Statin Treatment Can Stabilize Coronary Plaque Vulnerability: A Double-Blind, Randomized Study

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Disclosure Statement of Financial Interest

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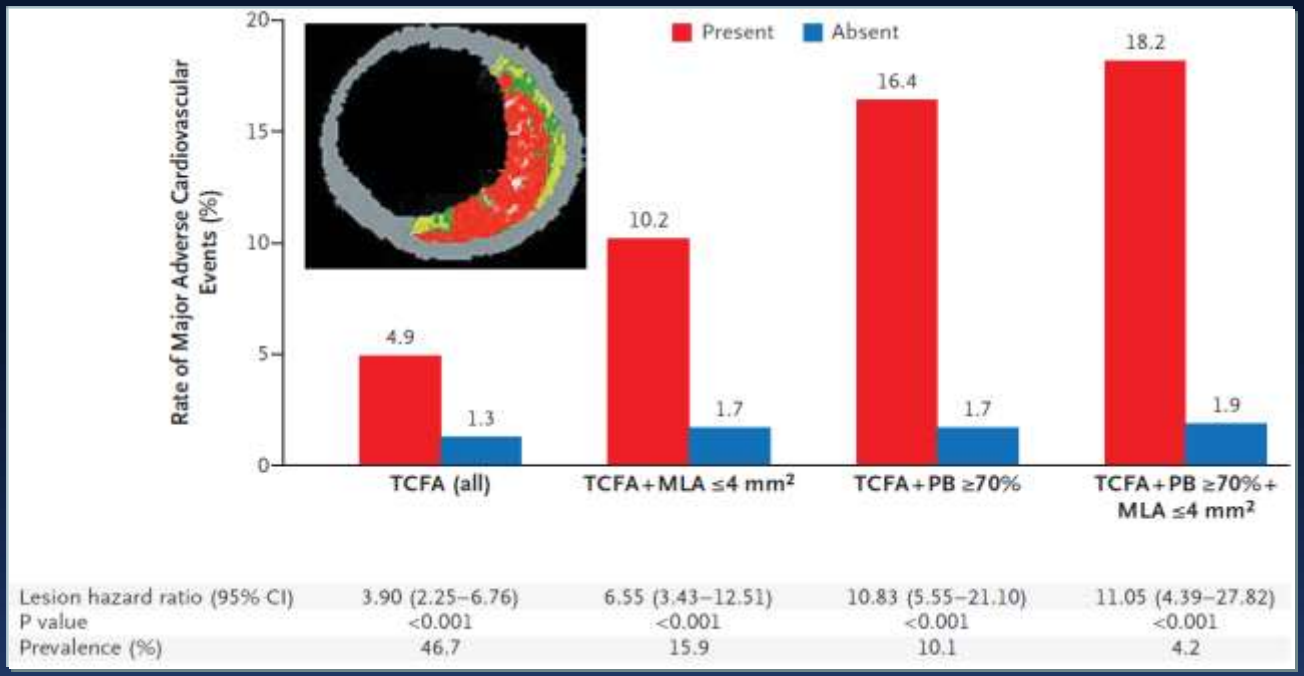
Background



Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Stone G et al. PROSPECT, N Engl J Med 2011;364:226-5

- It is unclear how statin alters the natural course of coronary atherosclerosis in vulnerable plaques
- To see the effect of statin on stabilizing plaque vulnerability in *fibroatheroma-containing* target segments, and to compare the efficacy of high- vs. moderate-intensity rosuvastatin

Eligibility

- Consecutive patients 18 to 75 years of age with clinical indication of coronary angiography

- At least 1 deferred native coronary lesion with
  1) visually-estimated angiographic DS 20–50% or
  2) DS>50% without inducible ischemia*

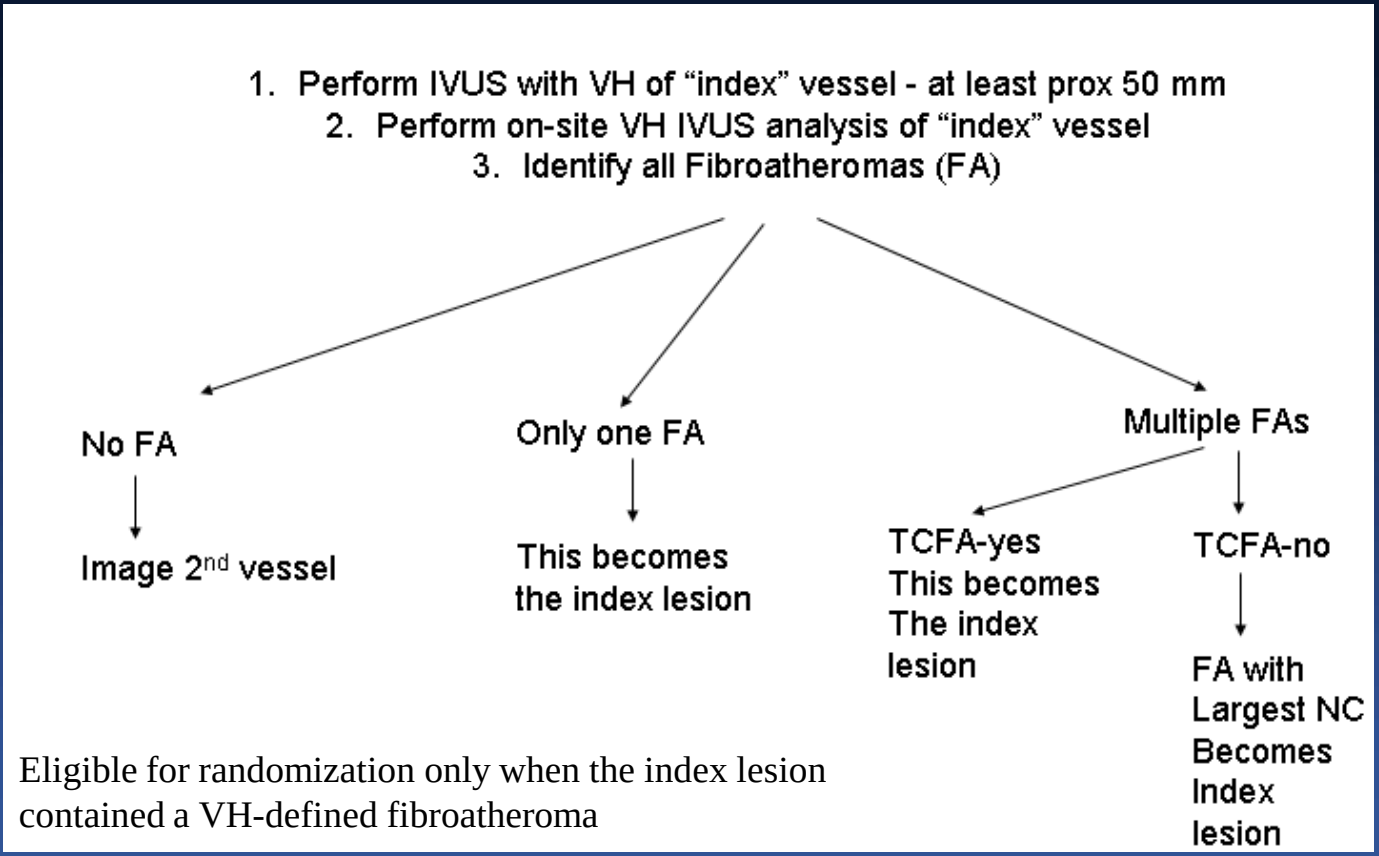
**FFR≥0.8 or no thallium perfusion defect in target vessel territory*

Exclusion Criteria

1.	Planned cardiac surgery
2.	Stroke or resuscitated sudden death in the past 6 months.
3.	Chronic disease requiring treatment with corticosteroids
4.	Untreated hyperthyroidism, or hypothyroidism with TSH >1.5 times UNL
5.	A diagnosis of cancer (other than superficial squamous or basal cell skin cancer) in the past 3 years or current treatment for the active cancer
6.	Any clinically significant abnormality identified at the screening visit,
7.	Evidence of congestive heart failure, or LV ejection fraction < 40%.
8.	Significant renal disease manifested by serum creatinine $\geq$ 2.0mg/dL, or creatinine clearance of < 40 ml/min (by Cockcroft-Gault method)
9.	Hepatic disease or biliary tract obstruction, or ALT or AST > 3 times UNL
10.	History of myopathy or elevated creatine kinase (CK) > 3 times UNL
11.	History of asthma in the past 6 months, or currently taking anti-asthmatic med
12.	Unwillingness or inability to comply with the procedures
13.	History of arterial bypass or PCI involving the target vessel.
14.	The luminal narrowing in the target vessel or in LMCA (DS > 50%)
15.	Reference vessel diameter of the target vessel < 2.5mm on angiogram
16.	Presence of thrombus in the target vessel (high risk of distal embolism)
17.	Severe tortuosity of the target vessel (inappropriate for IVUS procedures)

Selection of Index Lesion
eligible for the study

Flow of VH-IVUS Screening



Eligible for randomization only when the index lesion contained a VH-defined fibroatheroma

STABLE Trial

(*ST*atin and *A*theroma Vulnera*B*i*L*ity *E*valuation)

Prospective, Single Center, Double-blinded, Randomized

Total 312 patients who had at least 1 deferred native coronary lesion with ***VH-defined FA***-containing index lesion

2:1 randomization (double-blinded)

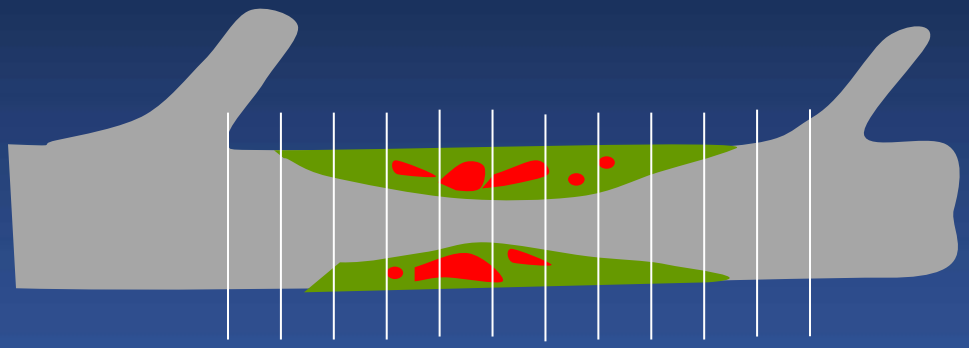
High-intensity	Moderate-intensity
Rosuvastatin 40mg/d	Rosuvastatin 10mg/d

40MHz Grayscale- and 20MHz VH-IVUS at baseline and 12 mo

- Primary: change in %NC volume within the target segment
- Secondary: change in %NC volume in rosuvastatin 40 vs. 10mg

Grayscale- and VH-IVUS

- Every 1.0mm interval within the target segment between distal and proximal fiduciary points, volumetric analysis was done by Simpson's method and then normalized for length
- Normalized TAV and PAV
- With EEM/lumen VH-IVUS contouring every 0.40mm, %NC volume, plaque type and VH-TCFA were measured



Nissen et al. ASTEROID, JAMA 2004;291:1071–80
Stone et al. PROSPECT, N Engl J Med 2011;364:226-5

Sample Size

- *Primary endpoint;* To assess the segmental %NC volume change in the target segment 265 patients were required for 90% power and 2-sided type I error of 5% to detect an expected 1.0% difference, assuming SD of 5%. With a dropout rate of 15%, enrollment of 312 patients (allocated to rosuvastatin 40mg vs. 10mg in 2:1 ratio) was pre-specified

- *Secondary endpoint:* To assess the %NC volume change between rosuvastatin 40mg vs. 10mg, 276 patients were required for 90% power and 2-sided type I error of 5% to detect an expected 5.0% difference between the groups, assuming SD of 12%. A total of 312 patients was calculated

F/U imaging was completed in 225 (72%) patients and 225 non-culprit lesions

Reasons for Discontinuation in 87 (28%) Pts.

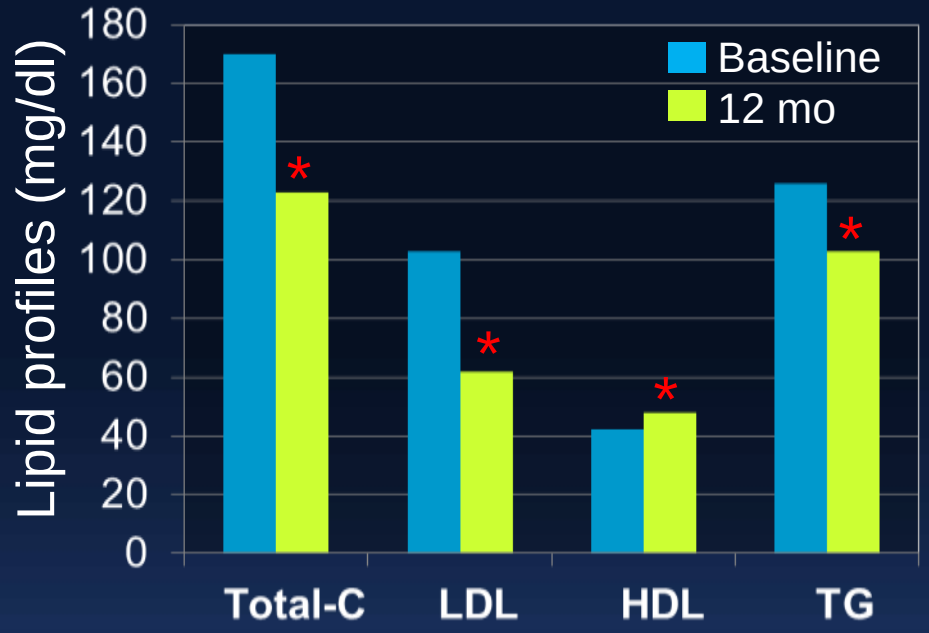
Adverse statin effects AST/ALT elevation (9), Urticaria (1), Myalgia (2), Azote Headache (1), Chest discomfort (1), Leg edema (1), Vo	
New diagnosis of colon cancer	
Disease progression	
Noncompliance	
Loss to follow-up	
Pt. withdrawal of consent *before statin admi*	
Pt. withdrawal of consent *during treatment*	
Patient's refusal of follow-up imaging study	23

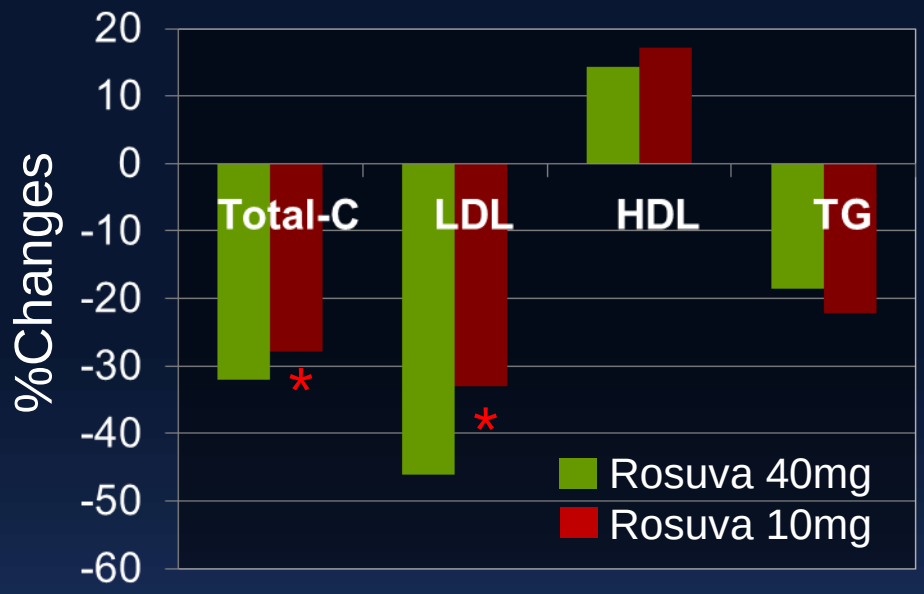
Results

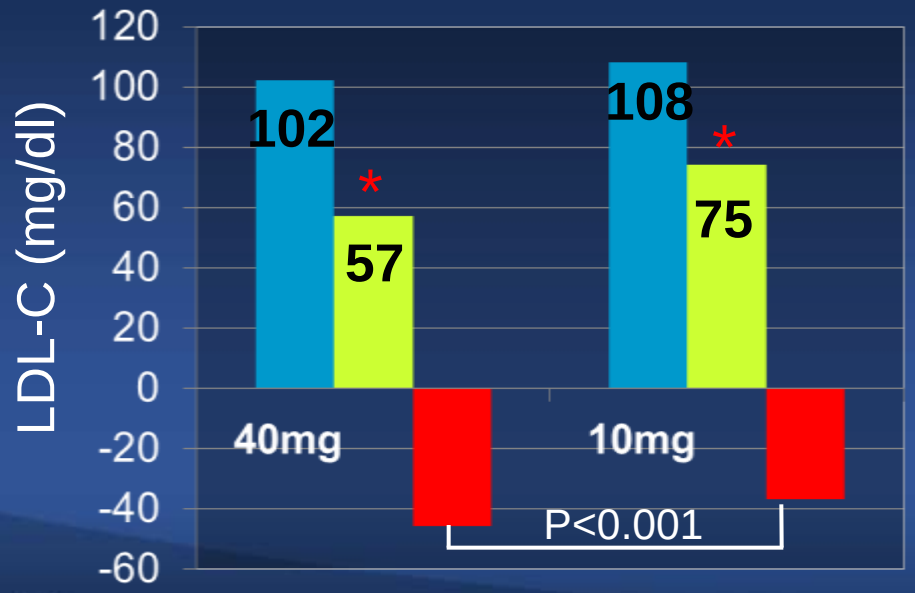
Characteristics of Patients at Baseline

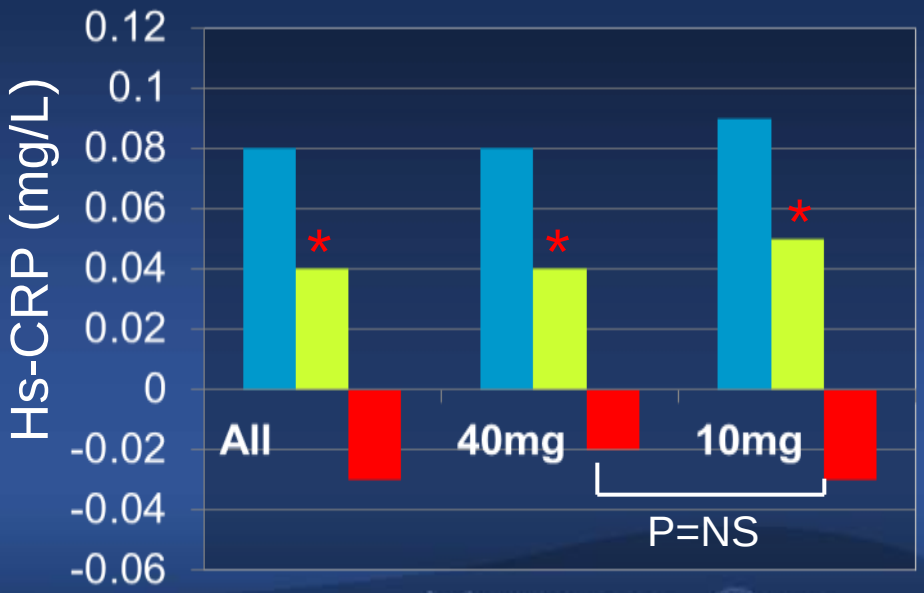
	Total	40mg	10mg	P
N	225	152	73	
Age (years)	62.0 (57.0–69.0)	62.0 (56.2–70.0)	62.0 (57.0–68.0)	0.632
Male	164 (73%)	108 (71%)	56 (77%)	0.425
Diabetes	56 (25%)	40 (26%)	16 (22%)	0.762
Hypertension	142 (63%)	103 (68%)	42 (58%)	0.180
Smoking	71 (32%)	46 (30%)	25 (34%)	0.465
Hyperlipidemia	132 (59%)	84 (55%)	28 (65%)	0.390
Statin-naïve	153 (68%)	47 (31%)	25 (34%)	0.805
BMI, kg/m^2	24.9 (23.5–26.8)	24.7 (23.2–26.7)	25.7 (23.7–27.3)	0.099
ACS	94 (42%)	61 (40%)	33 (45%)	0.281

Lipid Profiles and hs-CRP



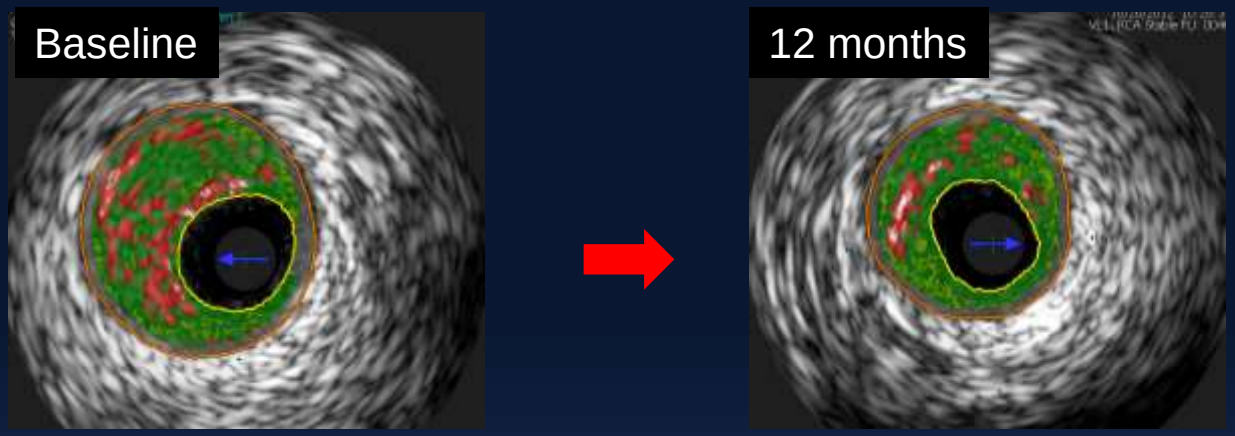


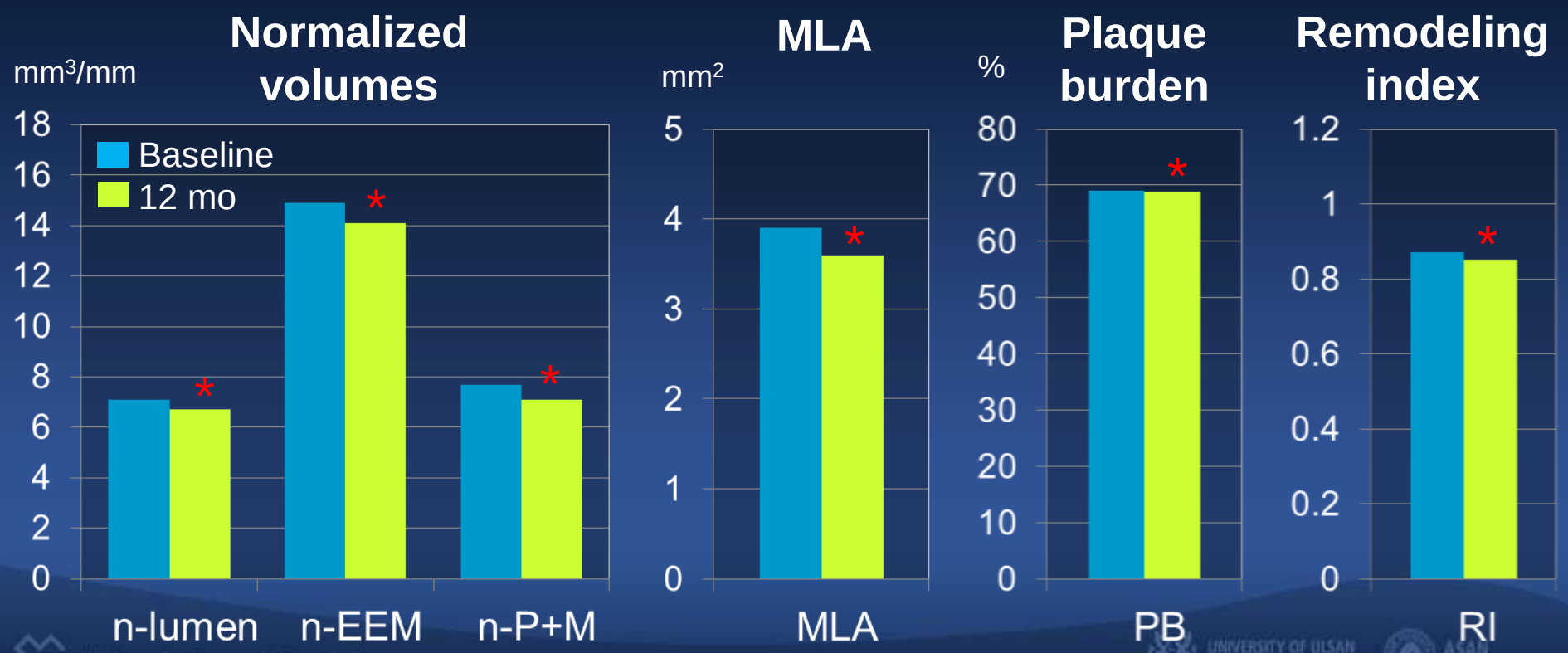




*p value <0.05

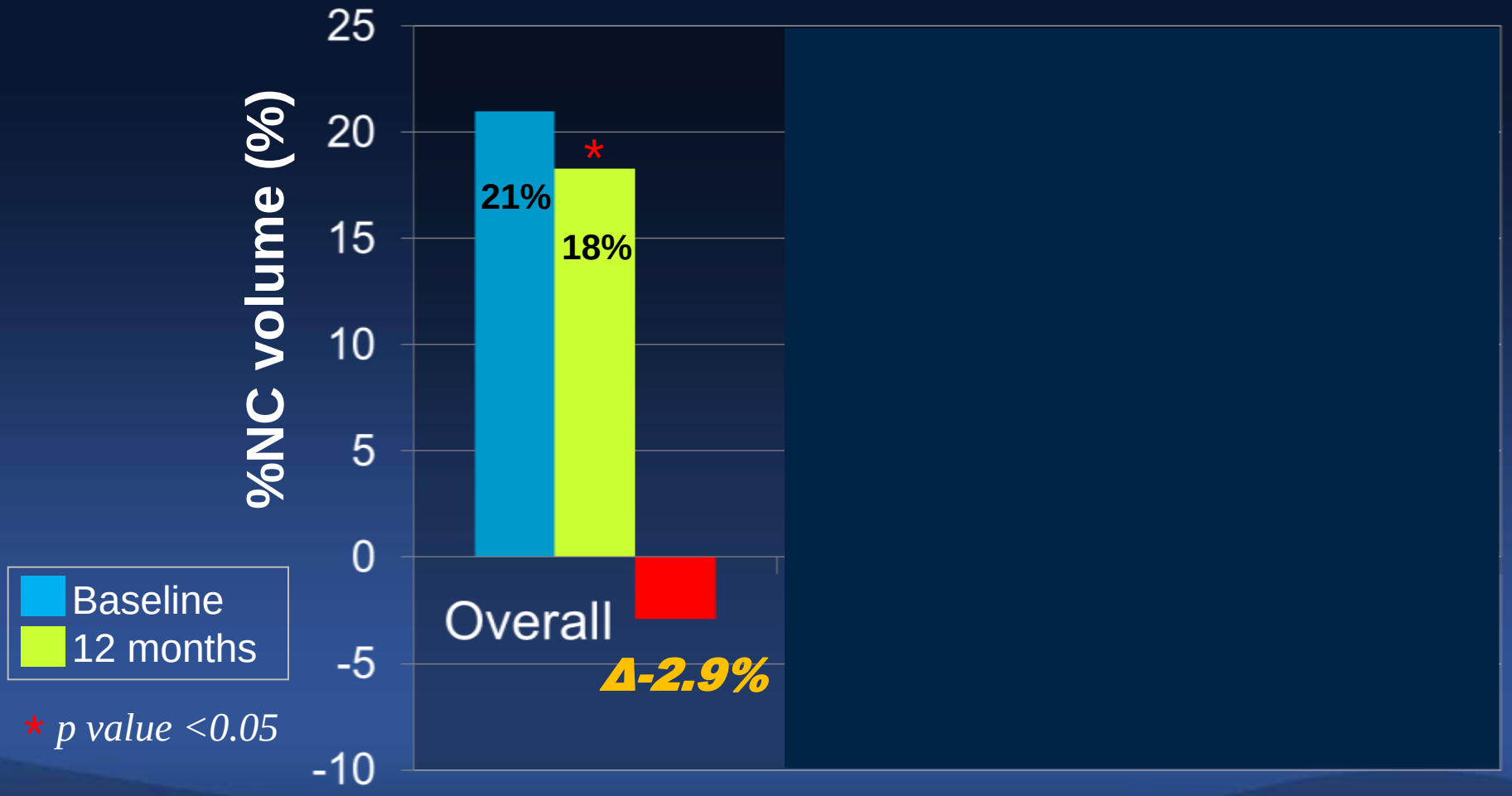
Vascular Changes after 12-month Statin





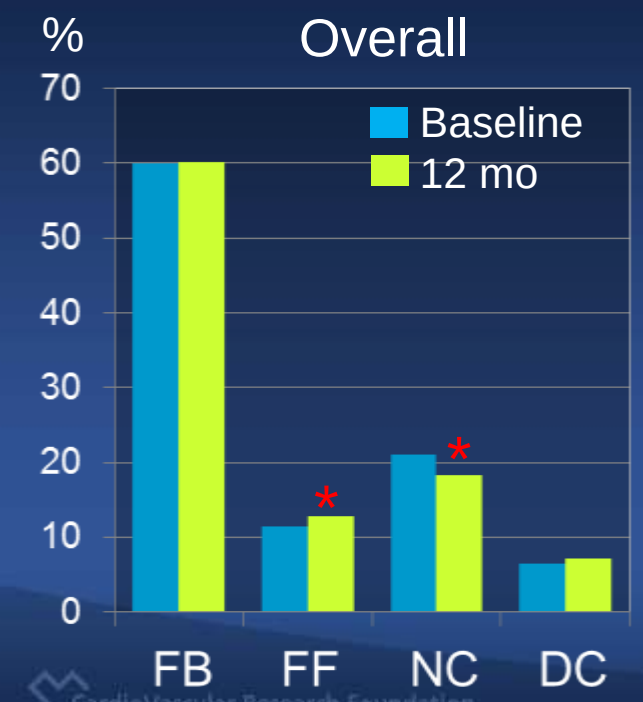
Pre-specified Endpoints

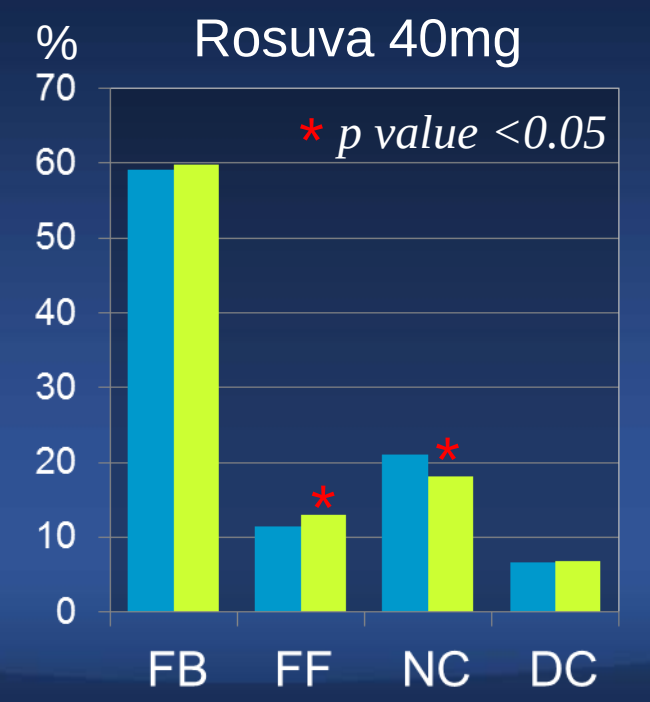
- Primary: change in %NC volume within the target segment
- Secondary: change in %NC volume in rosuvastatin 40 vs. 10mg

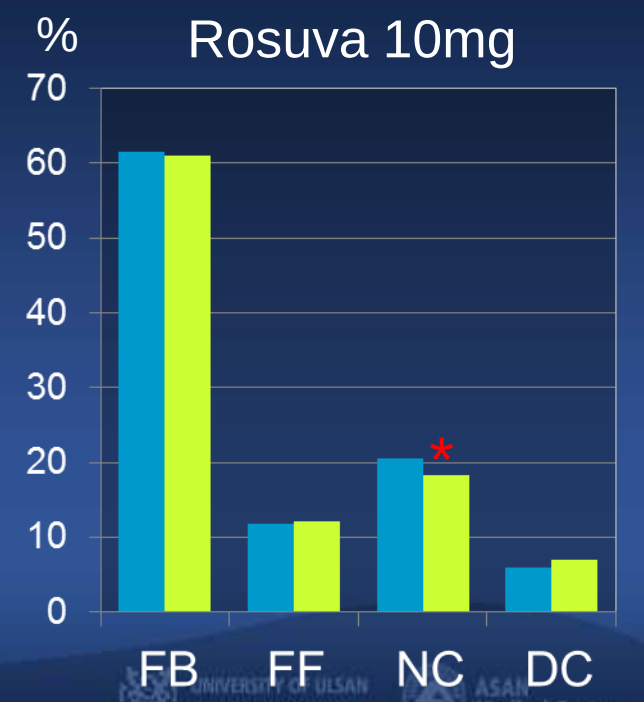


Changes in Plaque Types and Composition

At the index site	Baseline	Follow-up	p
VH-TCFA	123 (54.7%)	44 (19.6%)	
Thick-cap fibroatheroma	102 (45.3%)	159 (70.7%)	
Pathologic intimal thickening	0 (0%)	19 (8.4%)	<0.001
Fibrous	0 (0%)	3 (1.3%)	
Fibrocalcific	0 (0%)	0 (0%)	



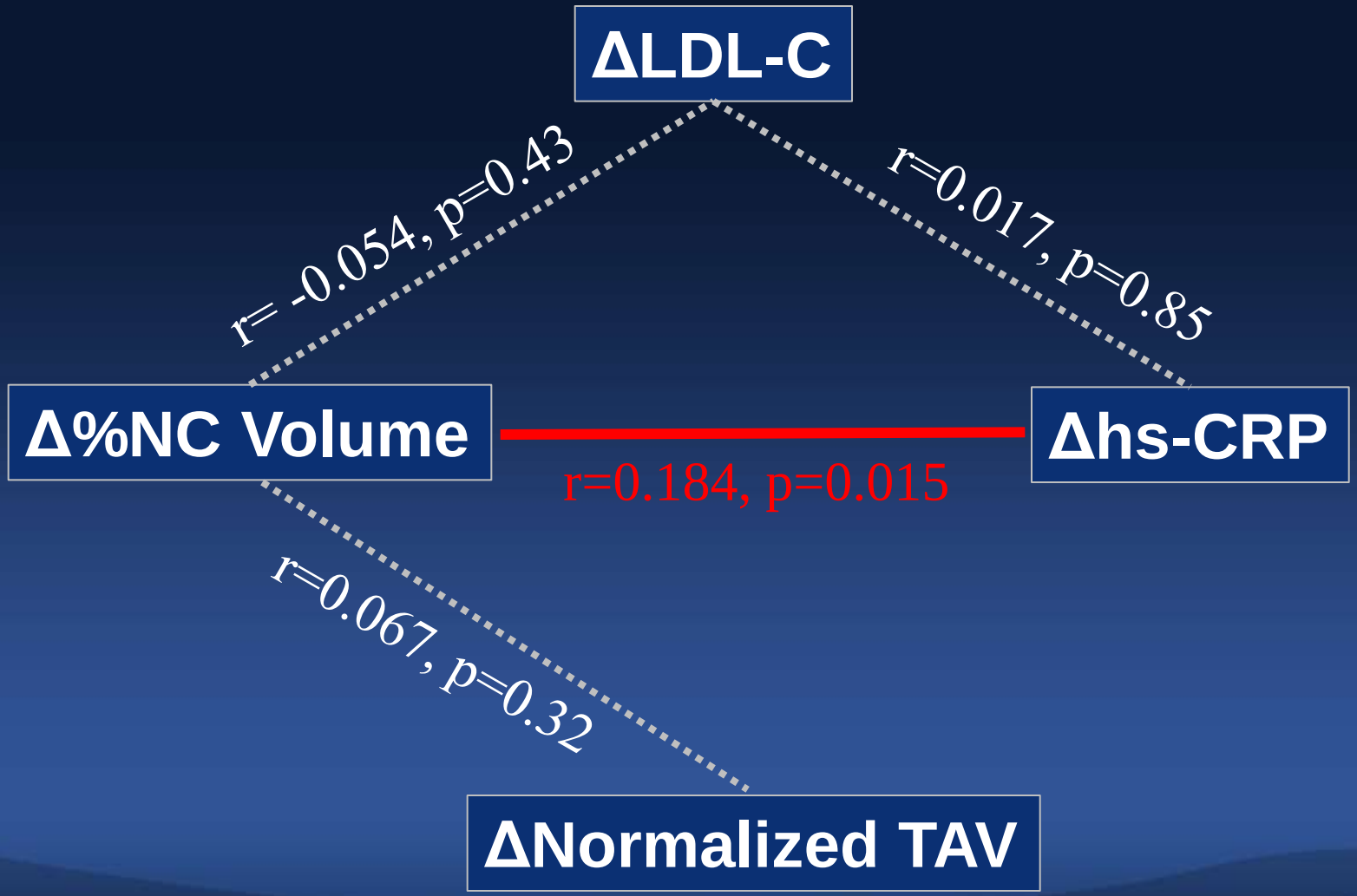




Changes in Atheroma and %NC Volume

	Overall	Rosuvastatin 40mg	Rosuvastatin 10mg	P
ΔNormalized TAV	**-12.6** mm^3/mm (-28.3 – 4.5)	-12.7 mm^3/mm (-29.0 – 3.3)	-12.4 mm^3/mm (-26.7 – 8.6)	0.72
ΔPAV	**-0.6%** (-3.8 – 2.0)	-0.6% (-3.7 – 2.0)	-0.3% (-3.9 – 2.1)	0.73
Frequency of normalized TAV reduction	**67.1%**	69.1%	63.0%	0.22
Frequency of %NC volume reduction	**62.7%**	64.5%	58.9%	0.25

Correlations Among Biological and Morphological Parameters



Multivariable Predictors of Change in %NC

Variables at baseline	Change %NC volume		
	Beta	SE	p value
Age	0.013	0.064	0.84
Male	1.212	1.308	0.35
Diabetes mellitus	1.741	1.342	0.19
Body mass index	β=0.37, 95% CI=0.05– 0.70		
ACS	-0.539	1.181	0.65
Statin-naïve	-1.205	1.854	0.52
Statin 10mg (vs. 40mg)	1.548	1.240	0.21
LDL cholesterol	-0.002	0.017	0.89
Hs-CRP	β=-3.16, 95% CI= -5.64– -0.69		
Normalized TAV	-0.009	0.008	0.25
%NC volume	β=-0.44, 95% CI= -0.68– -0.19		
TCFA at index site	-4.308	1.134	<0.001

Subgroup-specific Effects of Statins

Changes According to MLA, PB and VH-TCFA

	MLA		Plaque burden		VH-TCFA	
	≤4.0mm^2	>4.0mm^2	<70%	≥70%	No TCFA	TCFA
N	117 (52%)	108 (48%)	120 (53%)	105 (47%)	102 (45%)	123 (55%)
ΔNormalized TAV, mm^3/mm	-7.9 (-24.8–4.5)	-16.6 (-36.1–5.4)	-7.4 (-23.6–8.2)	-18.3 (-38.7–2.1)	-6.7 (-23.5– -6.8)	-13.9 (-32.9 – 3.9)
ΔPAV,%	-0.90% (-3.85–1.95)	0.29% (-3.70–2.10)	0.56% (-3.5– 2.5)	-1.81% * (-3.97–1.39)	0.25% (-3.9–2.31)	-0.98% (-3.77–1.74)
Δ%NC volume	-2.1% (-8.8 – 3.5)	-3.3% (-7.8 – 1.6)	-2.1% (-6.5 – 4.8)	-4.1% * (-11.0 – 1.2)	-1.1% (-6.2–3.7)	-4.2% # (-10.4–1.9)
Δ%NC, index	-11.5% (-18.7– -3.1)	-10.6% (-20.1– -3.6)	-9.9% (-18.2– -2.8)	-11.7% * (-21.7– -5.0)	-9.7% (-16– -3.7)	-13.2% # (-24.2– -3.0)

Clinical Outcomes at 12 Months

	Non-culprit related	Culprit-related
Patient No	225	175
12-month MACE	8 (3.6%)	4 (2.3%)
Death	0%	0%
Clinically-driven TLR	7 (3.1%)	3 (1.7%)
MI	1 (0.5%)	1 (0.6%) ST

No difference in non-culprit related MACE between Rosuvastatin 40mg vs. 10mg (3.9% vs. 2.7%, p=NS)

*MACEs defined as the composites of death, myocardial infarction, TLR

Limitations

- High drop-out rate of 28%
- Relatively short follow-up duration
- Insufficient sample size for detailed subgroup-specific analysis and for proving an incremental effect of LDL-C
- Inability of VH-IVUS to identify histologic TCFA (<65μm)
- Validation issue of VH-IVUS in serial follow-up study
- Lack of placebo group to compare natural history
- Do not apply these results to more advanced ischemia-producing lesions or non-FA containing lesions

Summary

- In fibroatheroma-containing target segment, rosuvastatin 10 mg and 40mg stabilized plaque vulnerability (decrease in %NC volume and TCFA) and reduced atheroma volumes
- At baseline a lower BMI, a higher hs-CRP and a larger %NC volume predicted more reduction in %NC volume
- Although high- (vs. moderate-) intensity statin more intensely reduced LDL-C, intravascular imaging effects were equivalent in Asian
- Considering the correlation between the changes in %NC volume and hs-CRP (not LDL-C), anti-inflammatory action may be the main mechanism of plaque stabilization