 1.3

APOLLO

A study to evaluate the efficacy of rosuvastatin for **P**atients with c**O**ronary plaque utilizing aggressive **L**ipid **LO**wering treatment

Trial Design

Primary endpoint
Changes of MLD and ALD at month 24 measured by QCA

Patients required elective PCI

20-80 years old
80≦LDL-C＜140

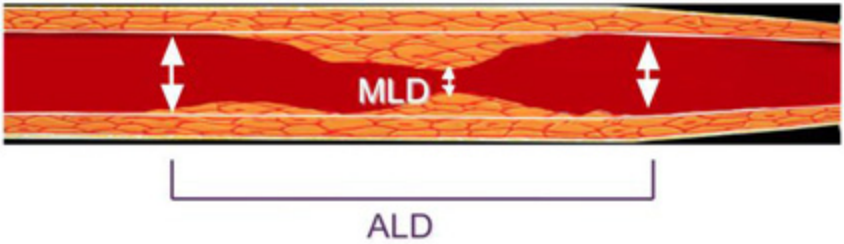
Rosuvastatin 5mg

Control — No serum lipid lowering agents including statin will be administered

MLD:minimal lumen diameter ALD:average lumen diameter
QCA:quantitative coronary angiography

QCA (Quatitative Coronary Angiography)

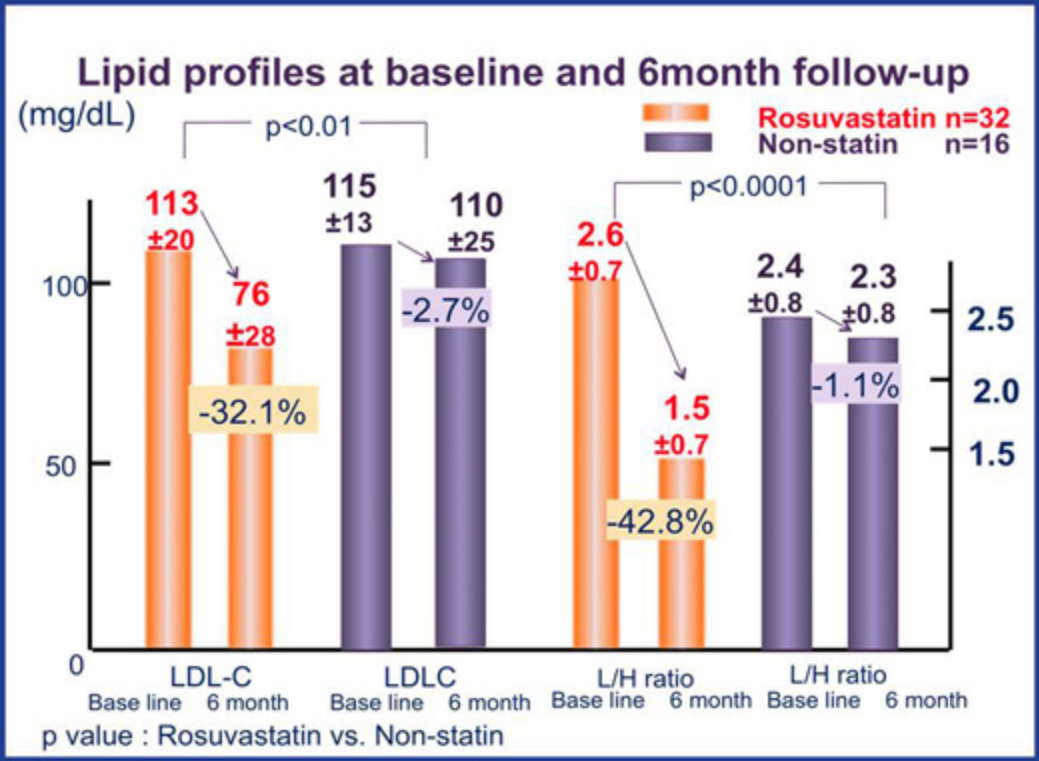
Cardiovascular Angiographic Analysis System II (CAAS II)



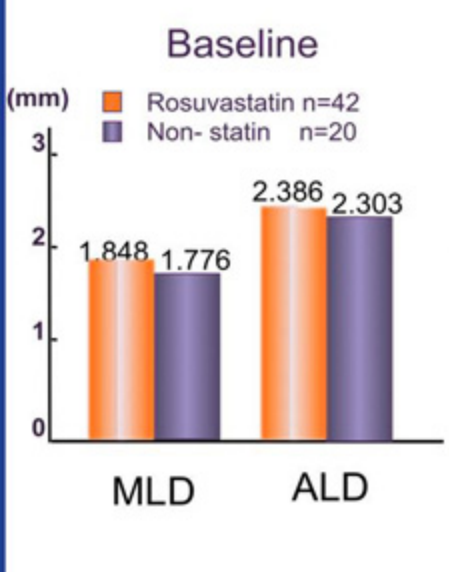
QCA Parameters : MLD (minimum lumen diameter **ALD** (average lumen diameter)

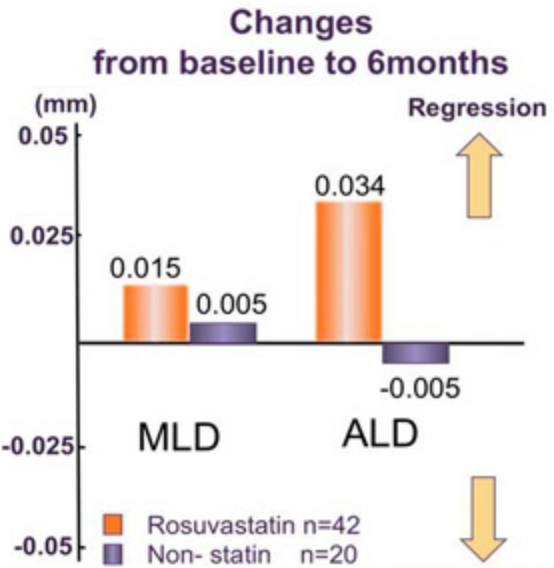
The QCA data from segments1, 2, 3, 5, 6, 7, 9, 11, 12, and 13 in the AHA reporting system were assessed .

If those segments were not suitable for the assesment, segments 4,8,10,14 and 15 were used for the analysis.

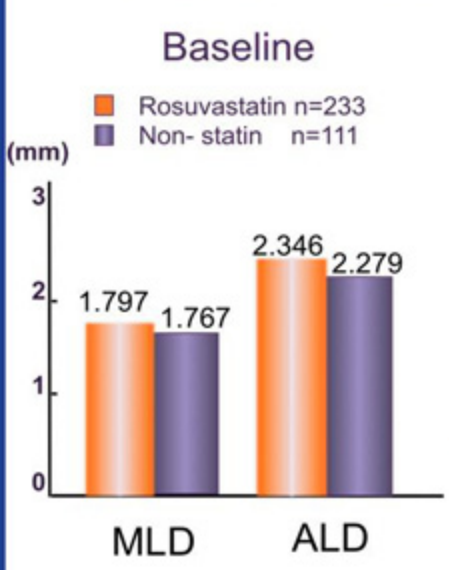

Lipid profiles at baseline and 6month follow-up
(mg/dL)
p<0.01
Rosuvastatin n=32
Non-statin n=16
p<0.0001
113
±20
76
±28
-32.1%
115
±13
110
±25
-2.7%
2.6
±0.7
1.5
±0.7
-42.8%
2.4
±0.8
2.3
±0.8
-1.1%
100
50
0
2.5
2.0
1.5
LDL-C
Base line 6 month
LDLC
Base line 6 month
L/H ratio
Base line 6 month
L/H ratio
Base line 6 month
p value : Rosuvastatin vs. Non-statin

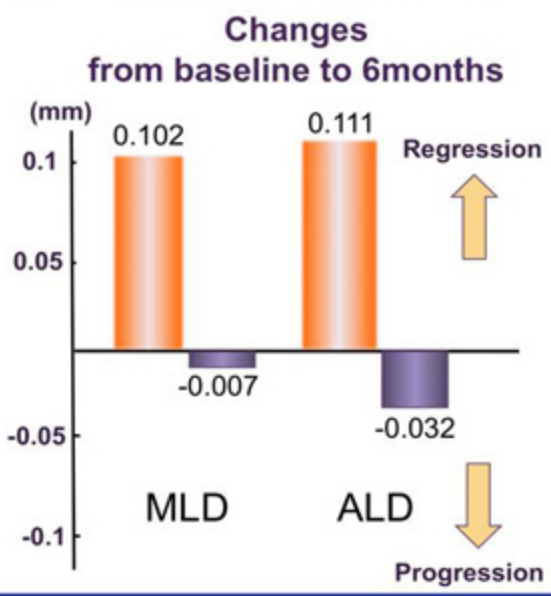
QCA assessment ≪Per Patient≫





QCA assessment ≪Per Segment : Non-target vessel≫





Conclusion

- It is suggested that the intensive control of LDL-C and other lipid parameters by Rosuvastatin is effective for slowing/regression of atherosclerosis in the Japanese population