Integrated Biomarker and Imaging Study 3 (IBIS-3) to assess the ability of rosuvastatin to decrease necrotic core in coronary arteries

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ABSTRACT

Aims: Statins are highly effective in reducing major adverse clinical events, but the direct effects on coronary plaque composition remain debatable. Our aim was to mechanistically evaluate the treatment effect of high-intensity statin therapy on compositional coronary plaque changes.

Methods and results: The third Integrated Biomarker and Imaging Study (IBIS-3) was a prospective, investigator-initiated, single-center study. Serial radiofrequency intravascular ultrasound (RF-IVUS) measurements of a predefined non-stenotic segment in a non-culprit coronary artery were performed to evaluate the effect of rosuvastatin (intended dose: 40 mg daily) on necrotic core (NC) volume in patients with stable angina or acute coronary syndrome. Changes in lipid core burden index (LCBI) were evaluated through serial near-infrared spectroscopy (NIRS) imaging in a subset.

Serial RF-IVUS (and NIRS) data of a median segment of 41 (interquartile range: 32 to 49) mm were complete in 164 (103) patients. Follow-up measurements were performed at 6 and 12 months in 30 (26) and 134 (77) patients, respectively. Mean levels of low-density lipoprotein cholesterol decreased by 30%, from 2.49 mmol/l to 1.73 mmol/l at the end of follow-up. High-dose rosuvastatin therapy resulted in a non-significant (P=0.074) change of −1.4 mm^3 (95% confidence interval [CI]: −3.0 to 0.1) in NC volume during follow-up. The change in NC *percentage* of total plaque volume was −1.4% (95% CI:−2.4 to −0.4; P=0.006). A neutral effect was also observed on LCBI. Indications of significant regression of NC volume and LCBI in the highest baseline quartiles were observed, which should be cautiously regarded as hypothesis generating.

Conclusion: High-intensity rosuvastatin therapy during 1 year resulted in a neutral effect on NC and LCBI within non-stenotic, non-culprit coronary segments with a relatively low atheroma burden.

Keywords: Atherosclerosis, Statin, Radiofrequency Intravascular Ultrasonography, Near-Infrared Spectroscopy

INTRODUCTION

The presence of coronary plaque phenotypes with large necrotic core (NC) volumes is associated with a high incidence of major adverse cardiac events.(1-3) In the second Integrated Biomarker and Imaging Study (IBIS-2), the lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor darapladip – added to statins – halted coronary NC volume progression.(4) We now report IBIS-3, evaluating high-dose rosuvastatin to reduce coronary NC volume, assessed by radiofrequency intravascular ultrasound (RF-IVUS), and intracoronary cholesterol accumulation, assessed by near-infrared spectroscopy (NIRS).(5)

METHODS

The IBIS-3 study details have been published elsewhere.(5) Briefly, patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) were treated with high-dose (40 mg daily) rosuvastatin for 12 months. Near completion of the study, the protocol was amended to enable a treatment duration of 6 months.

IBIS-3 was approved by the Medical Ethics Committee of the Erasmus MC. Written informed consent was obtained from all participants.

Subsequent to the index CAG/PCI, RF-IVUS was performed in a non-culprit coronary segment with the Volcano Corporation Eagle-Eye catheter, and NIRS with the InfraReDx system, at a pullback speed of 0.5 mm/sec. Initially, the NIRS system was non-CE marked and several patients refused to provide consent for its use. Intracoronary imaging was repeated at the end of the scheduled rosuvastatin treatment period. RF-IVUS and NIRS images were analyzed offline by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands).

The primary endpoint was the change in NC volume. Secondary endpoints included the change in NC percentage, and the change in NIRS-derived lipid core burden index (LCBI) for the entire region of interest (ROI), and the 10- and 4 mm segments with the highest LCBI, the $LCBI_{max10mm}$ and $LCBI_{max4mm}$, respectively.

We aimed to enroll 300 patients. Assuming an attrition rate of 15%, the sample size was determined at 350 patients.(5) The actual attrition rate appeared to be approximately 30% (Figure 1). We therefore decided to terminate patient enrollment in June 2013.

The study design paper specified that treatment effects be tested with paired Student's t-tests.(5) However, because study endpoints had non-normal distributions, we decided to perform non-parametric statistics instead. Furthermore, we decided to square our data analysis methods with IBIS-4 study, including the use of linear mixed models and regression.(6) We report changes in serum cholesterol levels and study end-

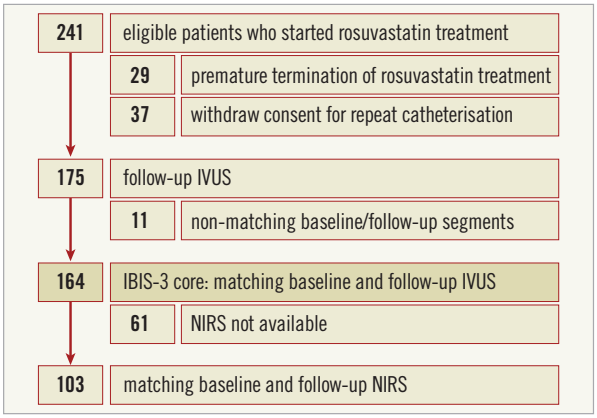


Figure 1. Study flowchart describing inclusion, attrition and the final IBIS-3 core of 164 patients with matching baseline and follow-up RF-IVUS. IVUS: radiofrequency intravascular ultrasound.

points as follow-up minus baseline values, and negative values indicate a decrease over time. All statistical tests were two-sided, and a P-value <0.05 was considered statistically significant.

RESULTS

Serial RF-IVUS was available in 164 patients, including 103 with serial NIRS (Figure 1). Table 1 shows baseline characteristics. Rosuvastatin was taken during a median of 372 (interquartile range: 357 to 395) days, with 90.9% of the patients being titrated to the maximum dose. At the time of the recatheterization, 92% of patients were on rosuvastatin 20-40 mg (online Table 1).

Mean LDL-C decreased by 30%, from 2.49 to 1.73 mmol/l, and HDL-C increased by 11%, from 1.11 to 1.23 mmol/l (Table 2; online Figure 1).

NC volume changed with −1.4 mm^3 (95% confidence interval [CI]: −3.0 to 0.1; Table 2; Figure 2). NC percentage of total plaque volume changed with −1.4% (95% CI:−2.4 to −0.4). The latter finding should be interpreted in conjunction with a modest, but significant rise in percent atheroma volume (PAV). The change in serum LDL-C levels was not associated with the change in coronary plaque characteristics (online Table 2; online Figure 2). Regression of NC volume was observed in patients within the highest baseline quartile (online Table 3; Figure 2).

Within the 103 patients with repeat NIRS, changes in LCBI were non-significant (Table 2; Figure 3). LCBI regression might be pronounced in the highest baseline quartile (online Table 3; Figure 3). There was no correlation between LDL-C change and LCBI

Table 1. Baseline characteristics.

	IBIS-3 core: patients with completed treatment phase and matching baseline and follow-up RF-IVUS (N=164)	Patients without matching follow-up RF-IVUS* (N=77)	*p*-value
Age, years	60.4 (55.3, 65.9)	57.5 (51.6, 66.0)	0.22
Male	84.1	79.2	0.35
Diabetes mellitus	20.7	20.8	0.99
Hypertension	64.2	54.6	0.15
Hypercholesterolaemia	63.6	61.8	0.80
LDL-c, mmol/l	2.41 (1.89, 3.00)	2.69 (1.99, 3.50)	0.030
HDL-c, mmol/l	1.09 (0.91, 1.30)	1.01 (0.91, 1.30)	0.43
Total cholesterol, mmol/l	3.99 (3.29, 4.61)	4.48 (3.60, 5.21)	0.024
Statin use¶	95.1	92.2	0.37
Current smoker	28.0	37.7	0.13
Positive family history	54.6	64.5	0.15
Previous MI	29.9	33.8	0.54
Previous PCI	36.0	40.3	0.52
Previous CABG	0.6	0	1.0
Previous stroke	9.1	13.0	0.36
Peripheral artery disease	4.3	13.0	0.014
History of renal insufficiency	3.7	6.5	0.33
History of heart failure	1.2	1.3	0.96
Indication for coronary angiography			0.009
STEMI	14.7	31.6	
NSTE ACS	26.8	22.4	
Stable angina	58.5	46.1	
Extent of coronary artery disease			0.97
No significant stenosis	3.7	3.9	
1-vessel disease	51.2	49.4	
2-vessel disease	39.0	39.0	
3-vessel disease	6.1	7.8	
PCI performed	89.0	87.0	0.65

Continuous data are presented as median (25th, 75th percentile) values. Categorical data are presented as percentages. *39 patients with premature termination of rosuvastatin treatment, 27 with withdrawal of consent for repeat catheterisation. An additional seven patients did complete the treatment phase and underwent repeat catheterisation, but had non-matching baseline/follow-up segments. ¶ 12 (63%) of the 19 statin naïve patients had no history of vascular disease, as compared to 51% of statin users. CABG: coronary artery bypass grafting; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; MI: myocardial infarction; NSTE ACS: non-ST-elevation acute coronary syndromes; PCI: percutaneous coronary intervention; RF-IVUS: radiofrequency intravascular ultrasound; STEMI: ST-elevation myocardial infarction

Table 2. Baseline and follow-up serum cholesterol and intracoronary imaging endpoints.

	Baseline		Follow-up		Change	
	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (95% CI)	*p*-value*
LDL-c, mmol/l	2.49 (0.85)	2.36 (1.92, 2.99)	1.73 (0.71)	1.60 (1.26, 2.01)	–0.76 (–0.91, –0.61)	<0.001
HDL-c mmol/l	1.11 (0.31)	1.07 (0.90, 1.29)	1.23 (0.37)	1.18 (0.97, 1.46)	0.12 (0.08, 0.16)	<0.001
Total cholesterol, mmol/l	4.11 (0.93)	4.0 (3.3, 4.6)	3.34 (0.87)	3.3 (2.7, 3.8)	–0.77 (–0.93, –0.61)	<0.001
External elastic membrane volume, mm^3	579.6 (278.0)	520.8 (376.6, 724.9)	577.0 (273.4)	518.3 (378.1, 715.6)	–2.7 (–9.4, 4.0)	0.42
Lumen volume, mm^3	335.4 (149.7)	314.8 (227.6, 409.1)	329.2 (145.8)	309.4 (225.5, 403.4)	–6.6 (–12.0, –1.2)	0.015
Atheroma volume, mm^3	243.9 (151.3)	204.0 (142.7, 304.8)	247.8 (148.6)	210.9 (145.4, 301.8)	3.9 (–0.2, 8.0)	0.064
Percent atheroma volume, %	40.7 (10.2)	41.5 (32.9, 48.8)	41.6 (9.7)	41.5 (33.8, 49.8)	1.0 (0.4, 1.5)	0.001
NC volume, mm^3	29.1 (31.9)	17.8 (7.3, 38.0)	27.7 (31.2)	19.2 (6.2, 35.1)	–1.4 (–3.0, 0.1)	0.074
DC volume, mm^3	13.0 (15.9)	7.9 (2.3, 17.4)	13.4 (16.9)	8.2 (2.2, 17.2)	0.4 (–0.4, 1.2)	0.31
FI volume, mm^3	71.1 (63.9)	51.3 (31.1, 93.4)	70.8 (61.8)	52.8 (30.6, 94.6)	–0.3 (–2.7, 2.2)	0.83
FF volume, mm^3	13.7 (14.6)	9.0 (3.9, 18.8)	15.7 (15.3)	10.9 (5.4, 22.1)	2.0 (0.6, 3.4)	0.005
NC percentage, %	20.2 (8.2)	20.0 (15.2, 25.0)	18.9 (7.3)	19.5 (14.6, 24.0)	–1.4 (–2.4, –0.4)	0.006
DC percentage, %	9.0 (5.6)	8.4 (4.6, 12.7)	9.1 (5.9)	8.4 (4.4, 13.1)	0.0 (–0.6, 0.7)	0.85
FI percentage, %	60.0 (11.0)	60.5 (52.6, 66.8)	58.7 (11.0)	60.7 (50.6, 66.2)	–1.2 (–2.6, 0.2)	0.076
FF percentage, %	10.7 (5.2)	9.9 (7.5, 13.7)	13.2 (9.9)	11.8 (8.5, 15.6)	2.6 (1.1, 4.1)	0.001
LCBI, full region of interest	44.9 (51.1)	33.0 (6.0, 67.0)	46.1 (43.2)	35.0 (8.0, 72.0)	1.2 (–8.5, 11.0)	0.80
LCBImax10mm	127.8 (121.7)	107.0 (25.0, 197.0)	130.5 (114.0)	109.0 (30.0, 194.0)	2.7 (–16.9, 22.2)	0.79
LCBImax4mm	201.9 (163.8)	182.5 (60.0, 319.0)	206.8 (154.5)	192.0 (72.0, 323.0)	4.9 (–21.7, 31.4)	0.72

*based on linear mixed models (patient as random intercept) to test if change is different from 0. CI: confidence interval; DC: dense calcium tissue; FF: fibro-fatty tissue; FI: fibrous tissue; HDL-c: high-density lipoprotein cholesterol; IQR: interquartile range; LCBI: lipid core burden index; LDL-c: low-density lipoprotein cholesterol; NC: necrotic core tissue; SD: standard deviation

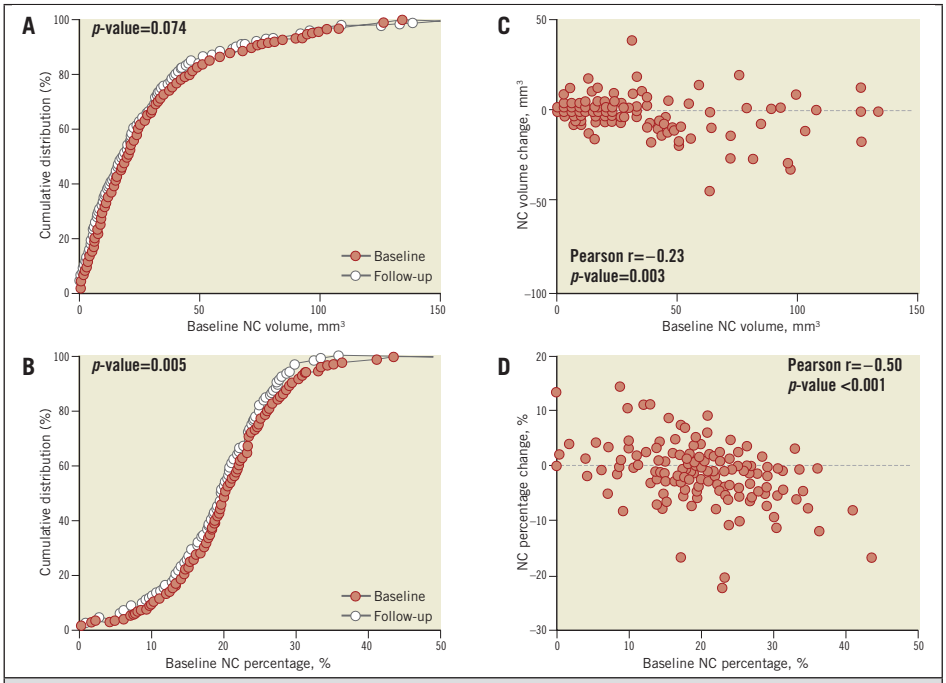


Figure 2. Necrotic core volume and percentage at baseline and follow-up.
High-intensity rosuvastatin therapy led to a neutral effect on NC volume (A) and a significant decrease in NC percentage (B). The highest reductions were observed in those patients with a relatively high necrotic core burden at baseline. Panel C depicts the change of NC under high-intensity rosuvstatine therapy against the baseline NC volume. Panel D illustrates the same for NC percentage.

change (online Table 2; online Figure 2). LCBI change was similar in statin-naïve patients and previous statin users.

All effects were similar in patients with repeat imaging at 6 and 12 months (online Tables 4-6).

DISCUSSION

High-intensity rosuvastatin therapy resulted in a neutral effect on NC and LCBI within non-stenotic coronary segments with a relatively low baseline atheroma burden. IBIS-2 showed a stabilization of NC volume by darapladib, with 91% of patients on statin therapy.(4) IBIS-3 suggests that NC stabilization might be possible with a potent statin alone.

Our findings concur with a meta-analysis of 17 studies involving 2171 patients on at least six different statins, which showed that longer-duration and higher-intensity statin therapy may result in plaque volume regression, but not in a significant NC reduction.

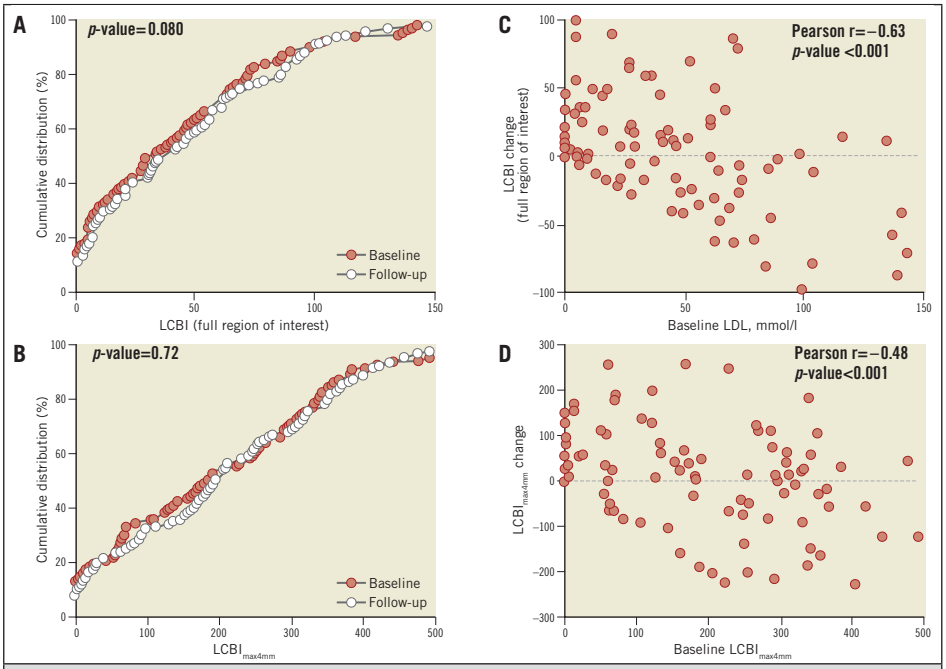


Figure 3. LCBI at baseline and follow-up.
The effect of high-intensity rosuvastatin therapy on LCBI of the full region of interest (A) and the $LCBI_{max4mm}$ (B). Panels C and D indicate that the degree of LCBI regression might be dependent on the baseline LCBI. LCBI: lipid core burden index; $LCBI_{max4mm}$: the 4 mm segment with the highest LCBI.

(7) Lack of change in NC burden after high-intensity statin therapy was also observed in SATURN (8) and in IBIS-4, which studied STEMI patients.(6)

The YELLOW trial demonstrated a significant LCBI reduction in 44 patients after 6-8 weeks of high-intensity rosuvastatin therapy.(9) In the comparator group of 43 patients, who were kept on their 'regular' statin, LCBI remained unchanged. However, YELLOW evaluated the effect of rosuvastatin on untreated obstructive coronary lesions with a fractional flow reserve < 0.8. In contrast, we studied non-flow-limiting coronary segments with a low median LCBI of 33 (versus 95-132 in YELLOW). As a consequence, high-intensity statin therapy in IBIS-3 only had a limited substrate with respect to regression of LCBI. Still, our observation of a significant LCBI reduction in patients with high baseline values might be relevant, since they are at increased risk of adverse cardiac events.(10)

The fact that changes in NC and LCBI were not correlated to changes in serum LDL-C levels may support the abundance of data on the pleiotropic effects of statins that are not directly related to serum lipid levels.(11) We only studied the effect of rosuvastatin on plaque composition in relation to its effect on LDL-C. However, recent studies suggest that LDL-C will not be atherogenic until it becomes oxidized in the arterial wall.(11)

IBIS-3 was an uncontrolled, observational study, similar to IBIS-4 and ASTEROID.(6,12) A disadvantage of such approach is that true treatment effects cannot be distinguished from 'regression to the mean'. In our study, the most pronounced regression of plaque components occurred within the highest baseline quartiles, which might be an expected and logical consequence of a real treatment effect. On the other hand, the simultaneous increase in most plaque parameters that was observed in the lowest baseline quartiles is suggestive for at least a component of regression to the mean.

IBIS-3 was designed to be embedded in our routine clinical practice, which we consider important for external validity. Consequently, however, the IBIS-3 patients were somewhat older and had more comorbidities than observed in similar studies with repeat imaging,(12,13) which may explain their higher than expected drop-out rate. We enrolled 164 of 300 planned patients with repeat IVUS. The observed 1.4 mm^3 NC reduction was smaller than anticipated, but the standard deviation was also smaller (10.0 versus 13.9 mm^3). Consequently, the power of IBIS-3 was still high enough (90%) to declare the anticipated 2.5 mm^3 NC reduction statistically significant, but too small (50%) with regard to the observed effect.

Conclusion

The IBIS-3 study, a prospective, mechanistic, single-arm, open-label study designed to evaluate the treatment effect of high-intensity rosuvastatin therapy, demonstrated a neutral effect on NC volume in a non-culprit coronary artery segment without significant luminal narrowing. Indications of regression of NC percentage and NC volume and LCBI in the highest baseline quartiles should only be cautiously regarded as hypothesis generating.

FUNDING

IBIS-3 was sponsored by AstraZeneca (Wilmington, Delaware, USA), by InfraredX (Burlington, Massachusetts, USA) and Volcano Corporation (San Diego, California, USA). The study was initiated by the authors, and was designed, conducted, interpreted, and reported independently of these sponsors.

REFERENCES

1. Stone GW, Maehara A, Lansky AJ, et al. A Prospective Natural-History Study of Coronary Atherosclerosis. N Engl J Med. 2011;364:226-235.
2. Cheng JM, Garcia-Garcia HM, Boer SPM de, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. Eur Heart J. 2014;35:639-647.
3. Calvert PA, Obaid DR, O'Sullivan M, et al. Association Between IVUS Findings and Adverse Outcomes in Patients With Coronary Artery Disease: The VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. JACC: Cardiovascular Imaging. 2011;4:894-901.
4. Serruys PW, García-García HM, Buszman P, et al. Integrated Biomarker and Imaging Study-2 Investigators. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. Circulation. 2008;118:1172-1182.
5. Simsek C, Garcia-Garcia HM, Geuns R-J van, et al. The ability of high dose rosuvastatin to improve plaque composition in non-intervened coronary arteries: rationale and design of the Integrated Biomarker and Imaging Study-3 (IBIS-3). EuroIntervention. 2012;8:235-241.
6. Räber L, Taniwaki M, Zaugg S, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. Eur Heart J. 2015;36:490-500.
7. Tian J, Gu X, Sun Y, et al. Effect of statin therapy on the progression of coronary atherosclerosis. BMC Cardiovascular Disorders. 2012;12:70.
8. Puri R, Libby P, Nissen SE, et al. Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: insights from SATURN. Eur Heart J Cardiovasc Imaging. 2014; 15:380-388.
9. Kini AS, Baber U, Kovacic JC, et al. Changes in Plaque Lipid Content After Short-Term Intensive Versus Standard Statin Therapy The YELLOW Trial. J Am Coll Cardiol. 2013;62:21-29.
10. Oemrawsingh RM, Cheng JM, García-García HM, et al. Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease. J Am Coll Cardiol. 2014;64:2510-2518.
11. Burchardt P, Zurawski J, Zuchowski B, et al. Low-density lipoprotein, its susceptibility to oxidation and the role of lipoprotein-associated phospholipase A2 and carboxyl ester lipase lipases in atherosclerotic plaque formation. Arch Med Sci. 2013;9:151-8.
12. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006;295:1556-1565.
13. Nicholls SJ, Hsu A, Wolski K et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol. 2010;55:2399-2407.

SUPPLEMENTAL DATA

Online Table 1. Rosuvastatin treatment.		
Days to start treatment		23 (18, 31)
Starting dose, mg	5	0.6
	10	84.2
	20	14.6
	40	0.6
Maximum dose, mg	20	9.1
	40	90.9
Days to maximum dose		52 (45, 62)
Total duration of rosuvastatin use, days		372 (357, 395)
Dose at day of repeat catheterisation, mg	rosuvastatin discontinuation	4.9
	5	0.6
	10	2.4
	20	24.4
	40	67.7

Continuous data are presented as median (25th, 75th percentile) values. Categorical data are presented as percentages.

Online Table 2. Study endpoints by quartiles of LDL cholesterol change.					
Study endpoint	Δ LDL-c<−1.33	−1.33≤Δ LDL-c <−0.68	−0.68≤Δ LDL-c <−0.24	−0.24≤Δ LDL-c	*p*-value for trend*
Atheroma volume, mm^3	7.51 (−1.82, 16.8)	1.50 (−6.58, 9.58)	−1.77 (−9.92, 6.39)	10.5 (1.98, 19.0)	0.15
Percent atheroma volume, %	1.40 (0.20, 2.60)	0.51 (−0.59, 1.61)	1.07 (−0.04, 2.17)	1.23 (0.04, 2.43)	0.38
NC volume, mm^3	−0.04 (−2.21, 2.14)	−1.58 (−4.02, 0.87)	−1.77 (−4.11, 0.58)	−1.50 (−6.59, 3.59)	0.71
NC percentage, %	0.53 (−1.45, 2.50)	−0.94 (−2.02, 0.15)	−1.89 (−3.34, −0.44)	−2.83 (−5.75, 0.08)	0.018
LCBI, full region of interest	−13.5 (−27.0, −0.06)	15.4 (−1.10, 31.9)	7.29 (−10.7, 25.3)	−4.0 (−33.7, 25.6)	0.24
$LCBI_{max4mm}$	−28.2 (−71.2, 14.7)	46.3 (0.58, 91.9)	9.29 (−52.5, 71.1)	0.04 (−63.7, 63.8)	0.33

*based on a linear trend test across the four quartiles of Δ LDL-c in a linear regression model, with adjustment for age, sex, diabetes, smoking, previous use of statins, and time to recatheterisation. LCBI: lipid core burden index; $LCBI_{max4mm}$: 4 mm segment with the highest LCBI; Δ LDL-c: change in low-density lipoprotein cholesterol (follow-up – baseline); the 25^{th}, 50^{th} and 75th percentile of the Δ LDL-c distribution were −51, −26 and −9 mg/dl, respectively; NC: necrotic core

Online Table 3. Study endpoints by quartiles of baseline values.

Study endpoint	25th, 50th, 75th percentiles of baseline values	Mean change (95% CI)				*p*-value for trend¶
		Baseline Q1	Baseline Q2	Baseline Q3	Baseline Q4	
LDL-c, mmol/l	1.92, 2.36, 2.99	−0.24 (−0.43, −0.06)	−0.37 (−0.60, −0.14)	−0.62 (−0.87, −0.37)	−1.82 (−2.06, −1.57)	<0.001
Atheroma volume, mm^3	143, 204, 305	11.0 (5.83, 16.3)	4.00 (−3.79, 11.8)	2.01 (−3.75, 7.77)	−1.57 (−14.5, 11.4)	0.19
Percent atheroma volume*, %	32.9, 41.5, 48.8	2.35 (1.28, 3.42)	1.69 (0.58, 2.79)	0.19 (−0.84, 1.23)	−0.44 (−1.58, 0.70)	0.001
NC volume, mm^3	7.3, 17.8, 38.0	0.54 (−0.35, 1.42)	−0.15 (−1.97, 1.66)	1.44 (−1.15, 4.03)	−7.45 (−12.4, −2.46)	<0.001
NC percentage, %	15.2, 20.0, 25.0	1.67 (−0.32, 3.67)	−0.08 (−1.48, 1.32)	−2.38 (−4.20, −0.57)	−4.61 (−6.69, −2.51)	<0.001
LCBI, full region of interest	6, 33, 67	19.3 (7.7, 30.9)	16.3 (4.4, 28.2)	1.81 (−12.6, 16.2)	−31.7 (−61.7, −1.7)	0.001
LCBImax4mm	60, 183, 319	83.6 (40.6, 126.6)	46.6 (0.2, 93.0)	−26.1 (−76.0, 23.7)	−82.7 (−138.7, −26.7)	<0.001

¶ based on a linear trend test across the four quartiles in a linear regression model, with adjustment for age, sex, diabetes, smoking, previous use of statins, and time to recatheterisation. * None of the interrogated segments represented a percent atheroma volume ≥70%. CI: confidence interval; LCBI: lipid core burden index; $LCBI_{max4mm}$: 4 mm segment with the highest LCBI; LDL-c: low-density lipoprotein cholesterol; NC: necrotic core

Online Table 4. Serial cholesterol measurements.

	Baseline		Follow-up		Change		
	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (95% CI)	*p*-value¶	*p*-value‡
Patients with follow-up IVUS at 6 months (n=30)							
LDL-c, mmol/l	2.34 (0.75)	2.28 (1.92, 2.92)	1.67 (0.56)	1.70 (1.31, 1.88)	−0.76 (−1.00, −0.52)	<0.001	0.98
HDL-c, mmol/l	1.11 (0.31)	1.09 (0.86, 1.31)	1.21 (0.39)	1.13 (0.92, 1.58)	0.10 (0.04, 0.16)	0.004	0.52
Total cholesterol, mmol/l	3.89 (0.89)	3.7 (3.2, 4.5)	3.21 (0.73)	3.3 (2.8, 3.6)	−0.67 (−0.94, −0.40)	<0.001	0.47
Patients with follow-up IVUS at 12 months (n=134) *							
LDL-c, mmol/l	2.51 (0.87)	2.37 (1.91, 3.00)	1.74 (0.74)	1.59 (1.22, 2.02)	−0.77 (−0.94, −0.60)	<0.001	
HDL-c, mmol/l	1.11 (0.31)	1.07 (0.91, 1.28)	1.24 (0.37)	1.19 (0.98, 1.44)	0.13 (0.08, 0.18)	<0.001	
Total cholesterol, mmol/l	4.16 (0.93)	4.0 (3.5, 4.6)	3.36 (0.89)	3.2 (2.7, 3.8)	−0.80 (−0.99, 0.61)	<0.001	
All patients (N=164) *							
LDL-c, mmol/l	2.49 (0.85)	2.36 (1.92, 2.99)	1.73 (0.71)	1.60 (1.26, 2.01)	−0.76 (−0.91, −0.61)	<0.001	
HDL-c, mmol/l	1.11 (0.31)	1.07 (0.90, 1.29)	1.23 (0.37)	1.18 (0.97, 1.46)	0.12 (0.08, 0.16)	<0.001	
Total cholesterol, mmol/l	4.11 (0.93)	4.0 (3.3, 4.6)	3.34 (0.87)	3.3 (2.7, 3.8)	−0.77 (−0.93, −0.61)	<0.001	

* Six patients had missing baseline and/or follow-up measurements. ¶ based on linear mixed models (patient as random intercept) to test if change is different from 0. ‡based on two-sample Student's t-tests (equal variances not assumed) for the difference in change between patients with 6 versus 12 months of follow-up. CI: confidence interval; HDL-c: high-density lipoprotein cholesterol; IQR: interquartile range; LDL-c: low-density lipoprotein cholesterol; SD: standard deviation

Online Table 5. Serial intravascular ultrasound measurements.

	Baseline		Follow-up		Change		
	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (95% CI)	*p*-value¶	*p*-value‡
Patients with follow-up IVUS at 6 months (n=30)							
External elastic membrane volume, mm^3	560.4 (278.2)	495.7 (345.7, 724.9)	548.1 (255.7)	510.8 (344.1, 713.2)	−12.3 (−25.8, 1.2)	0.083	0.42
Lumen volume, mm^3	321.4 (150.6)	280.6 (192.7, 438.8)	316.3 (139.7)	292.1 (196.6, 407.8)	−5.1 (−16.0, 5.8)	0.37	0.015
Atheroma volume, mm^3	239.1 (144.4)	200.2 (137.7, 304.1)	231.8 (132.4)	193.6 (139.6, 287.2)	−7.2 (−16.5, 2.0)	0.12	0.010
Percent atheroma volume, %	41.7 (8.3)	43.6 (33.3, 47.0)	41.5 (8.5)	42.9 (33.2, 48.9)	−0.2 (−1.2, 0.8)	0.68	0.018
NC volume, mm^3	23.2 (25.6)	16.2 (8.7, 35.3)	21.5 (25.5)	13.8 (5.7, 31.4)	−1.7 (−4.1, 0.8)	0.18	0.84
DC volume, mm^3	9.1 (9.2)	6.6 (2.0, 12.2)	8.9 (8.8)	6.3 (2.2, 12.3)	−0.2 (−1.2, 0.9)	0.75	0.32
FI volume, mm^3	71.4 (66.4)	50.1 (32.7, 87.7)	66.4 (57.9)	53.1 (28.7, 82.6)	−5.0 (−10.2, 0.2)	0.058	0.051
FF volume, mm^3	16.0 (16.8)	10.1 (4.5, 21.8)	15.8 (17.8)	9.7 (5.4, 21.8)	−0.3 (−3.8, 3.3)	0.88	0.15
NC percentage, %	18.1 (5.6)	18.6 (14.9, 22.4)	17.2 (6.1)	18.1 (13.3, 21.0)	−0.9 (−2.4, 0.6)	0.22	0.52
DC percentage, %	7.7 (4.5)	6.7 (4.2, 10.2)	7.8 (4.4)	7.2 (4.8, 10.8)	0.0 (−0.8, 0.9)	0.92	0.99
FI percentage, %	61.6 (8.9)	63.9 (57.9, 68.0)	61.8 (9.0)	63.3 (56.4, 66.7)	0.3 (−1.5, 2.0)	0.76	0.13
FF percentage, %	12.6 (4.5)	12.9 (8.9, 15.4)	13.2 (5.7)	12.6 (9.9, 15.5)	0.6 (−1.0, 2.2)	0.44	0.048
Patients with follow-up IVUS at 12 months (n=134)							
External elastic membrane volume, mm^3	583.9 (278.8)	527.6 (384.2, 754.1)	583.5 (277.7)	521.5 (381.7, 718.1)	−0.6 (−8.1, 6.9)	0.87	
Lumen volume, mm^3	338.5 (149.9)	325.5 (231.8, 409.1)	332.1 (147.5)	316.1 (227.3, 398.9)	−7.0 (−13.0, −1.0)	0.025	
Atheroma volume, mm^3	245.0 (153.3)	204.0 (144.0, 304.8)	251.4 (152.2)	214.0 (152.2, 312.2)	6.4 (1.8, 10.9)	0.006	
Percent atheroma volume, %	40.5 (10.7)	40.5 (32.5, 49.0)	41.7 (10.0)	41.4 (33.9, 50.1)	1.2 (0.6, 1.9)	<0.001	
NC volume, mm^3	30.5 (33.1)	19.9 (7.2, 43.3)	29.1 (32.3)	20.1 (6.3, 37.1)	−1.4 (−3.2, 0.5)	0.14	
DC volume, mm^3	13.9 (17.0)	7.9 (2.4, 19.3)	14.4 (18.1)	8.7 (2.2, 18.1)	0.5 (−0.4, 1.5)	0.27	
FI volume, mm^3	71.1 (63.6)	51.3 (30.9, 94.2)	71.8 (62.8)	52.8 (31.0, 95.0)	0.8 (−2.0, 3.6)	0.57	
FF volume, mm^3	13.2 (14.1)	8.5 (3.5, 17.8)	15.7 (14.7)	10.9 (5.4, 23.3)	2.5 (1.0, 4.0)	0.001	
NC percentage, % *	20.7 (8.7)	20.8 (16.2, 25.7)	19.3 (7.6)	20.1 (15.2, 24.4)	−1.5 (−2.6, −0.4)	0.012	

Online Table 5 *(continued)*

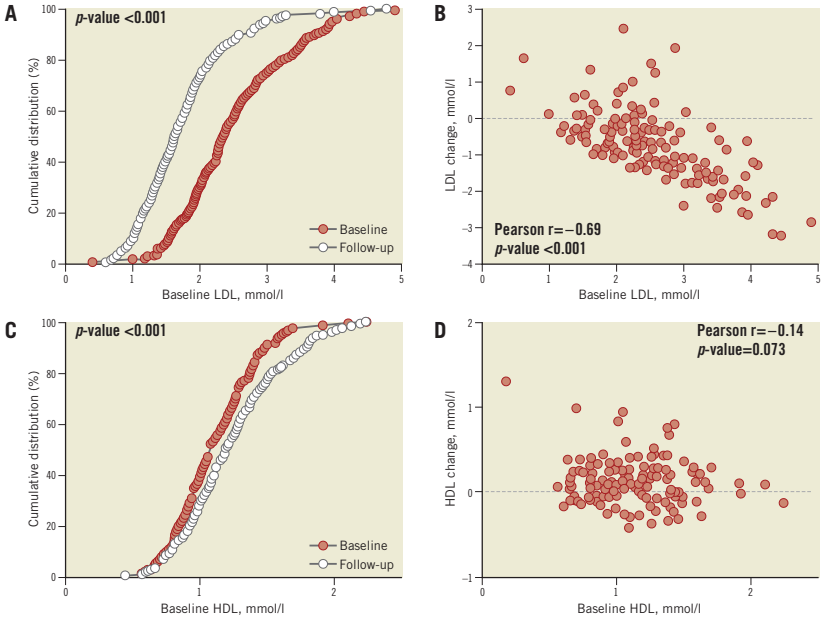
	Baseline		Follow-up		Change		
	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (95% CI)	*p*-value¶	*p*-value‡
DC percentage, % *	9.3 (5.8)	8.7 (4.9, 13.0)	9.5 (6.2)	8.9 (4.2, 13.4)	0.1 (−0.8, 0.9)	0.86	
FI percentage, % *	59.7 (11.4)	59.4 (51.9, 66.5)	58.0 (11.3)	59.2 (50.4, 65.5)	−1.5 (−3.2, 0.1)	0.058	
FF percentage, % *	10.3 (5.3)	9.4 (7.3, 13.0)	13.2 (10.6)	11.8 (8.1, 15.6)	3.0 (1.2, 4.8)	0.002	
All patients (N=164)							
Atheroma volume, mm^3	243.9 (151.3)	204.0 (142.7, 304.8)	247.8 (148.6)	210.9 (145.4, 301.8)	3.9 (−0.2, 8.0)	0.064	
Percent atheroma volume, %	40.7 (10.2)	41.5 (32.9, 48.8)	41.6 (9.7)	41.5 (33.8, 49.8)	1.0 (0.4, 1.5)	0.001	
NC volume, mm^3	29.1 (31.9)	17.8 (7.3, 38.0)	27.7 (31.2)	19.2 (6.2, 35.1)	−1.4 (−3.0, 0.1)	0.074	
DC volume, mm^3	13.0 (15.9)	7.9 (2.3, 17.4)	13.4 (16.9)	8.2 (2.2, 17.2)	0.4 (−0.4, 1.2)	0.31	
FI volume, mm^3	71.1 (63.9)	51.3 (31.1, 93.4)	70.8 (61.8)	52.8 (30.6, 94.6)	−0.3 (−2.7, 2.2)	0.83	
FF volume, mm^3	13.7 (14.6)	9.0 (3.9, 18.8)	15.7 (15.3)	10.9 (5.4, 22.1)	2.0 (0.6, 3.4)	0.005	
NC percentage, % *	20.2 (8.2)	20.0 (15.2, 25.0)	18.9 (7.3)	19.5 (14.6, 24.0)	−1.4 (−2.4, −0.4)	0.006	
DC percentage, % *	9.0 (5.6)	8.4 (4.6, 12.7)	9.1 (5.9)	8.4 (4.4, 13.1)	0.0 (−0.6, 0.7)	0.85	
FI percentage, % *	60.0 (11.0)	60.5 (52.6, 66.8)	58.7 (11.0)	60.7 (50.6, 66.2)	−1.2 (−2.6, 0.2)	0.076	
FF percentage, % *	10.7 (5.2)	9.9 (7.5, 13.7)	13.2 (9.9)	11.8 (8.5, 15.6)	2.6 (1.1, 4.1)	0.001	

*One patient had missing follow-up measurements. ¶ based on linear mixed models (patient as random intercept) to test if change is different from 0. ‡ based on two-sample Student's t-tests (equal variances not assumed) for the difference in change between patients with 6 versus 12 months of follow-up. CI: confidence interval; DC: dense calcium tissue; FF: fibro-fatty tissue;
FI: fibrous tissue; IQR: interquartile range; NC: necrotic core tissue; SD: standard deviation

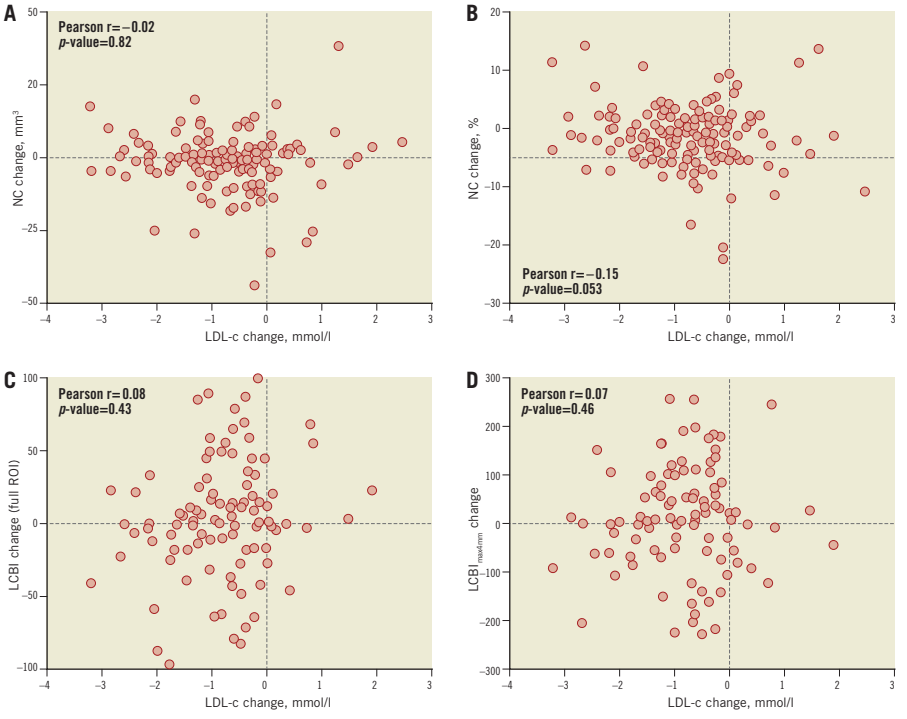
Online Table 6. Serial near-infrared spectroscopy measurements.

	Baseline		Follow-up		Change		
	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (95% CI)	*p*-value¶	*p*-value‡
Patients with follow-up NIRS at 6 months (n=26)							
LCBI, full region of interest	48.6 (42.5)	40.0 (10.0, 67.0)	45.0 (39.8)	40.0 (7.0, 72.0)	−3.6 (−22.2, 15.1)	0.70	0.55
LCBI, worst 10 mm	141.9 (123.0)	147.0 (29.0, 201.0)	131.2 (111.2)	128.5 (29.0, 188.0)	−10.7 (−54.9, 33.4)	0.62	0.46
LCBI, worst 4 mm	220.2 (157.4)	242.5 (69.0, 310.0)	206.5 (157.7)	201.0 (60.0, 305.0)	−13.7 (−68.3, 40.9)	0.61	0.42
Patients with follow-up NIRS at 12 months (n=77)							
LCBI, full region of interest	43.6 (53.9)	28.0 (5.0, 63.0)	46.5 (44.6)	35.0 (9.0, 66.0)	2.8 (−8.8, 14.5)	0.63	
LCBI, worst 10 mm*	123.0 (121.7)	98.0 (21.5, 189.0)	130.2 (115.7)	104.5 (36.5, 196.0)	7.2 (−14.8, 29.3)	0.52	
LCBI, worst 4 mm*	195.6 (166.5)	174.5 (52.5, 324.0)	206.9 (154.5)	190.0 (77.0, 324.0)	11.2 (−19.7, 42.2)	0.47	
All patients (N=103)							
LCBI, full region of interest	44.9 (51.1)	33.0 (6.0, 67.0)	46.1 (43.2)	35.0 (8.0, 72.0)	1.2 (−8.5, 11.0)	0.80	
LCBI, worst 10 mm*	127.8 (121.7)	107.0 (25.0, 197.0)	130.5 (114.0)	109.0 (30.0, 194.0)	2.7 (−16.9, 22.2)	0.79	
LCBI, worst 4 mm*	201.9 (163.8)	182.5 (60.0, 319.0)	206.8 (154.5)	192.0 (72.0, 323.0)	4.9 (−21.7, 31.4)	0.72	

*One patient had missing follow-up measurements. ¶based on linear mixed models (patient as random intercept) to test if change is different from 0. ‡ based on two-sample Student's t-tests ssumed) for the difference in change between patients with 6 versus 12 months of follow-up. CI: confidence interval; IQR: interquartile range; LCBI: lipid core burden index; SD: standard deviation



Online Figure 1. Serum cholesterol levels at baseline and follow-up.
High-intensity rosuvastatin therapy during a median follow-up of 372 days resulted in a significant decrease in serum LDL-c (A) and increase in HDL-c levels (C), despite the fact that 95% of the patients were already on standard-of-care statin therapy at baseline. The degree of reduction in LDL-c was related to the baseline LDL-c level (B). Such a correlation was not observed with respect to HDL-c (D). HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol



Online Figure 2. Change in LDL-c in relation to change in necrotic core and LCBI.
Changes in NC and LCBI were independent of changes in LDL levels under rosuvastatin therapy. A) NC volume; B) NC percentage; C) Full region of interest; D) $LCBI_{max4mm}$. LCBI: lipid core burden index; $LCBI_{max4mm}$: the 4 mm segment with the highest LCBI; LDL-c: low-density lipoprotein cholesterol; NC: necrotic core