

Relationship between Serum Inflammatory Marker Levels and the Dynamic Changes in Coronary Plaque Characteristics following Statin Therapy

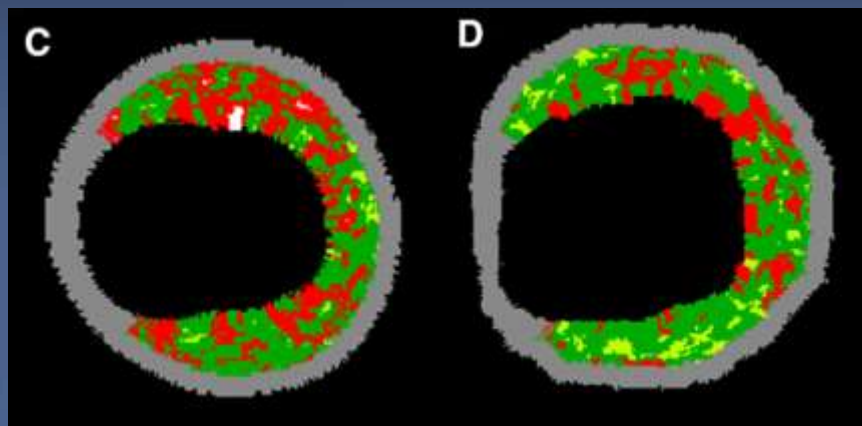
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Disclosure

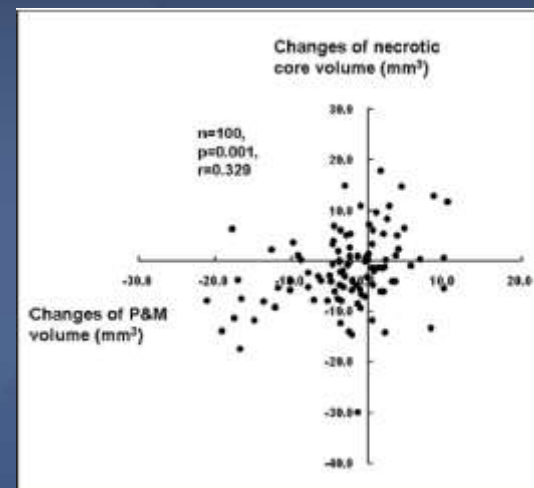
I do have nothing to disclose

Introduction

- Statin therapy not only attenuates coronary atheroma progression but also modifies plaque composition, which may consequently lead to a decrease in the risk of adverse cardiovascular events.



Decreased in Necrotic core in VH-IVUS
(C) Baseline and (D) 12-month follow-up after rosuvastatin treatment



The correlation between the change in necrotic core volume change in plaque & media volume

Backgrounds

- The pleiotropic effect of statin regardless of its LDL-cholesterol lowering effect has been considered to play a pivotal role in plaque regression and stabilization.

Jain MK, et al., Nature review Drug discovery. 2005

- The relationship between baseline hsCRP levels and plaque morphology was previously demonstrated using a cross sectional approach.

Kubo T, et al., Coronary artery disease 2009

- However, the interrelations between on-treatment changes in serum biomarkers and the dynamic nature of coronary lesion morphology have not been fully elucidated.

Aims

- We aimed to link the changes in serum inflammatory biomarker levels following 1-year rosuvastatin therapy with the modification of plaque characteristics within fibroatheroma-containing target coronary artery segments.

Post-hoc analysis of STABLE trial (Statin and Atheroma Vulnerability Evaluation), prospective, single-center, randomized double-blinded trial

✓ Inclusion

- At least 18 years of age
- Presented with chest pain (STEMI excluded) or silent ischemia
- Non-culprit de novo lesion in a native artery with at deferred coronary lesions with
 - 1) visually DS 20-50% or
 - 2) % DS >50% without any evidence of inducible ischemia

312 patients indicated CAG or PCI with a least 1 differed and untreated native lesion

1:2 randomization

103 Rosuvastatin 10mg

209 Rosuvastatin 40mg

Grayscale-IVUS, VH-IVUS, and blood laboratory tests

✓ 87 excluded

- 17 adverse reaction
- 6 non-compliance
- 1 New diagnosis of cancer
- 1 Disease progression
- 4 loss to follow-up
- 23 refusal
- 35 withdrawal

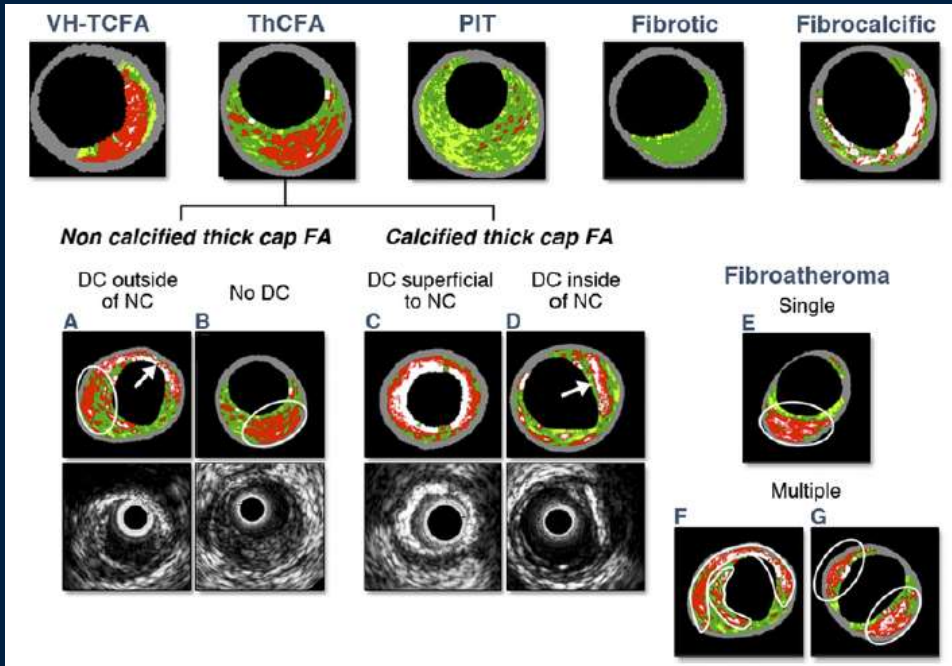
1-year follow-up

70 Rosuvastatin 10mg

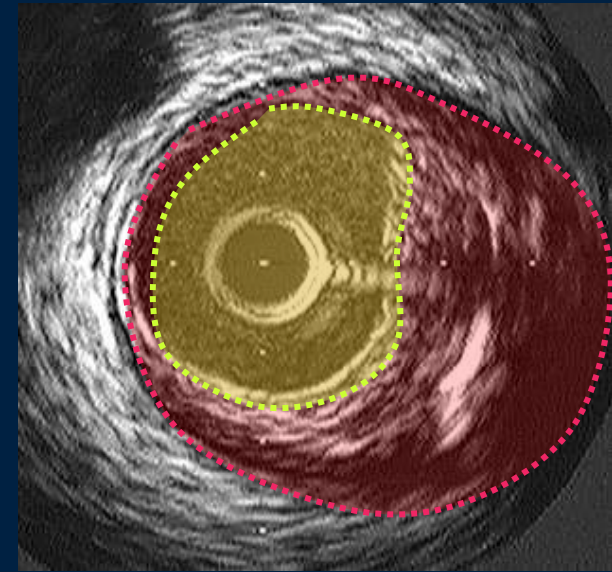
148 Rosuvastatin 40mg

218 patients with 218 lesions with complete data of grayscale-IVUS, VH-IVUS and blood laboratory tests

Definitions



Maehara A, et al., JACC Cardiovascular imaging 2012



Plaque+Media area = EEM area – lumen area
 Plaque burden = P+M area / EEM area x 100

Mintz GS, JACC 2001

- The normalized total atheroma volume (TAV) = $(\sum \text{EEM} - \text{lumen}) / n$
 (n, the number of evaluable cross-sections)
- Percent atheroma volume (PAV) = $(\sum \text{EEM} - \text{lumen}) / \sum \text{EEM} \times 100$.

Nicholls SK, NEJM 2011

Baseline characteristics

	Total (N=218)
Age (years)	62.4 ± 9.2
Male	162 (74.3%)
Body mass index (kg/m ²)	25.2 ± 2.9
Current tobacco use	69 (31.7%)
Hypertension	138 (63.3%)
Diabetes mellitus	54 (24.8%)
Hyperlipidemia	128 (58.7%)
Previous myocardial infarction	4 (1.8%)
Previous PCI	15 (6.9%)
Previous CABG	1 (0.5%)
Clinical presentation	
Silent or stable angina	128 (58.7)
Acute coronary syndrome	90 (41.3%)

Baseline characteristics

	Total (N=218)
Number of narrowed coronary arteries	
None	34 (15.6%)
1	104 (47.7%)
2	63 (28.9%)
3	17 (7.8%)
Left anterior descending / Left circumflex artery	87 (39.9%) / 42 (19.3%)
Right coronary artery	89 (40.8%)
Medication at discharge	
Aspirin / Clopidogrel	218 (100.0%) / 182 (83.5%)
β -blocker / CCB	139 (63.8%) / 178 (81.7%)
ACE inhibitor or ARB	61 (28.0%)
Nitrate	22 (10.1%)

Blood biochemical values

	Baseline	Follow-up at 12 months	Change (follow-up – baseline)	p value
Lipid profiles (mg/dl)				
Total cholesterol	172.3 ± 39.6	127.2 ± 31.6	-45.3 ± 42.5	<0.001
HDL-cholesterol	43.5 ± 12.0	49.2 ± 11.9	5.8 ± 9.1	<0.001
LDL-cholesterol	105.7 ± 35.4	67.1 ± 28.1	-38.8 ± 40.3	<0.001
LDL/HDL-cholesterol (ratio)	2.6 ± 1.1	1.4 ± 0.7	-1.2 ± 1.1	<0.001
Triglyceride	145.4 ± 81.9	115.6 ± 66.1	-30.0 ± 69.3	<0.001
Serum biochemical markers				
ApoA1 (mg/dl)	125.0 ± 22.1	137.7 ± 23.9	14.0 ± 18.5	<0.001
ApoB100 (mg/dl)	87.7 ± 25.2	61.9 ± 19.3	-25.1 ± 26.8	<0.001
ApoB100/ApoA1 (ratio)	0.7 ± 0.2	0.5 ± 0.2	-0.3 ± 0.2	<0.001
Leukocyte count (×10 ³ /μl)	6.8 ± 2.0	6.6 ± 2.0	-0.1 ± 1.9	0.15
hsCRP (mg/l)	2.2 ± 3.7	1.2 ± 2.0	-0.9 ± 3.9	<0.001
Homocysteine (mg/dl)	12.5 ± 3.5	11.9 ± 3.3	-0.8 ± 3.4	0.002
Fibrinogen (mg/dl)	258.1 ± 52.7	278.4 ± 55.1	16.1 ± 65.3	0.001
Lipoprotein (a) (μmol/L)	23.8 ± 23.3	30.5 ± 32.0	8.9 ± 15.7	<0.001

Intracoronary imaging parameters

	Baseline	Follow-up at 12 months	Change (follow-up – baseline)	p value
Grayscale-IVUS				
MLA (mm²)	4.4 ± 2.0	4.3 ± 2.1	- 0.1 ± 1.1	0.03
EEM area at the MLA (mm²)	13.7 ± 4.7	12.8 ± 4.4	- 0.9 ± 2.6	<0.001
P + M area at the MLA (mm²)	9.4 ± 3.9	8.6 ± 3.7	- 0.8 ± 2.5	<0.001
Plaque burden at the MLA (%)	67.4 ± 10.9	66.2 ± 12.2	- 1.7 ± 8.4	0.06
Percent atheroma volume (%)	51.3 ± 8.3	50.4 ± 8.8	- 0.8 ± 4.6	0.01*
Normalized lumen (mm³/mm)	7.9 ± 3.3	7.6 ± 3.6	- 0.3 ± 1.6	0.001
Normalized EEM (mm³/mm)	16.1 ± 5.4	15.3 ± 5.4	- 0.8 ± 2.1	<0.001
Normalized total atheroma volume (mm³)	8.2 ± 2.9	7.6 ± 2.8	- 0.6 ± 1.2	<0.001
Virtual histology-IVUS				
Percent volume, segment (%)				
Fibrous	59.4 ± 7.8	59.1 ± 8.7	-0.3 ± 7.0	0.88
Fibrofatty	11.7 ± 5.8	14.6 ± 9.2	2.9 ± 8.9	0.01
Necrotic core	21.3 ± 6.7	18.4 ± 7.4	-3.0 ± 8.5	<0.001
Dense calcium	7.6 ± 5.1	8.0 ± 5.6	0.4 ± 4.3	0.67

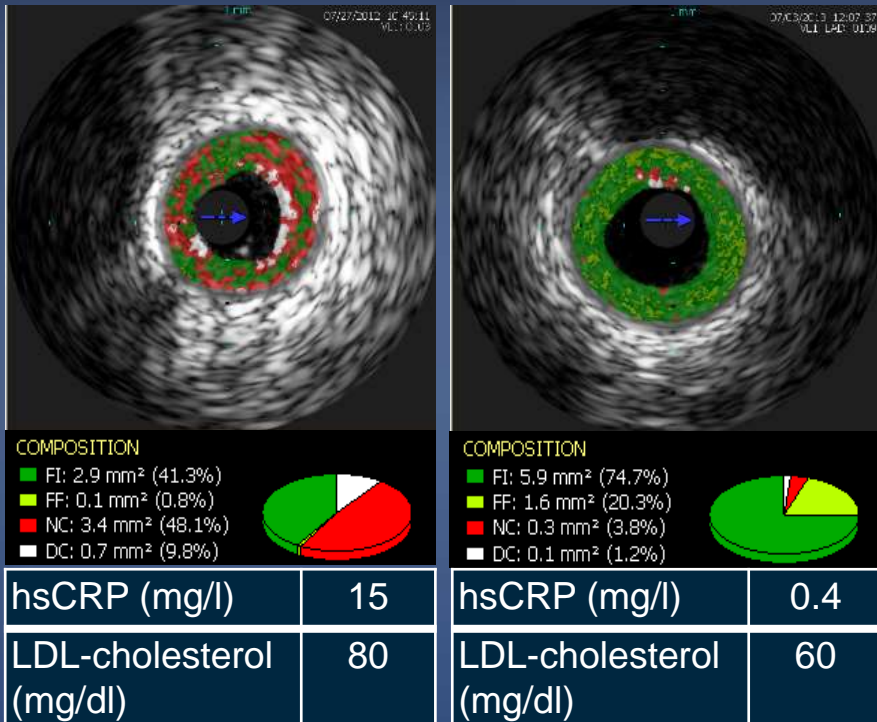
Values are presented as a mean ± standard deviation. *p-values were obtained using the paired t-test, otherwise the Wilcoxon-signed rank test was used, as indicated.

Abbreviations: Apo, apolipoprotein; EEM, external elastic membrane; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IVUS, Intravascular ultrasound; LDL, low-density lipoprotein; MLA, minimal lumen area; P + M, plaque plus media; TCFA, Thin-cap fibroatheroma

Examples of plaque modification following rosuvastatin treatment

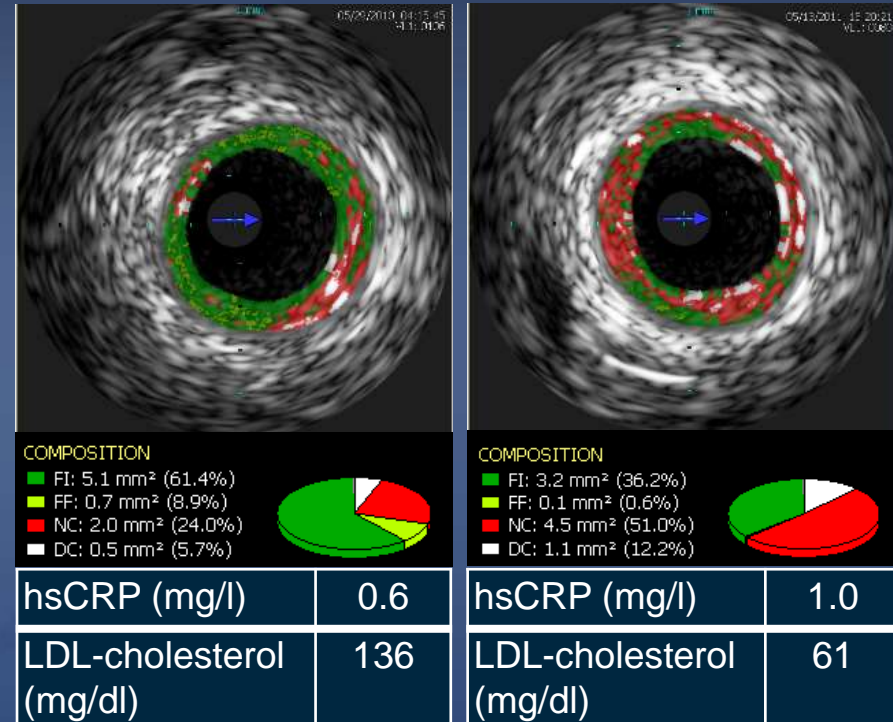
Regression

Baseline → At 12 month

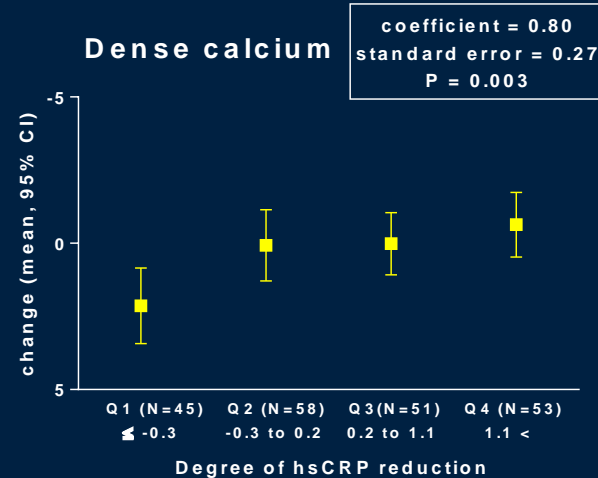
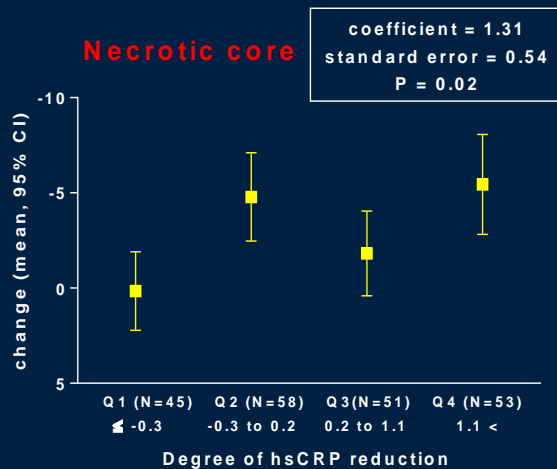
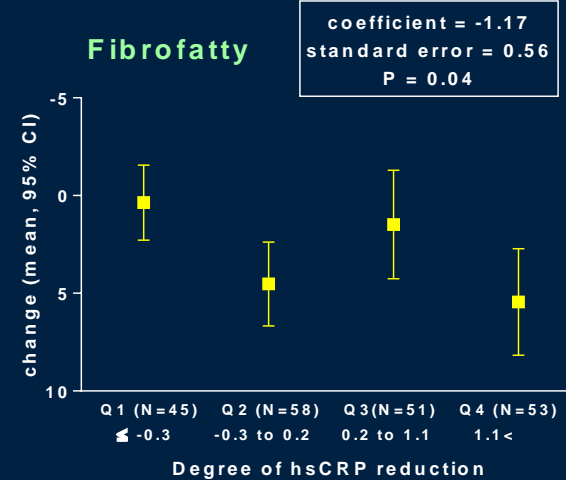
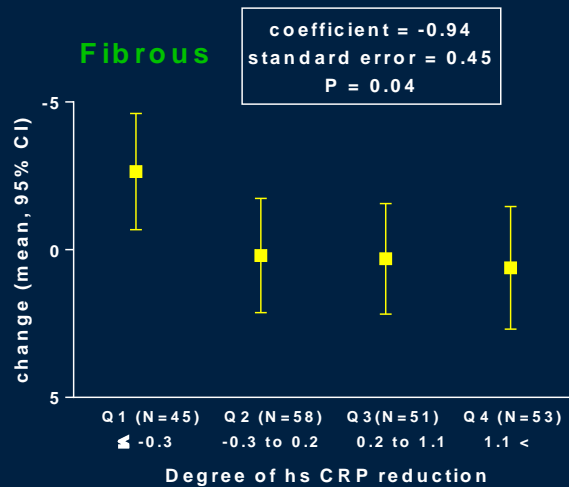


Progression

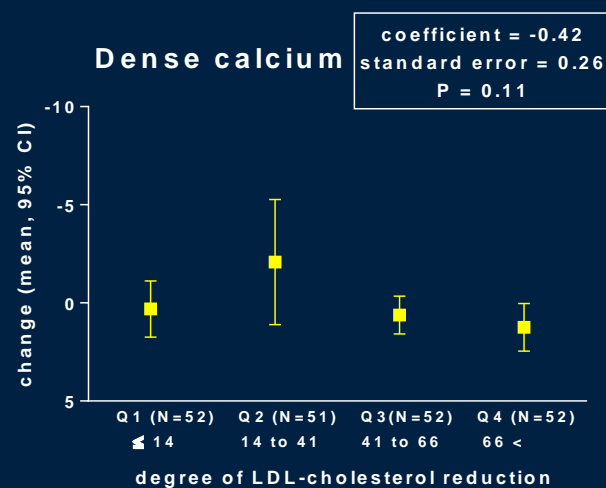
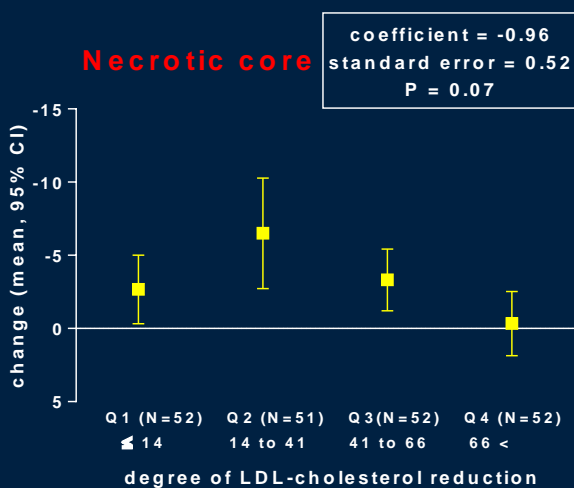
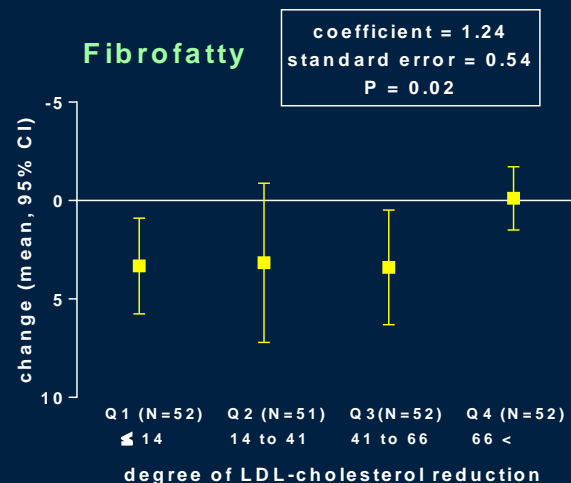
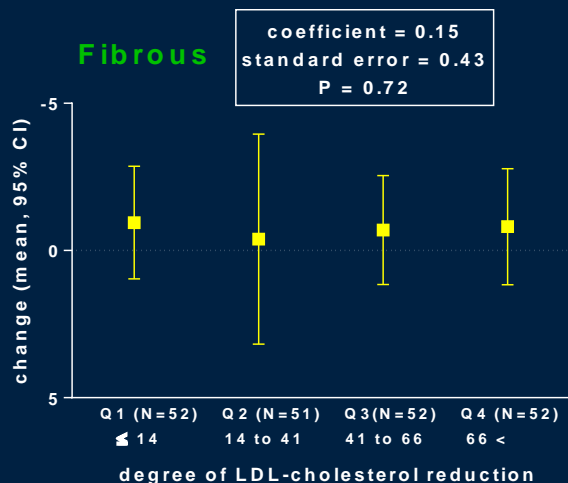
Baseline → At 12 month



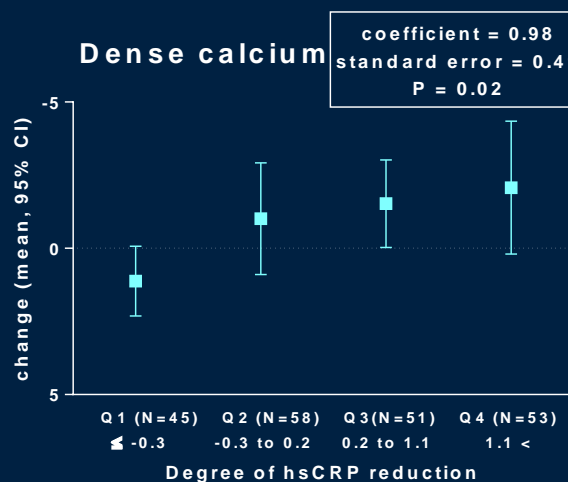
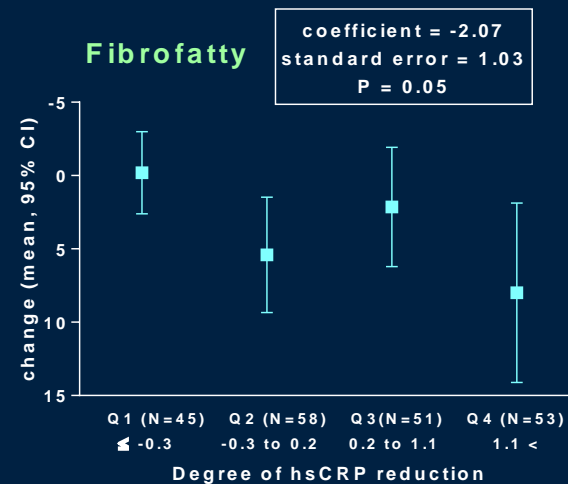
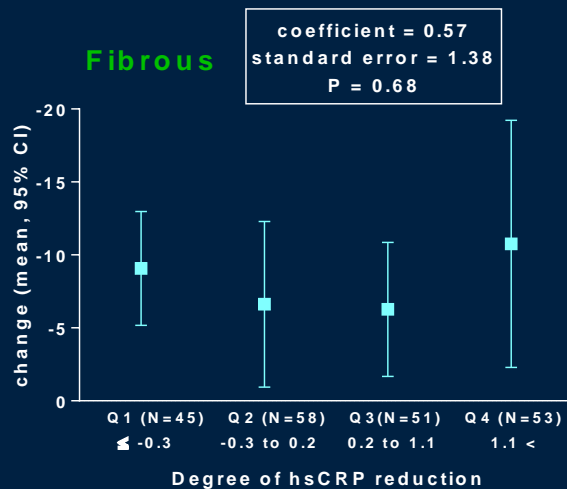
Serial Changes in the percent volume across the quartiles of hsCRP level change



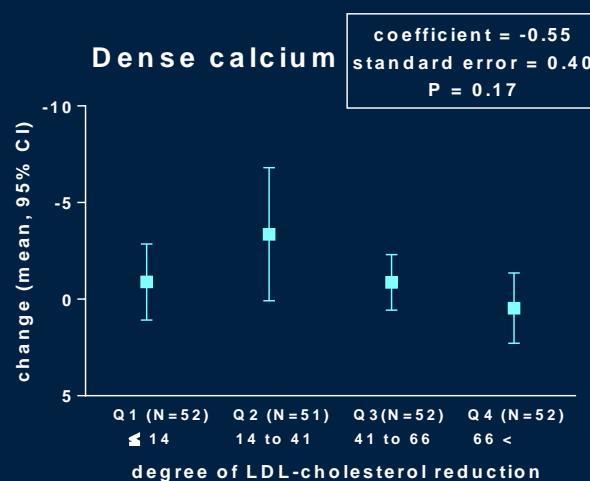
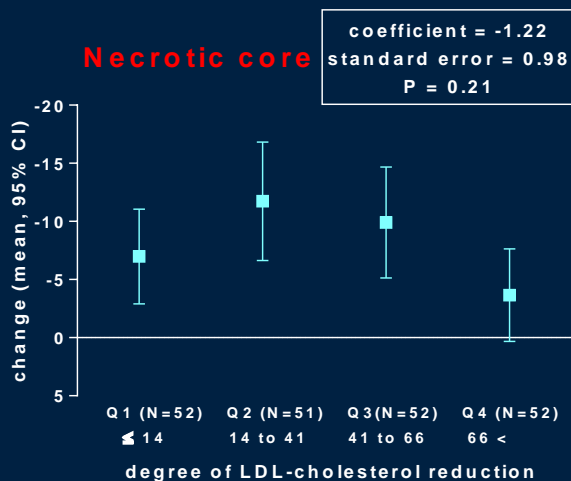
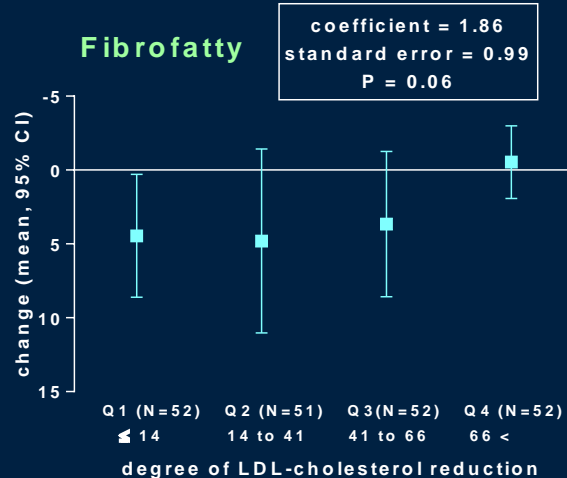
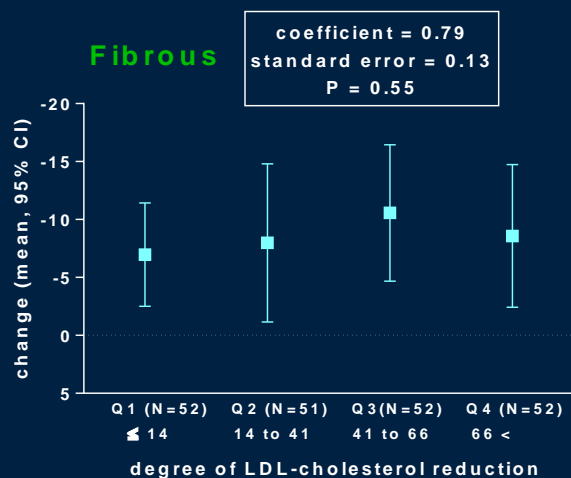
Serial Changes in the percent volume across the quartiles of LDL-cholesterol level change



Serial Changes in the absolute volume across the quartiles of hsCRP level change



Serial Changes in the absolute volume across the quartiles of LDL-cholesterol level change



Absence vs. Presence of TCFA at 12-months F/U

At 12-month follow-up (N=218)	Absence of TCFA (N=175)	Presence of TCFA (N=43)	p value
Clinical characteristics			
Age (years)	62.3 ± 9.2	62.9 ± 9.3	0.79*
Male	131 (74.9%)	31 (72.1%)	0.86
Body mass index (kg/m ²)	25.0 ± 2.9	25.8 ± 2.6	0.10
Rosuvastatin 40mg	120 (68.6%)	28 (65.1%)	0.80
Hypertension	107 (61.1%)	31 (72.1%)	0.25
Diabetes mellitus	35 (20.0%)	19 (44.2%)	0.002
Hyperlipidemia	108 (61.7%)	20 (46.5%)	0.10
Current tobacco use	57 (32.6%)	12 (27.9%)	0.69
Acute coronary syndrome	72 (41.1%)	18 (41.9%)	1.00
TCFA at baseline	81 (46.3%)	38 (88.4%)	<0.001

Absence vs. Presence of TCFA at 12-months F/U

At 12-month follow-up (N=218)	Absence of TCFA (N=175)	Presence of TCFA (N=43)	p value
Blood biochemical values, change over the 12 months			
Total cholesterol (mg/dl)	-46.4 ± 41.1	-40.9 ± 48.2	0.84*
HDL-cholesterol (mg/dl)	5.3 ± 8.9	7.8 ± 9.6	0.12
LDL-cholesterol (mg/dl)	-39.0 ± 40.3	-38.2 ± 40.7	0.98*
LDL/HDL-cholesterol (ratio)	-1.2 ± 1.1	-1.2 ± 1.0	0.81
Triglyceride (mg/dl)	-27.8 ± 68.6	-38.8 ± 71.8	0.28*
ApoA1 (mg/dl)	13.5 ± 17.9	15.3 ± 20.7	0.63
ApoB100 (mg/dl)	-26.3 ± 25.7	-21.1 ± 30.1	0.86*
ApoB100/ApoA1 (ratio)	-0.3 ± 0.2	-0.2 ± 0.2	0.99*
Leukocyte count (×10 ³ /μl)	-0.1 ± 1.9	0.04 ± 1.6	0.45*
hsCRP (mg/l)	-1.2 ± 3.9	0.5 ± 3.4	0.02*
Homocysteine (mg/dl) †	-0.7 ± 3.3	-1.3 ± 3.5	0.42*
Fibrinogen (mg/dl) †	13.7 ± 64.5	24.6 ± 68.3	0.39
Lipoprotein (a) (μmol/L) †	8.0 ± 14.7	12.1 ± 18.4	0.25*

Values are presented as a mean ± standard deviation or number (%).

*p values were obtained using the Mann-Whitney test; otherwise, the Student's t-test was used, as indicated.

Prediction of the presence of TCFA at follow-up

	Univariate			Multivariate		
	OR	95 % CI	p value	OR	95 % CI	p value
Diabetes mellitus	3.17	1.55–6.43	0.001	4.01	1.62–9.97	0.003
Hyperlipidemia	0.54	0.27–1.06	0.07			
Total cholesterol at baseline	0.99	0.98–1.00	0.10			
HDL-cholesterol < median level of 42.0 mg/dl at baseline	2.02	1.00–4.09	0.05	2.24	0.96–5.24	0.06
ApoB100 at baseline	0.98	0.97–1.00	0.03	0.99	0.97–1.00	0.09
Change hsCRP	1.18	1.03-1.35	0.02	1.19	0.98-1.44	0.07
PAV at baseline	1.06	1.02–1.11	0.004			
nTAV at baseline	1.21	1.09–1.37	0.001	1.18	1.04–1.35	0.01
TCFA at baseline	8.82	3.61–26.55	<0.001	9.21	3.04–27.92	<0.001

Limitations

- The findings cannot be extrapolated to more advanced, culprit lesions or lesions without fibroatheroma.
- The results from this underpowered, small-sized study evaluating Asians cannot be generalized.
- The absence of a placebo group with potential regression to the mean could be a limitation.
- The clinical outcomes based on inflammatory activity was not assessed.
- The poor resolution of VH-IVUS limits the ability to identify histologically-defined TCFA.

Conclusions

- A greater hsCRP level reduction (not LDL-cholesterol level reduction) is associated with a greater decrease in the %NC volume and the absence of VH-TCFA after 12-month rosuvastatin treatment.
- This provides a link between the anti-inflammatory action of statin and plaque stabilization by reducing NC and reinforcing fibrous cap.
- Further studies are required to elucidate the precise mechanism of statin-mediated atheroma modification and the effect of different type and dosage of statin.