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Imaging

Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study

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Aim The effect of long-term high-intensity statin therapy on coronary atherosclerosis among patients with acute ST-segment elevation myocardial infarction (STEMI) is unknown. The aim of this study was to quantify the impact of high-intensity statin therapy on plaque burden, composition, and phenotype in non-infarct-related arteries of STEMI patients undergoing primary percutaneous coronary intervention (PCI).

Methods and results Between September 2009 and January 2011, 103 STEMI patients underwent intravascular ultrasonography (IVUS) and radiofrequency ultrasonography (RF-IVUS) of the two non-infarct-related epicardial coronary arteries (non-IRA) after successful primary PCI. Patients were treated with high-intensity rosuvastatin (40 mg/day) throughout 13 months and serial intracoronary imaging with the analysis of matched segments was available for 82 patients with 146 non-IRA. The primary IVUS end-point was the change in per cent atheroma volume (PAV). After 13 months, low-density lipoprotein cholesterol (LDL-C) had decreased from a median of 3.29 to 1.89 mmol/L ($P < 0.001$), and high-density lipoprotein cholesterol (HDL-C) levels had increased from 1.10 to 1.20 mmol/L ($P < 0.001$). PAV of the non-IRA decreased by −0.9% (95% CI: −1.56 to −0.25, $P = 0.007$). Patients with regression in at least one non-IRA were more common (74%) than those without (26%). Per cent necrotic core remained unchanged (−0.05%, 95% CI: −1.05 to 0.96%, $P = 0.93$) as did the number of RF-IVUS defined thin cap fibroatheromas (124 vs. 116, $P = 0.15$).

Conclusion High-intensity rosuvastatin therapy over 13 months is associated with regression of coronary atherosclerosis in non-infarct-related arteries without changes in RF-IVUS defined necrotic core or plaque phenotype among STEMI patients.

Keywords Intravascular Ultrasound • Radiofrequency • Statin • Atherosclerosis • ST-elevation myocardial infarction

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Introduction

Coronary atherosclerosis is a chronic inflammatory disease, which may go undetected for decades before it gives rise to disease manifestations such as stable, obstructive coronary artery disease, or acute coronary syndromes (ACS).[1] Statin therapy effectively reduces cardiovascular events in the setting of primary and secondary prevention, with a particular benefit occurring early after treatment initiation in ACS patients.[2] High-intensity rosuvastatin therapy has been shown to more effectively lower LDL-C and increase HDL-C compared with other statins.[3] Insights from intracoronary imaging studies suggest that statins result in atheroma regression in patients with stable, non-obstructive coronary artery disease.[4,5] Patients with STEMI are at high risk for recurrent atherothrombotic events, which is related to multifocal disease with a high prevalence of vulnerable plaques,[6,7] typically extending beyond the culprit site due to widespread inflammation in other plaques including increased protease activity.[8] The primary hypothesis of the present study was that coronary atherosclerosis regression can be achieved in the presence of the high-intensity rosuvastatin therapy (40 mg daily) in the proximal segments of non-infarct-related arteries (IRA) within 13 months.

Due to the importance of plaque phenotype for future cardiovascular events, there is an interest in the study of changes in plaque composition in response to high-intensity statin therapy. The use of radiofrequency intravascular ultrasonography (RF-IVUS) has been validated for the detection of a necrotic core[9] and plaque characterization[10] based on *ex vivo* histological analyses, providing the means for serial *in vivo* assessment of plaque composition and phenotype. Therefore, the secondary hypothesis of this study was that high-intensity rosuvastatin therapy results in a reduction of RF-IVUS defined necrotic core and a decrease in the frequency RF-IVUS defined thin cap fibroatheromas (TCFA).

Methods

Study design

Integrated biomarker imaging study (IBIS 4) (NCT00962416) is a prospective cohort study nested into the COMFORTABLE-AMI, a trial which compared the safety and efficacy of biolimus-eluting stents with bare metal stents in 1161 STEMI patients undergoing primary PCI at 11 international centres.[11,12] A total of 103 patients were enrolled in this intracoronary imaging study at five predefined centres using serial IVUS and RF-IVUS investigations to quantify changes in atherosclerotic plaque characteristics in non-IRA under long-term high-intensity statin therapy. Patients enrolled in the clinical trial were screened for clinical and anatomic feasibility to undergo the serial intracoronary imaging protocol. All the patients provided written informed consent, and the study was approved by the institutional review boards of all participating centres.

Patient population

Patients were considered for enrolment if they were included in the COMFORABLE-AMI trial and fulfilled the following additional criteria: age <90 years, preserved renal, and liver function, haemodynamic stability allowing the repetitive administration of nitroglycerine, TIMI flow ≥ 2 of the IRA at the completion of primary PCI, and a coronary anatomy suitable for intracoronary imaging in two major proximal coronary arteries in the absence of a lesion qualifying for treatment (stenosis $>50\%$). Intracoronary imaging was directed at the non-treated proximal part (50 mm) of non-IRA. The inclusion was independent of the lipid status and intake of pre-existing lipid-lowering therapy. All the patients received treatment with rosuvastatin at an initial dose of 20 mg once daily during the first 2 weeks to assess compliance and adverse effects followed by 40 mg once daily for the remainder of the follow-up period.

Procedures

Intravascular ultrasonography at baseline

Following successful primary PCI (i.e. TIMI flow ≥ 2), the infarct-related vessel was imaged first (data not reported here), followed by intracoronary imaging of the proximal 50 mm of the two non-IRA. The region of interest (ROI) was selected between two anatomical landmarks (distal: sidebranch, proximal: LM bifurcation or ostium of the RCA). A 20-MHz ultrasound catheter (Eagle Eye, Volcano Cooperation, Rancho Cordova, CA) was advanced beyond the distal landmark and a motorized pullback at a speed of 0.5 mm/s was performed after the administration of 200 μg intracoronary nitroglycerine. Images were acquired with 30 frames per second and recorded on a DVD. Recordings were sent to an independent Core Laboratory (Cardialysis B.V., Rotterdam, The Netherlands) for quality control; only if pre-specified criteria were met, the runs were considered for analysis.

Intravascular ultrasonography at follow-up

All the patients were scheduled for intracoronary imaging follow-up at 13 months. Prior to the imaging, the operator was provided with a summary information on the distal and proximal landmarks used at baseline to achieve a maximal overlap of the acquired pullbacks. If a patient underwent symptom-driven repeat angiography prior to the 13 months visit, the intracoronary imaging protocol was allowed to be repeated as early as 10 months after primary PCI but not earlier. In case of an intermittent revascularization of a previously imaged ROI, it was recommended to perform IVUS prior to revascularization at any timepoint if technically and clinically feasible.

Intravascular ultrasonography analysis

Only after availability of the serial IVUS recordings, an independent person randomly allocated a code to the baseline and follow-up pullbacks in order to ensure blinding of the analysts to the temporal sequence of paired images. An analyst not involved in the actual analysis evaluated the quality of the recordings and was responsible for deleting the procedure date and any other identifying information. The statistician was provided with the coding list to unblind the temporal sequence and to perform the data analysis only after the entire imaging analysis had been completed and the statistical analysis was at an advanced stage. A technician assessed the largest common ROI available from the two serial recordings with the help of a dedicated matching software and identified as much common matching points within the pullbacks (e.g. sidebranches, calcifications). Within the matched ROI, the lumen and the external elastic membrane were measured in every frame ($\sim$0.4 mm) using a validated software (QIVUS, Medis, Leiden, The Netherlands).

Intravascular ultrasonography end-points

Serial IVUS data were derived from the matched ROI and for the most diseased 10 mm segment at baseline. The primary end-point of the study was the change in per cent atheroma volume (PAV). The calculation of all IVUS and RF-IVUS end-points is shown in Supplementary material online, *Appendix*.

Radiofrequency intravascular ultrasonography

The secondary end-point of the study was the change in RF-IVUS defined per cent volume necrotic core. The plaque composition analysis using IVUS was obtained by processing the RF signals in a dedicated offline software (QIVUS, Medis, Leiden, The Netherlands). In this software Volcano's proprietary virtual histology (VH®) IVUS analysis technology is integrated. This results in the characterization of four different tissue types: necrotic core (red), dense calcium (white), fibro-fatty (light green), and fibrous (green). In addition, a lesion type analysis was performed according to the PROSPECT study methodology.[13,14] The detailed lesion assessment is explained in Supplementary material online, *Appendix*.

Statistical analysis

Baseline and medication characteristics were analysed with Pearson χ^2, Wilcoxon rank-sum, Fisher's exact, and *t*-tests as appropriate. Lipid values were reported as median and inter-quartile range (IQR). Change in lipid values was analysed with paired patient-level data with Wilcoxon signed-rank tests. Absolute changes were reported and tested except, if necessary to fulfil symmetry assumption, analysis was done on the log-transformed values and relative changes were reported and tested. In most patients, IVUS data were available for two non-IRA at baseline and 13-month follow-up. The absolute change from baseline to follow-up was derived at vessel level as end-point (FUP) minus end-point (BL) such that a negative value indicates a decrease over time. The changes were analysed with linear mixed models with patient as random intercept to account for the non-independence of end-points from the same patient. Two-sided *P*-values quantify the statistical evidence that the absolute change is different from zero. The results of the stratified analysis in *Figure 3* is based on the same method but an additional interaction *P*-value is provided to quantify the evidence that change was different between the strata. To assess the association between changes in LDL-C and HDL-C and change in PAV (*Figure 4*), we stratified the patients into four groups with a quartile split on the

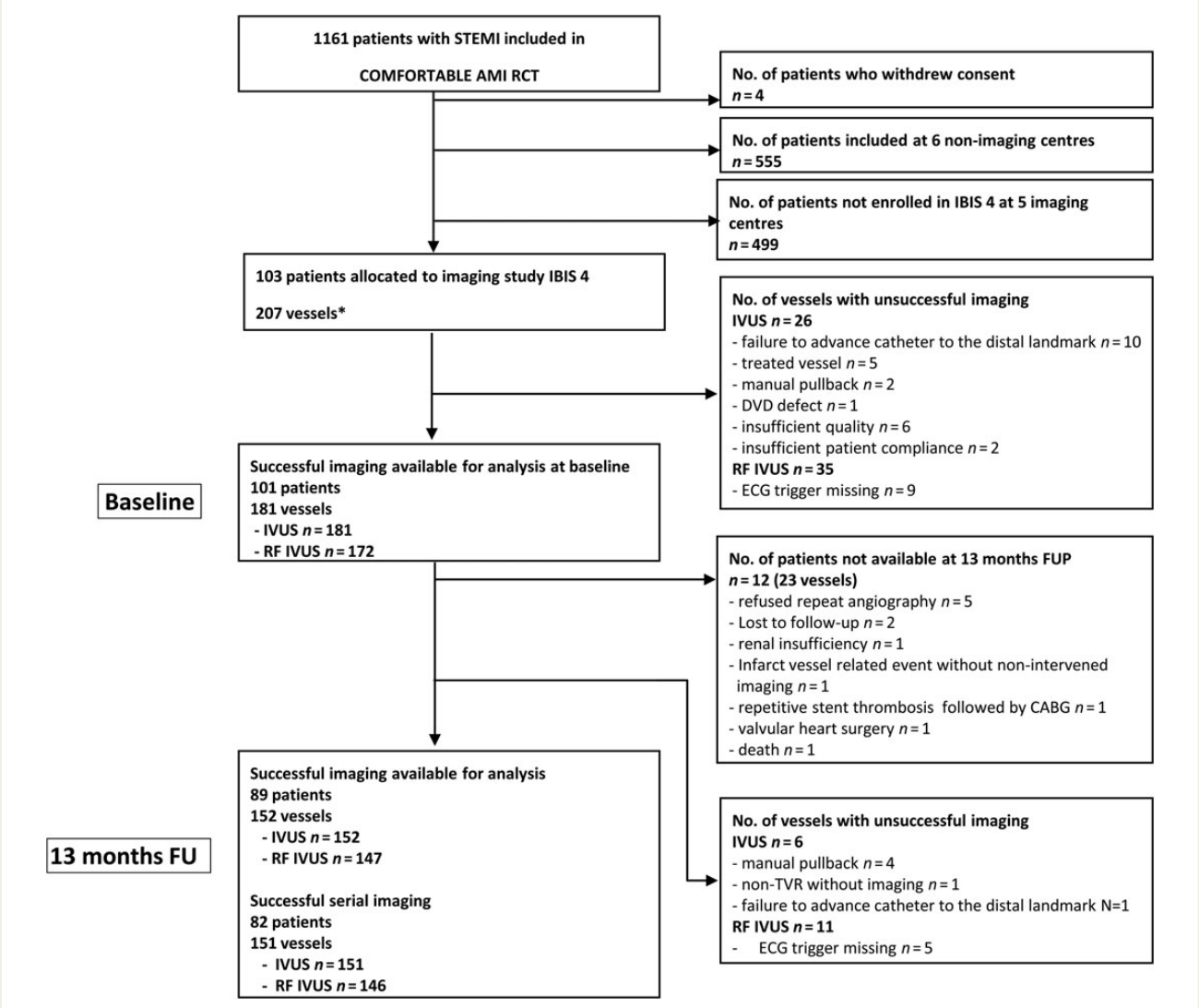

Figure 1 Flow chart of integrated biomarker imaging study 4 imaging study; *1 patient had 3 major non-infarcted epicardial coronary vessels (e.g. intermediate branch) who underwent serial intracoronary imaging.

Table 1 Baseline patient characteristics

Number of patients	All imaging patients ($n = 103$)	Serial IVUS available ($n = 82$)	No serial IVUS available ($n = 21$)	*P* value (serial vs. no serial)
Age	58.2 ± 10.5	58.5 ± 9.9	57.1 ± 12.9	0.58
Female sex (%)	10 (9.7)	6 (7.3)	4 (19.0)	0.12
BMI	27.8 ± 4.2	27.5 ± 3.8	29.0 ± 5.5	0.17
Cardiovascular risk factors (%)				
Diabetes	13 (12.6)	9 (11.0)	4 (19.0)	0.46
Hypertension	48 (46.6)	39 (47.6)	9 (42.9)	0.81
Hypercholesterolaemia[a]	42 (40.8)	36 (43.9)	6 (28.6)	0.23
Current smoker	47 (45.6)	35 (42.7)	12 (57.1)	0.33
Family history of CAD	31 (31.0)	25 (31.6)	6 (28.6)	1.00
Renal failure[b]	5 (5.0)	3 (3.8)	2 (9.5)	0.28
Previous myocardial infarction	2 (1.9)	2 (2.4)	0 (0.0)	1.00
Previous PCIs	1 (1.0)	1 (1.2)	0 (0.0)	1.00
Clinical presentation				
Time from symptom onset to balloon inflation (min)	258 (170; 472)	262 (170; 479)	238 (167; 387)	0.67
Left ventricular ejection fraction (angiography)	47.8 ± 9.4	47.5 ± 8.8	49.4 ± 12.0	0.47
Resuscitation prior to hospital arrival (%)	5 (4.9)	5 (6.1)	0 (0.0)	0.58

Values reported are *n* (%); mean ± SD; or median (lower quartile; upper quartile).
[a]Total cholesterol >5.0 mmol or 190 mg/dL or requiring treatment.
[b]<60 eGFR.

change in cholesterol values. The association was assessed by estimating the linear trend from a regression model for PAV change against the four ordered groups. Change in proportion of the TCFA lesion type was analysed with binomial generalized estimating equations to account for correlation of lesions within patient. Statistical analyses were performed with Stata (StataCorp, College Station, TX, USA) and the computing environment R (The R Foundation for Statistical Computing) with package nlme and geepack. All reported confidence intervals have 95% coverage.

Results

Patient characteristics

Between September 2009 and January 2011, 103 (out of 602 STEMI patients enrolled into the COMORTABLE AMI trial at all intracoronary imaging sites) underwent primary PCI and IVUS and RF-IVUS of both non-IRA. The flow chart in *Figure 1* provides detailed information on the number of patients and vessels included into the final analysis. For the final serial IVUS and RF-IVUS analysis, a total of 82 patients with 146 vessels were available. Baseline clinical characteristics were similar for patients undergoing serial intracoronary imaging and those not undergoing serial imaging (*Table 1*). Patients enrolled into the intracoronary imaging study—as opposed to those participating in the clinical trial only—were younger, more likely male, more obese, and had a lower frequency of hyperlipidaemia compared with those participating in the clinical follow-up protocol (Supplementary material online, *Table S1*). Cardiovascular medication and statin therapy is summarized in *Table 2*. A total of 8 (10%) patients were on statin treatment at the timepoint of study inclusion with none of them receiving high-intensity statin therapy.

Lipid profile

The lipid profile at the timepoint of inclusion, 30, and 13 months is summarized in *Figure 2*. HDL-C levels increased from 1.10 mmol/L (IQR: 0.96–1.26) to 1.20 mmol/L (IQR: 1.00–1.48) ($P < 0.0001$), and LDL-C decreased from a from 3.29 mmol/L (IQR: 2.78–3.75) to 1.89 mmol/L (IQR: 1.60–2.32) at 13 months ($P < 0.0001$). A total of 44% of patients achieved a guideline-recommended LDL-C level of ≤1.8 mmol/L at a 13-month follow-up.

Ultrasonography findings

Table 3 summarizes the results of the serial changes in IVUS parameters. After 13 months of high-intensity rosuvastatin therapy, the primary IVUS end-point change in PAV amounted to −0.90% (CI: −1.56 to −0.25%; $P = 0.007$) with a reduction from 43.95 ± 9.66% at baseline to 43.02 ± 9.82% at follow-up. The reduction within the worst 10 mm was more pronounced as shown in *Table 3*; 74% of patients had at least one vessel with disease regression, 54% of patients showed regression in both vessels, and 65% of patients had a mean PAV reduction (i.e. mean PAV change <0). In stratified analyses of the primary IVUS end-point change in PAV (*Figure 3*), the decrease in PAV was consistent in most subgroups with the exception of patients with diabetes mellitus, in whom a less pronounced reduction of PAV was observed compared with

Table 2 Cardiovascular medications

Number of patients	Serial IVUS available ($n = 82$)	NO serial IVUS available ($n = 21$)	*P*-value
Statin use prior to enrolment[a] (%)	8 (9.8)	3 (14.3)	0.69
At 30 days (%)			
Aspirin	82 (100.0)	19 (95.0)	0.20
Prasugrel	64 (78.0)	15 (75.0)	0.77
Clopidogrel	18 (22.0)	4 (20.0)	1.00
Any DAPT	82 (100.0)	18 (90.0)	0.04
Beta-blocker	78 (95.1)	18 (90.0)	0.34
ACE inhibitor	60 (73.2)	13 (65.0)	0.58
Statin	82 (100.0)	20 (100.0)	
Rosuvastatin (%)			
10 mg	1 (1.2)	2 (9.5)	0.09
20 mg	9 (11.0)	1 (4.8)	0.68
40 mg	69 (84.1)	15 (71.4)	0.70
Atorvastatin (%)			
40 mg	1 (1.2)	2 (9.5)	0.40
80 mg	2 (2.4)	0 (0.0)	0.40
At 1 year (%)			
Aspirin	80 (100.0)	17 (94.4)	0.18
Prasugrel	63 (78.8)	12 (66.7)	0.36
Clopidogrel	14 (17.5)	4 (22.2)	0.74
Any DAPT	76 (95.0)	16 (88.9)	0.30
Beta-blocker	67 (83.8)	15 (83.3)	1.00
ACE inhibitor	45 (56.3)	10 (55.6)	1.00
Statin	81 (98.8)	18 (100.0)	1.00
Rosuvastatin (%)			
10 mg	2 (2.4)	3 (14.3)	0.03
20 mg	16 (19.5)	5 (23.8)	0.30
40 mg	59 (72.0)	6 (28.6)	0.02
Atorvastatin (%)			
40 mg	1 (1.2)	2 (9.5)	0.40
80 mg	2 (2.4)	0 (0.0)	0.40

Values reported as number of patients (%).
[a]Other cardiovascular medication regularly taken at home was not recorded.

patients without diabetes (P for interaction = 0.054). The association between baseline LDL-C and HDL-C and their change over 13 months with the change in PAV is shown in *Figure 4*. When stratifying patients into quartiles according to LDL-C reduction or HDL-C increase, a significant linear trend was observed for the reduction in per cent atheroma. The change in PAV was independent of baseline HDL-C and LDL-C levels (*Figure 4*).

To eliminate concerns of bias introduced by imaging of more than one vessel per patient, we performed a sensitivity analysis, which only used data from one vessel in case there were two, giving preference to LAD over LCX over RCA. Results remained essentially the same (PAV reduction −1.07%, CI: −1.86 to −0.28%, $P = 0.009$) (Supplementary material online, *Table S2*).

Radiofrequency intravascular ultrasonography defined tissue composition

Serial RF-IVUS data are summarized in *Table 4*. There was no significant change in the secondary end-point of RF-IVUS defined per cent necrotic core between baseline and follow-up (−0.05%; CI: −1.05 to 0.96%; $P = 0.93$), whereas the proportion of calcified tissue components increased (+1.28%; CI: 0.66 to 1.90%; $P < 0.0001$) and fibrous tissue components decreased (−1.38%; CI: −2.28 to −0.47%; $P = 0.003$). As an exploratory analysis, we calculated the absolute changes in tissue composition (Supplementary material online, *Table S3*), and noted a small but significant reduction in a necrotic core [−0.08 mm^2 (−0.13 mm^2 to −0.03 mm^2, $P = 0.002$)].

Radiofrequency intravascular ultrasonography defined lesion phenotype

Serial lesion-related RF-IVUS at baseline and 13 months are provided in *Table 5*. In the entire proximal, non-infarct-related vessel segments, 164 atherosclerotic lesions were observed at baseline (2 per patient, 1 per analysed non-IRA), of which RF-IVUS defined TCFA were most frequent ($n = 124$ (75%). At 13-month follow-up, 158 lesions were observed (7 resolved, 1 new lesion), with 116 (70%) RF-IVUS defined TCFAs. A total of 17 RF-IVUS defined TCFAs observed at baseline converted into lower risk lesion types at follow-up and nine TCFAs were newly formated (7 from a ThCFA lesion and 1 from a PIT lesion), corresponding to a change in proportion of TCFA from 75% at baseline to 70% at 13 months ($P = 0.15$).

Discussion

This serial intracoronary imaging study investigated the effects of high-intensity rosuvastatin therapy on coronary atherosclerosis in terms of plaque burden, RF-IVUS defined plaque composition and phenotype in the proximal segments of non-IRA of patients presenting with acute STEMI (*Figure 5*).

In the present study, high-intensity rosuvastatin therapy over 13 months reduced mean plasma LDL-C achieving a treatment target of <1.8 mmol/L in 44% of patients. Serial intracoronary imaging revealed that high-intensity lipid-lowering therapy resulted in regression of coronary atherosclerosis in the proximal segments of non-IRA among STEMI patients. Two previous studies have reported regression of coronary atherosclerosis among lower risk patients with stable, non-obstructive coronary artery disease under high-intensity rosuvastatin therapy.[4,5] The results of the present study investigating high-risk STEMI patients using multi-vessel intracoronary imaging and analysis by a different Core Laboratory yielded similar results as those observed in the *Effect of very high-intensity statin therapy on regression of coronary atherosclerosis* (ASTEROID) trial. In this trial, the reduction in PAV amounted to −0.98 ± 3;15% and total atheroma volume was reduced by −14.7 ± 25.7 mm^3; despite a longer duration of therapy (13 vs. 24 months) and lower on target lipid levels. Of note, atheroma burden in the present study was in average higher (~10%) reflecting the higher risk population. Despite the exclusion of patients with obstructive coronary artery disease of non-IRA, this observation underscores

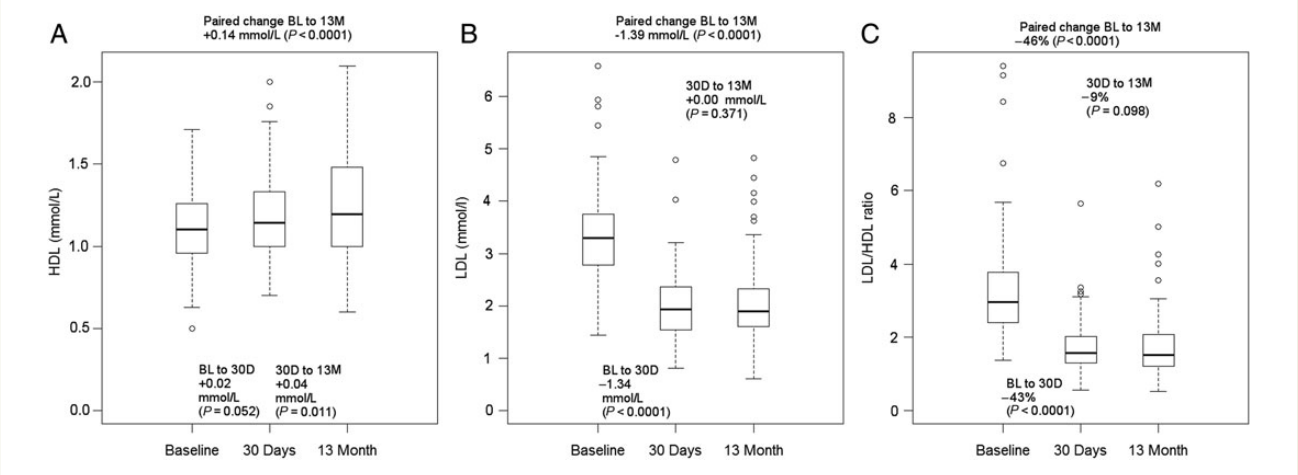

Figure 2 Box plots showing median and inter-quartile range for plasma LDL-C, HDL-C, and LDL-C/HDL-C ratio at baseline, 30 days, and 13 months. (*A*) HDL-C, (*B*) LDL-C, and (*C*) the LDL-C/HDL-C ratio. The median per-patient changes and corresponding *P*-values from the paired analysis are indicated in the figure.

Table 3 Serial intravascular ultrasonography results

Number of patients (vessels): 82 (146)	Baseline mean ± SD	Follow-up mean ± SD	Absolute change mean change (95% CI)	*P*-value
Entire regions				
Region length (mm)	36.15 ± 16.1	36.21 ± 16.05	0.06 (−1.06 to 1.17)	0.917
Average lumen area (mm^2)	8.64 ± 3.07	8.48 ± 2.89	−0.16 (−0.29 to −0.03)	0.020
Average vessel area (mm^2)	15.74 ± 5.64	15.23 ± 5.38	−0.51 (−0.67 to −0.35)	<0.001
Primary efficacy parameter				
Per cent atheroma volume (%)	43.95 ± 9.66	43.02 ± 9.82	−0.9 (−1.56 to −0.25)	0.007
Secondary efficacy parameters				
Total atheroma volume (mm^3)	258.31 ± 163.41	245.13 ± 152.95	−13.14 (−22.45 to −3.84)	0.006
Average atheroma area (mm^2)	7.1 ± 3.22	6.75 ± 3.15	−0.35 (−0.48 to −0.21)	<0.001
Normalized TAV (mm^3)	248.4 ± 112.69	235.95 ± 110.25	−12.18 (−16.91 to −7.44)	<0.001
Most diseased 10 mm segments				
Region length (mm)	9.96 ± 0.15	10.25 ± 2.23	0.29 (−0.08 to 0.66)	0.118
Average lumen area (mm^2)	7.59 ± 2.97	7.78 ± 2.96	0.22 (−0.01 to 0.45)	0.061
Average vessel area (mm^2)	16.26 ± 5.61	15.67 ± 5.52	−0.57 (−0.84 to −0.31)	<0.001
Primary efficacy parameter				
Per cent Atheroma volume (%)	52.31 ± 12.17	49.42 ± 11.65	−2.94 (−3.89 to −1.98)	<0.001
Secondary efficacy parameters				
Total atheroma volume (mm^3)	86.51 ± 37.94	81.01 ± 38.96	−5.5 (−8.99 to −2)	0.002
Average atheroma area (mm^2)	8.68 ± 3.79	7.9 ± 3.52	−0.78 (−0.99 to −0.56)	<0.001
Normalized TAV (mm^3)	86.44 ± 37.76	78.72 ± 35.08	−7.73 (−9.86 to −5.59)	<0.001

For descriptive purposes the mean ± SD over all vessels is reported for baseline and follow-up.
Two-sided *P*-values to test if change is different from 0 are from linear mixed models (patient as random intercept).
TAV, total atheroma volume; PAV, per cent atheroma volume.

the high atherosclerotic disease burden observed in the proximal segments of non-IRA among STEMI patients.

Although subgroup analyses were not pre-specified, there was no statistical heterogeneity concerning the change in PAV across major subgroups (*Figure 3*). It is of interest that the more pronounced changes in LDL-C reduction and HDL-C increase over 13 months resulted in larger changes of PAV reduction (*Figure 4*), which was not the case for baseline LDL-C and HDL-C (*Figure 4*). This observation as well as the results of a large meta-analysis of statin therapy, which reported a significant reduction in vascular events

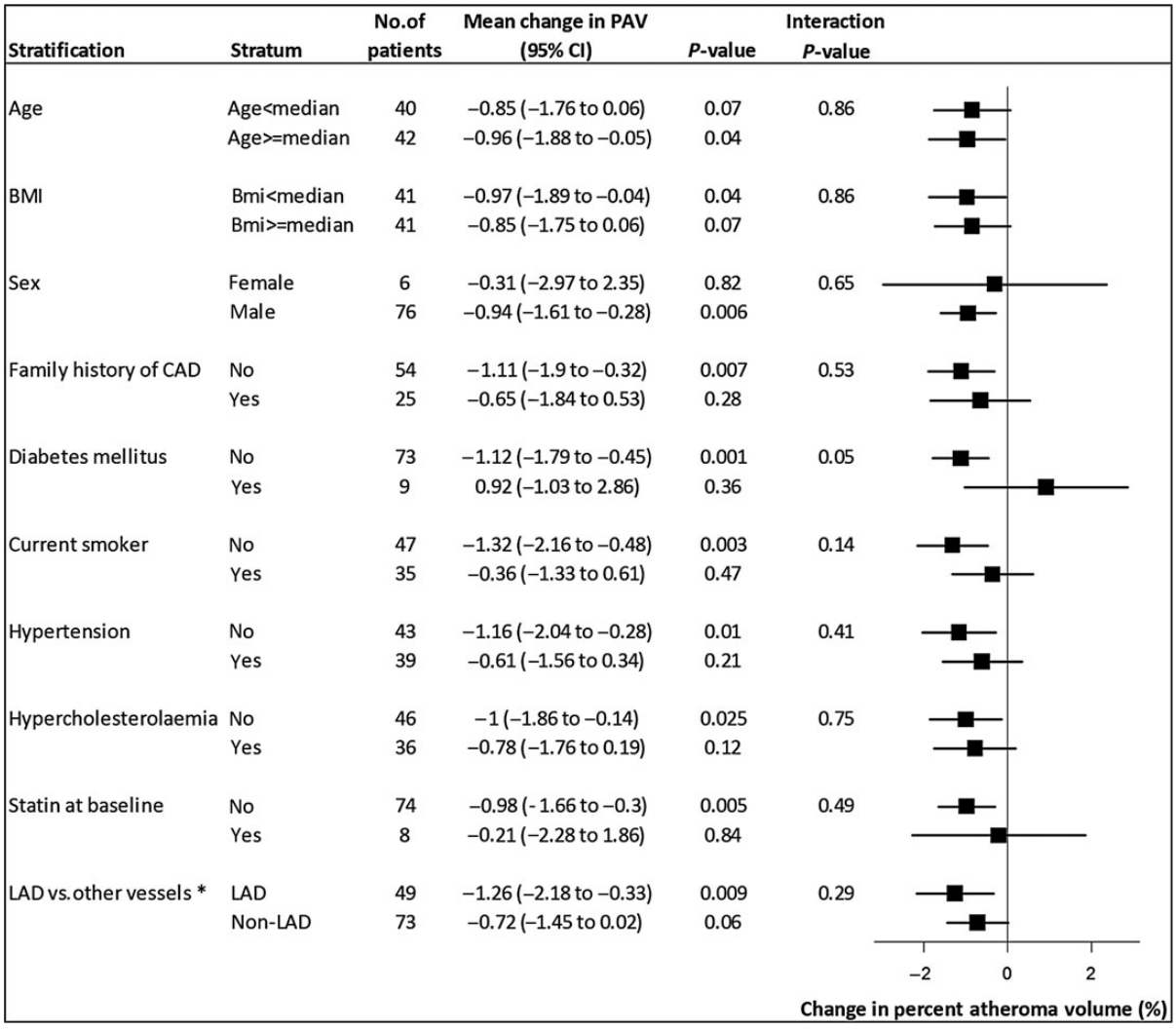

Figure 3 Forrest plot showing the change in PAV (%) stratified according to baseline patient characteristics. Two-sided *P*-values to test if change is different from 0 are from linear mixed models (patient as random intercept) and mean change and 95% CI are reported. An interaction *P*-value is provided to compare the change between the strata. Hypercholesterolaemia defined as total cholesterol >5.0 mmol or 190 mg/dL or requiring treatment. *A patient can be both in LAD and non-LAD group and therefore patient numbers sum to >82.

independent from the baseline LDL-C levels,[15] reinforce the benefit of high-intensity statin therapy in STEMI patients independent of the baseline lipid levels.

Radiofrequency intravascular ultrasonography defined changes in plaque composition

In two large-scale clinical outcome trials, the use of high-intensity statin therapy was associated with a significant decrease in cardiovascular events compared with the standard statin therapy.[2,16] The improved clinical outcome has not been directly attributed to atherosclerosis regression so far, and it remains unclear whether the beneficial effects of lipid-lowering therapy are related to other effects than reduction in plaque burden such as changes in plaque composition or plaque phenotype.[17]

Despite significant atheroma regression, no change in RF-IVUS defined per cent necrotic core was observed during serial examinations under high-intensity statin therapy. Two previous studies investigating serial changes in a necrotic core were performed in patients with stable, non-obstructive coronary artery disease. The integrated biomarker imaging study 2 study (IBIS-2)[18] using conventional doses of lipid therapy showed an increase in per cent necrotic core (2.5 ± 9.6%) throughout 12 months.[18] Similarly, the RF substudy of SATURN,[19] which recorded a lower proportion of a necrotic core at baseline (12.3%) compared with the present STEMI population in 71 patients, observed an increase of 1.9% in a necrotic core ($P < 0.001$) despite high-intensity statin therapy and a significant reduction of the atheroma volume. Available evidence therefore suggests that

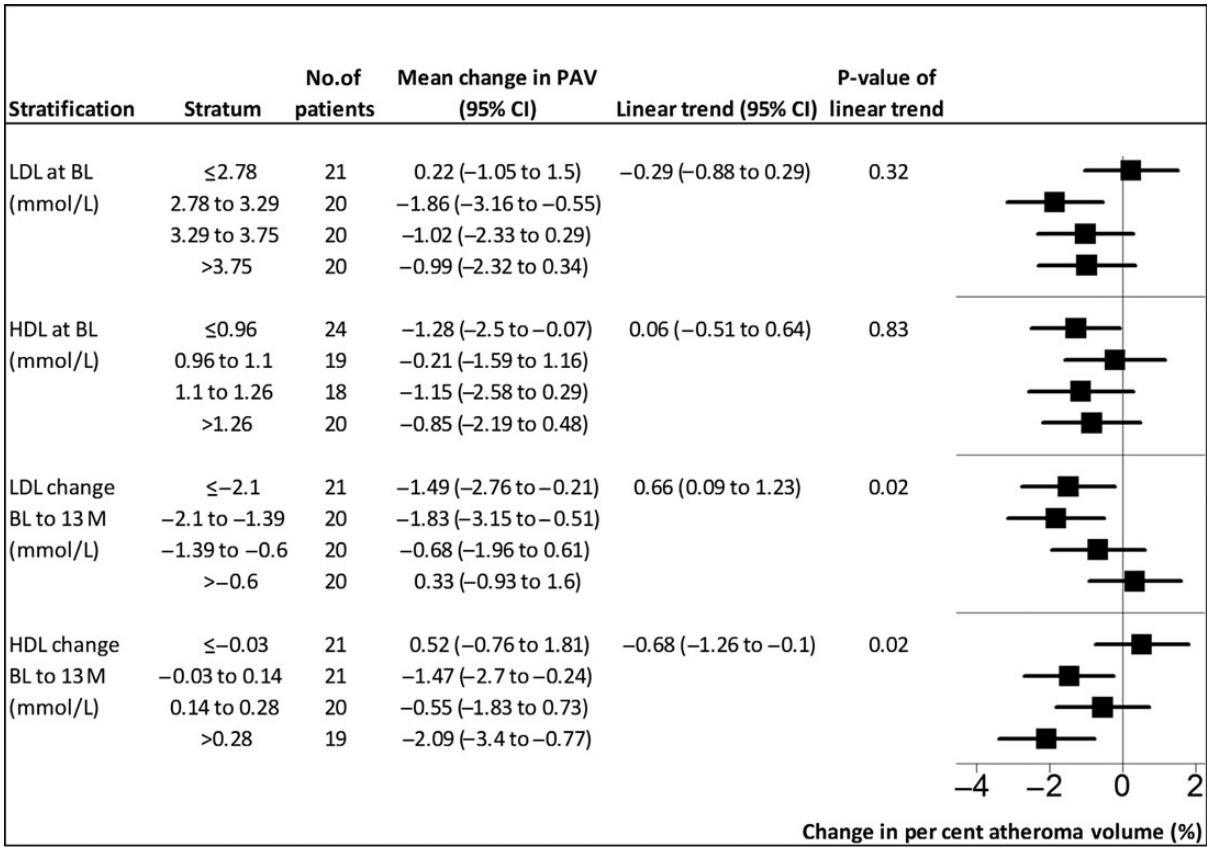

Figure 4 Forrest plot showing the change in PAV regressed against the baseline values and the changes in LDL-C or HDL-C. Patients were stratified into four groups with a quartile split according to their LDL-C or HDL-C baseline value or change. Reported values are the per group means (95% CI) and the linear trend across the four groups (95% CI) which represents the change in PAV between two consecutive groups. Analysis with linear mixed model (patient as random intercept).

Table 4 Serial radiofrequency ultrasonography analysis

Number of patients (vessels): 82 (142[a])	Baseline mean ± SD	Follow-up mean ± SD	Absolute change mean change (95% CI)	*P*-value
Entire regions				
Per cent volume NC (%)	21.14 ± 7.43	21.02 ± 7.04	−0.05 (−1.05 to 0.96)	0.926
Per cent volume DC (%)	8.33 ± 5.94	9.56 ± 6.66	1.28 (0.66 to 1.9)	<0.001
Per cent volume FI (%)	59.75 ± 9.33	58.4 ± 9.72	−1.38 (−2.28 to −0.47)	0.003
Per cent volume FF (%)	10.78 ± 5.19	11.02 ± 5.88	0.21 (−0.91 to 1.34)	0.705
Most diseased 10 mm segments				
Per cent volume NC (%)	23.11 ± 8.81	22.52 ± 8.8	−0.59 (−1.82 to 0.63)	0.338
Per cent volume DC (%)	8.77 ± 6.84	10.57 ± 8.03	1.82 (0.89 to 2.74)	<0.001
Per cent volume FI (%)	57.66 ± 11.27	56.45 ± 11.76	−1.21 (−2.51 to 0.09)	0.068
Per cent volume FF (%)	10.46 ± 6.34	10.46 ± 6.62	−0.01 (−1.12 to 1.1)	0.991

See footnote of *Table 3* for details.
NC, necrotic core tissue; DC, dense calcium tissue; FI, fibrous tissue; FF, fibro-fatty tissue.
[a]142 of 146 vessels analysed because if total VH area at baseline or follow-up is 0, the % change is not defined.

Table 5 **Serial radiofrequency ultrasonographic plaque characterization**

		13-month follow-up					
Baseline	**82 patients**	**TCFA**	**ThCFA**	**PIT**	**Fibrotic**	**Fibrocalcific**	**Resolved**
Total	165 lesions	116 (70.3%)	24 (14.5%)	8 (4.8%)	6 (3.6%)	4 (2.4%)	7 (4.2%)
TCFA	124 (75.2%)	107	10	1	2	0	4
ThCFA	22 (13.3%)	7	13	0	0	1	1
PIT	10 (6.1%)	1	1	5	1	0	2
Fibrotic	5 (3.0%)	1	0	1	3	0	0
Fibrocalcific	3 (1.8%)	0	0	0	0	3	0
No lesions	1 (0.6%)	0	0	1	0	0	0

Values reported are number of lesions (%).
TCFA, thin cap fibro-atheroma; ThCFA, thick cap fibro-atheroma; PIT, pathological intimal thickening.

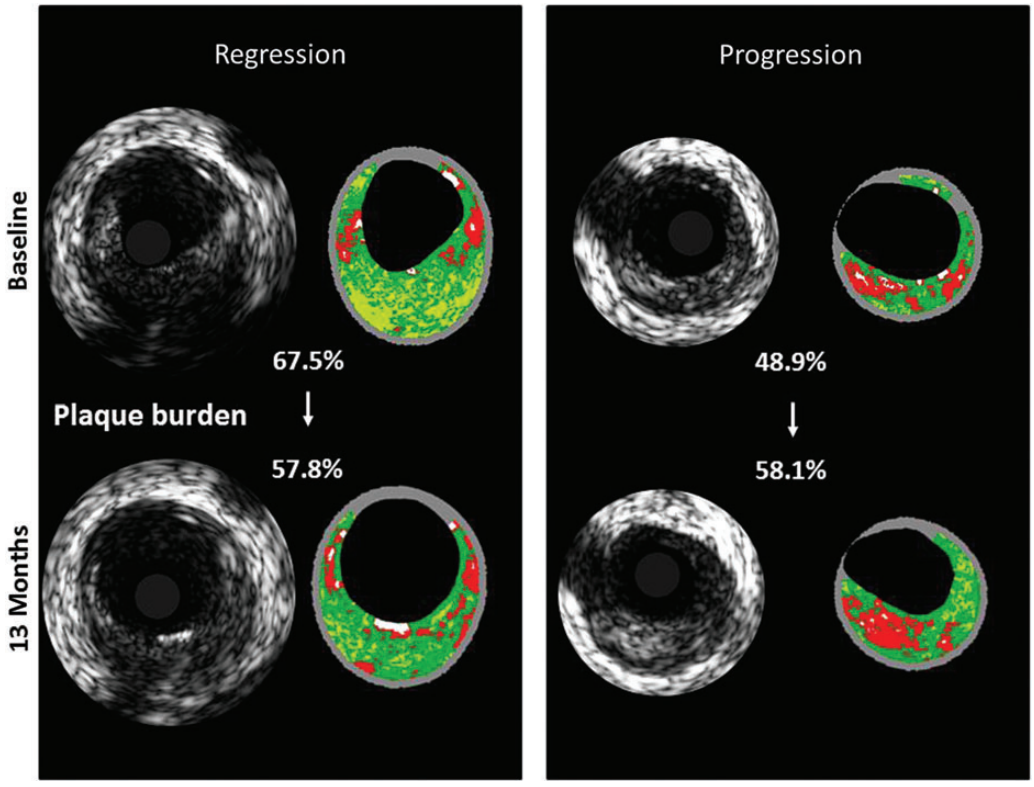

Figure 5 Example of a lesion showing a regression (left panel) and progression (right panel). The left cross section (black and white images) indicates the intravascular ultrasonography greyscale findings and the four coloured cross sections on the right indicate radiofrequency intravascular ultrasonography analysis.

high-intensity statin therapy does not reduce a necrotic core burden as determined by RF-IVUS during an observation period of 13 months, which is relatively short compared with otherwise permanent treatment recommendations for secondary prevention.

Statin therapy has been reported to reduce lipid content, oxidized LDL, and inflammatory cells in tissue extracted by means of atherectomy.[20] In contrast, we did not observe a reduction in RF-IVUS defined lipid-rich tissue (fibro-fatty or necrotic core) but rather an increase in calcium. An increase in calcium was previously noted independent of statin dose using investigation by coronary computed tomography and RF-IVUS performed at 12 months.[18,21,22] Similar to our findings, the RF-IVUS substudy of SATURN[19] observed a significant increase in calcium, suggesting that calcium may increase in the presence of high-intensity statin therapy. In view of the overall

plaque regression, the increase of calcium may be interpreted as conversion of non-calcified to calcified plaque rather than a progression of the underlying atherosclerotic process. Imaging studies in patients with ACS as well as autopsy studies in sudden cardiac death patients have suggested less calcification in unstable plaques when compared with stable plaques,[23,24] supporting the hypothesis that calcium may increase plaque stability. The absence of information on the distribution and localization of the observed calcification process prohibits a full understanding of the observed change in calcified tissue.

Radiofrequency intravascular ultrasonography defined changes in plaque phenotype

We observed in average 1.5 TCFAs as defined by RF-IVUS per patient in the proximal segment of non-IRAs. In a pathology study, TCFAs defined by histology have been shown to accumulate in the proximal 30 mm segments of the epicardial coronary arteries,[25] providing an explanation for the higher frequency of TCFAs in the present study compared with the only previous RF-IVUS study investigating non-IRA lesions.[26]

Plaque phenotype analysis indicated infrequent changes throughout the study period, without evidence for transformation into higher risk plaque phenotypes. Most RF-IVUS defined TCFAs did not change their characteristics over time with a minority of 14% converting into a lower risk phenotype ($P = 0.15$). In the only available study using serial intracoronary imaging in STEMI patients[26] who underwent treatment with the standard statin therapy during a follow-up duration of 13 months, the frequency of TCFAs increased over time (29%), providing indirect evidence for a hypothetical effect of high-intensity dose statin therapy, a finding which is hypothesis generating and warrants further investigation.

Limitations

The results have to be interpreted in the light of the following limitations. Firstly, the analysis was not based on a formal sample size consideration. Rather, it used data from 82 STEMI patients who were successfully enrolled as part of a substudy of a previously published randomized trial comparing two stent types in the setting of primary PCI.[12] In an exploratory analysis, the width of the actual 95% confidence interval of the difference in PAV suggests that there was ~80% power to detect a difference of 0.94% from baseline to follow-up. Secondly, the number of patients included into the study of patients with acute myocardial infarction is considerably smaller compared with previously reported regression trials in patients with stable coronary artery disease. Thirdly, this was an observational study without control group, as we regarded the absence of high-intensity statin therapy as clinically not acceptable. Another limitation is that only selected patients underwent serial intracoronary imaging, as multi-vessel intracoronary imaging in the setting of STEMI is technically demanding and can only performed in stabilized patients with patent infarct-vessel. Therefore, these findings may not apply to unselected STEMI patients with different lesion phenotype. Finally, repeat imaging was scheduled at 13 months, which might affect the ability to detect long-term changes in plaque composition and phenotype.

Conclusion

The proximal segments of non-IRA of STEMI patients feature a high-atherosclerotic plaque burden and harbour in average 1.5 TCFAs defined by RF-IVUS per patient. High-intensity rosuvastatin (40 mg/day) therapy throughout 13 months was associated with a significant reduction of coronary atherosclerosis but no changes in RF-IVUS defined proportion of necrotic core or other plaque phenotypes. Regression of coronary atherosclerosis as a result of high-intensity statin therapy among STEMI patients may have important long-term clinical implications.

Authors' contribution

L.R. and S.W. conceived the study. L.R. and S.W. wrote the study protocol. S.Z. and P.J. did the analysis and interpreted the analysis in collaboration with L.R., H.G.G., S.W., and all other authors. L.R., M.T., H.K., M.R., L.H., S.N., A.M., G.G.S., U.L., P.W., G.P., and S.W. were responsible for the acquisition of data. H.G.G. supervised the Core Laboratory activities. L.R. and S.W. wrote the first draft of the report. All other authors critically revised the report for important intellectual content and approved the final version.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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