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ORIGINAL PAPER

Effect of statin therapy on coronary inflammation assessed by pericoronary adipose tissue computed tomography attenuation

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Aims

Pericoronary adipose tissue (PCAT) attenuation on coronary computed tomography angiography (CCTA) is an imaging biomarker of coronary inflammation. The natural history of PCAT attenuation remains unknown. High-intensity statin therapy has pleiotropic anti-inflammatory effects. We sought to assess temporal changes in PCAT attenuation in patients with and without statin therapy.

Methods and results

This was a multicentre observational study that included consecutive patients with stable coronary artery disease (CAD) undergoing clinically indicated serial CCTA with identical scan parameters ≥ 12 months apart between May 2013 and July 2022. Using semi-automated software, PCAT attenuation was measured on a per-lesion level ($PCAT_{lesion}$) and per-patient level around the proximal right coronary artery ($PCAT_{RCA}$). Of the 96 patients (57 ± 11 years, 60% male), 34 patients were not on a statin at baseline or follow-up (statin-naive), 26 patients were commenced on a statin after the baseline scan (statin-commenced), and 34 patients were on a statin at both time points (statin-continued). There was no significant difference between the groups for age, sex, body mass index (BMI), and prevalence of traditional cardiovascular risk factors except for dyslipidaemia (25.0% vs. 34.6% vs. 64.7%, $P < 0.01$ for trend). At a median follow-up of 3.8 years, there was a significant reduction in $PCAT_{lesion}$ in the statin-commenced (−79.4 ± 11.7 to −86.5 ± 10 HU, $P < 0.001$) and the statin-continued (−83.5 ± 8.5 to −90.6 ± 8.5 HU, $P = 0.001$) groups. Meanwhile, no significant difference in $PCAT_{lesion}$ was observed in the statin-naïve group (−84.4 ± 9.7 to −86.6 ± 9.5, $P = 0.1$). Multivariate analysis showed statin intensity and LDL change to be independently associated with percentage change of $PCAT_{lesion}$, after correcting for cardiovascular risk factors, changes in body weight, and coronary artery calcium score.

Conclusion

Statin therapy was associated with a reduction in $PCAT_{lesion}$, while no significant change in $PCAT_{lesion}$ was observed without statin therapy. If validated in larger studies, PCAT attenuation could potentially be used to monitor the response of the coronary arteries to statins and guide treatment.

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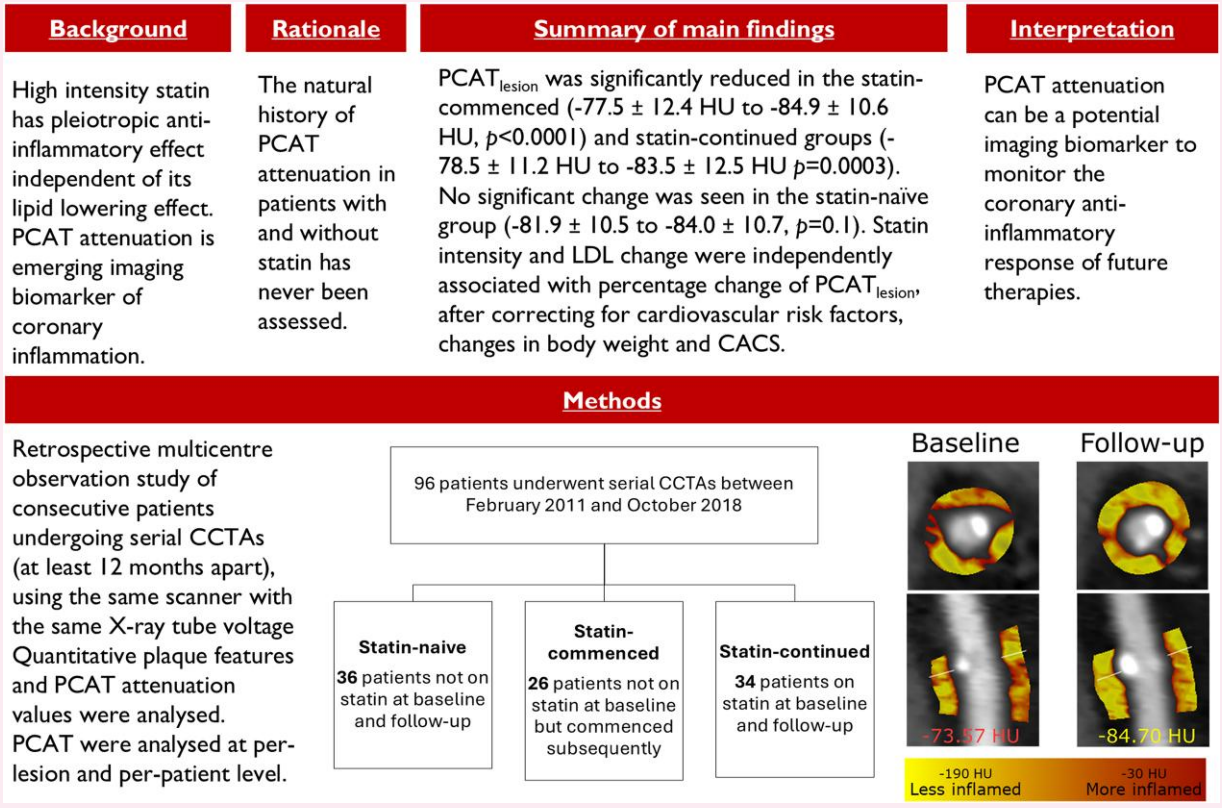
Graphical Abstract



A schematic overview of the main study aims and findings, with a representative image demonstrating a case example of changes in PCAT attenuation in a patient commenced on statin after the baseline CCTA. CACS, coronary artery calcium score, CCTA, coronary computed tomography angiography; HU, Hounsfield units; PCAT, pericoronary adipose tissue.

Keywords coronary computed tomography angiography • pericoronary adipose tissue • inflammation • atherosclerosis • statin

Introduction

Vascular inflammation is viewed as a crucial factor in the development of atherogenesis and the rupture of atherosclerotic plaques, leading to acute coronary syndrome.[1] Currently, it remains unclear how to identify patients with high levels of inflammation who would benefit most from targeted therapy. Advanced imaging tests such as sodium fluoride positron emission tomography (PET) incur high costs and have limited availability, which restricts their use in clinical settings.[2] Recent evidence demonstrates that coronary artery inflammation inhibits lipid accumulation in preadipocytes of pericoronary adipose tissue (PCAT) through paracrine signalling mechanisms, and this can be detected on routine coronary computed tomography angiography (CCTA) as an increase in the CT attenuation of PCAT.[3] This surrogate measure of coronary inflammation independently predicts plaque progression and cardiac mortality in patients undergoing CCTA for suspected coronary artery disease (CAD).[4,5] High-intensity statin therapy has pleiotropic anti-inflammatory effects which are independent of its lipid-lowering effect.[6] The JUPITER study showed that high-intensity statins reduced the risk of major cardiovascular events in patients without hyperlipidaemia but with elevated high-sensitive C-reactive protein.[7] A recent study demonstrated a reduction in PCAT attenuation surrounding non-calcified and mixed plaques, but not calcified plaques, following statin treatment.[8] However, the natural history of PCAT attenuation in the absence of statin intervention remains unexplored. Understanding this is pivotal for the design of future clinical trials, informing sample size calculations, and discerning if observed changes in PCAT are due to interventions or merely the passage of time. In this study, we sought out to assess the natural history of PCAT attenuation in patients with and without statin therapy.

Methods

Study population

We retrospectively studied 157 consecutive patients with suspected or known stable CAD who underwent serial CCTA at least 1 year apart with the same acquisition protocol and same CT scanner across two institutions (MonashHeart, Monash Medical Centre, Melbourne, Australia, and Mildura Base Public Hospital, Mildura, Australia). We excluded 34 patients with inadequate image quality, 22 patients without complete fasting lipid profile, and 3 patients with incomplete imaging data (*Figure 1*). Patients were divided into three groups based on their statin usage: (i) 'statin-naïve' group consisted of 36 patients who were not on a statin at baseline or follow-up CCTA; (ii) 'statin-commenced' group consisted of 26 patients who were not on a statin at baseline but were on a statin

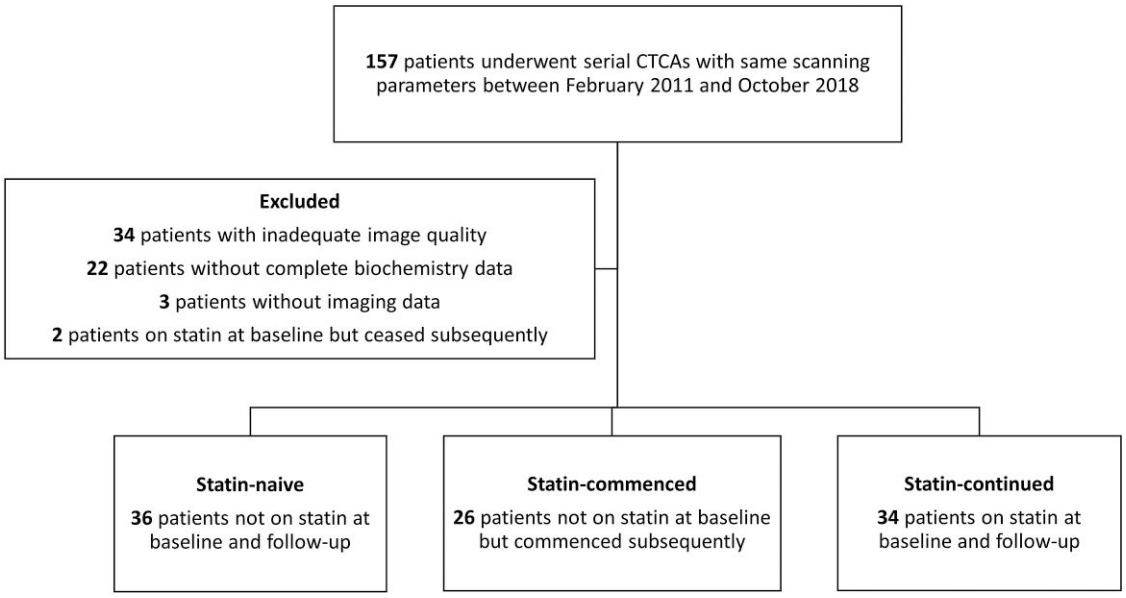


Figure 1 Patient selection and study design. Flow chart showing inclusion and exclusion criteria for the three cohorts.

at follow-up CCTA; and (iii) 'statin-continued' group consisted of 34 patients who were on a statin at the time of both scans. The study was approved by the institutional review board and registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12621001018808). Patient demographic data and traditional cardiovascular risk factors were determined from patient questionnaires at the time of CCTA and by review of electronic medical records. Total cholesterol, HDL, LDL cholesterol, and triglyceride levels were obtained within 3 months of CCTA. Diabetes was defined as treatment with oral hypoglycaemic agents or insulin or fasting glucose ≥ 7 mmol/L. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or patients treated with antihypertensive medication. Current smoking was defined as the use of cigarettes within the past 3 months, while ex-smoking was defined as smoking cessation ≥ 3 months before CCTA. Dyslipidaemia was defined as total cholesterol ≥ 5.5 mmol/L, LDL ≥ 3.5 mmol/L, HDL ≤ 1.0 mmol/L, triglycerides ≥ 2.0 mmol/L, or treatment with statins.

CCTA acquisition

Beta-blockade was administered to achieve a heart rate ≤ 60 beats/min. CCTAs were performed using the two systems, and the same acquisition parameters were used for both baseline and follow-up CCTA. Sixty-six patients underwent CCTA on a 320-detector-row (Aquilion ONE VISION, Canon Medical Systems, Japan). Before contrast injection, a non-contrast cardiac CT was performed. Sublingual nitro-glycerine (0.4–0.8 mg) was administered immediately before CTA scanning. Iodinated contrast [60–90 mL, 350 mg iodine per mL (Omnipaque)] was injected at a flow rate of 5 mL/s. CCTA was performed with prospective electrocardiogram gating and automatic tube current modulation.

Another 30 patients were scanned with a 128-detector system (Definition AS+, Siemens Healthcare AG, Erlangen, Germany). The scan was acquired during the injection of a non-ionic iodinated contrast agent, iopromide (Ultravist 370 mg/mL, Bayer Healthcare), in an antecubital vein by a dual injector (Medrad Stellant). Individualized weight-based contrast volumes were injected at 6 mL/s in a triple-phase pattern of pure contrast/50:50 saline mix/saline. The scan delay was determined using a contrast bolus monitoring method that measured the time until peak enhancement occurred in the left ventricle. CCTAs were performed using retrospective electrocardiogram with tube modulation technique (120 kV; 280–350 mAs; 300 ms gantry rotation time). Images were acquired at 0.6 mm slice thickness at 0.3 mm increments and reconstructed using a medium-smooth kernel (B26, Siemens Medical Solutions) throughout the cardiac cycle at 10% increments of the R-R interval.

Acquisition parameters on the 320-detector row scanner were as follows: detector collimation 320 mm 0.5 mm; tube current 300–500 mA [depending on body mass index (BMI)]; tube voltage 120 kV if BMI ≥ 25 (100 kV if BMI < 25); gantry rotation time 350 ms; and temporal resolution 175 ms. Prospective electrocardiogram gating covered 70–80% of the R-R interval. For images captured at heart rates of 65 bpm or less, the scanning was achieved in a single R-R interval using an 1808 segment.

CCTA interpretation

CCTAs were analysed on a dedicated workstation using a standard 18-segment model of the coronary tree.[9] Each coronary segment ≥ 1.5 mm in diameter was analysed for the presence of plaque and diameter stenosis and visually graded according to the following categories: no stenosis (0%), minimal stenosis (<25%), mild (25–49%), moderate (50–69%), severe (70–99%), and occluded (100%).

Coronary plaque quantification

Quantitative plaque analysis was performed with semi-automated software (Autoplaque v2.5, Cedars-Sinai Medical Center, Los Angeles, CA, USA) with appropriate manual adjustment of the vessel lumen and wall contouring using multiplanar views. A normal blood pool is defined by placing a circular region of interest in the ascending aorta. The absolute volumes of total plaque, non-calcified plaque (NCP), and calcified plaque were automatically computed using scan-specific thresholds.[10] Low-density NCP (LDNCP) was defined as NCP below a fixed threshold of 30 HU.[11] Plaque burden, defined as plaque volume × 100%/analysed vessel volume, was calculated for each of the respective plaque components. The maximum diameter stenosis was determined by dividing the smallest lumen diameter by the average of two normal, non-diseased reference points. The remodelling index was calculated as the ratio of the maximum vessel area to the area at a

Table 1 Clinical characteristics, risk factors, statin type, statin intensity, and lipid panel of the study population at the time of baseline CCTA acquisition

	Statin-naive ($n = 36$)	Statin-commenced ($n = 26$)	Statin-continued ($n = 34$)	*P*
Clinical characteristics				
Age, years	57 (49 to 64)	51 (48 to 60)	62 (52 to 66)	NS
Male gender	23 (64%)	19 (73%)	16 (47%)	0.4
BMI, kg/m^2	29 (26 to 33)	29 (25 to 32)	29 (27 to 33)	0.2
Hypertension	17 (47%)	13 (50%)	17 (50%)	0.06
Dyslipidaemia	9 (25%)	9 (35%)	22 (65%)	**<0.01**
Diabetes	2 (6%)	2 (8%)	7 (21%)	0.2
Current smoker	1 (3%)	5 (19%)	2 (6%)	0.3
Ex-smoker	11 (31%)	6 (23%)	7 (21%)	0.5
Family history	19 (28%)	16 (62%)	19 (56%)	NS
Statin type taken during the serial CTs				
Atorvastatin		9 (35%)	12 (35%)	NS
Rosuvastatin		14 (54%)	16 (47%)	0.8
Simvastatin		1 (4%)	4 (12%)	0.4
Pravastatin		2 (8%)	1 (3%)	0.6
Statin dose intensity taken during the serial CTs				
Low		11 (42%)	13 (38%)	0.8
Medium		10 (38%)	14 (41%)	NS
High		5 (19%)	7 (21%)	NS
Other medications taken during the serial CTs				
Aspirin	5 (14%)	9 (35%)	17 (50%)	**<0.01**
Ezetimibe	2 (6%)	2 (8%)	5 (15%)	0.4
Fenofibrate	1 (3%)	0	0	NS
Evolucumab	0	0	1 (3%)	NS
Baseline lipid profile, mmol/L				
Total cholesterol	5.07 ± 0.95	5.09 ± 1.11	4.70 ± 1.47	0.4
Triglyceride	1.37 ± 0.78	1.94 ± 1.26	1.51 ± 0.80	0.09
LDL	3.07 ± 0.87	2.91 ± 0.98	2.45 ± 0.91	**0.04**
HDL	1.37 ± 0.41	1.22 ± 0.39	1.31 ± 0.41	0.4
Duration between CTs, days	1485 (1158 to 2063)	1312 (1000 to 1741)	1340 (1059 to 1863)	0.4

Values are expressed as *n* (%), mean ± standard deviations, or median (interquartile range, 25th–75th). Boldface *P*-values indicate statistical significance.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

proximal normal reference point.[12] Lesion length (in mm) was the length of the diseased segment.

Image quality between the serial CTs was assessed by measuring the signal-to-noise ratio and the contrast-to-noise ratio. Signal-to-noise ratio was defined as the mean coronary luminal CT attenuation in HU adjacent to the plaque in a healthy segment divided by the standard deviation of the CT attenuation in the aorta measured in a region of interest at least 2 cm^2 at the level of the left main trunk. The contrast-to-noise ratio was calculated as the mean luminal HU minus the perivascular HU at the site of the plaque divided by the standard deviation of the aortic HU.

PCAT quantification

Following lesion-level quantitative plaque analysis, CT measurement of PCAT attenuation was fully automated by the software (Autoplaque). PCAT was analysed at both per-patient and per-lesion levels. PCAT attenuation surrounding the proximal right coronary artery (10 mm distal to the ostium for a length of 40 mm) was used as a standardized per-patient-level measurement ($PCAT_{RCA}$).[3,5] Per-lesion PCAT attenuation analysis ($PCAT_{lesion}$) was limited to the length of the plaque. PCAT was sampled in three-dimensional layers, progressing radially outwards from the outer vessel wall in 1 mm increments. Adipose tissue was defined as all voxels with attenuation values ranging from −190 to −30 HU. The CT attenuation of PCAT was calculated as the mean CT attenuation in HU of the adipose tissue within the specified volume of interest.[3,13]

Statistical analysis

All statistical analysis was performed on a per-patient level. Computations were performed with IBM SPSS Statistics for Windows (version 26.0. Armonk, NY). The one-sample Kolmogorov–Smirnov test was employed to verify the normal distribution assumption. Data are reported as mean ± standard deviation for normally distributed variables, median with interquartile range for non-normally distributed variables, and *n* (%) for

categorical variables. Normally distributed data were compared using the paired *t*-test, and non-normally distributed data were compared using the Wilcoxon signed rank test. The Pearson χ^2 test was used to compare categorical variables between groups. The average measures for inter- and intraobserver reliability were expressed as intraclass correlation coefficients (ICCs). $P < 0.05$ was considered statistically significant.

Results

Baseline patient demographics and CT imaging quality characteristics

There were 36 patients in the 'statin-naïve' group, 26 patients in the 'statin-commenced' group, and 34 patients in the 'statin-continued' group. At the time of baseline CCTA, there were no significant differences in age, gender, BMI, and prevalence of hypertension, diabetes, cigarette smoking, and family history of ischaemic heart disease between the three groups. Between the baseline and follow-up CCTAs, there were no significant differences between the statin type and dosage intensity taken by the statin-commenced and statin-continued groups. There was significantly higher aspirin usage in the statin-commenced and statin-continued group than the statin-naïve group. Patients in the statin-continued group had a significantly higher prevalence of dyslipidaemia (64% vs. 35% vs. 25%, $P < 0.01$) and a lower LDL cholesterol concentration (2.45 ± 0.91 vs. 2.91 ± 0.98 vs. 3.07 ± 0.87, $P = 0.04$). There was no significant between-group difference in the median interval between baseline and follow-up CCTA [1485 (1158 to 2063) vs. 1312 (1000 to 1741) vs. 1340 (1059 to 1863) days, $P = 0.4$]. These findings are presented in *Table 1*.

Across the three patient groups, we observed no significant difference between baseline and follow-up CCTA with the CT acquisition parameters such as heart rate, contrast dose, and radiation dose (*Table 2*). There was also no significant difference in contrast-to-noise and signal-to-noise ratios between the serial CCTA.

Serial changes in fasting lipid panel and coronary artery calcium score

In the statin-naïve group, there were no changes with any of the fasting lipid panel parameters (*Table 3*). In the statin-commenced group, we have observed a significant reduction in the total cholesterol level from 5.15 ± 1.18 to 3.87 ± 0.92 ($P < 0.0001$) and LDL cholesterol level from 2.98 ± 1.03 to 1.80 ± 0.64 ($P = 0.0002$). There was also a significant reduction observed in the statin-continued group with both the total cholesterol level (4.79 ± 1.54 to 4.22 ± 1.05, $P = 0.01$) and LDL cholesterol level (2.52 ± 0.93 to 2.12 ± 1.01, $P = 0.009$). There were also significant increases in the total and per-vessel coronary artery calcium scores in all three groups (*Table 3*).

Serial changes in quantitative coronary plaque characteristics

We examined the morphological changes in plaque features during the follow-up CCTA (*Table 4*). There was an increase in the prevalence of calcified lesions in all three groups (*Table 3*). In the statin-naïve group, there was a significant increase in the number of calcified plaques (11–48%, $P < 0.0001$), but no significant changes with the non-calcified and mixed plaque number. We also observed a significant increase in the total plaque volume (TPV), calcified plaque volume (CPV), non-calcified plaque volume (NPV), mean plaque burden, and lumen area stenosis.

In the statin-commenced group, we observed a significant reduction in the non-calcified plaques (30–11%, $P < 0.01$) and an increase in the calcified plaques (19–47%, $P < 0.01$). There was also a significant

Table 2 CCTA acquisition parameters and image quality metrics

	Statin-naïve ($n = 36$)			Statin-commenced ($n = 26$)			Statin-continued ($n = 34$)		
	Baseline	Follow-up	*P*	Baseline	Follow-up	*P*	Baseline	Follow-up	*P*
CCTA acquisition parameters									
Heart rate, bpm	55 ± 8	55 ± 6	0.6	58 ± 8	58 ± 6	0.8	58 ± 6	56 ± 8	0.5
Tube voltage									
100 kV	13 (36%)	13 (36%)		9 (35%)	9 (35%)		4 (12%)	4 (12%)	
120 kV	23 (64%)	23 (64%)		17 (65%)	17 (65%)		30 (88%)	30 (88%)	
Contrast dose, mL	75 (70–94)	75 (70–85)	0.1	75 (70–85)	85 (73–90)	0.3	75 (75–97)	75 (70–80)	0.3
Radiation dose, DLP	242 (130–414)	250 (152–317)	0.5	257 (135–345)	265 (171–347)	0.2	289 (232–370)	289 (259–453)	0.5
Image quality									
Contrast-to-noise ratio	16.1 (10.8–19.3)	15.9 (12.6–18.9)	0.9	12.8 (9.7–17.3)	15.4 (13.1–17.2)	0.05	15.9 (11.7–18.6)	14.9 (10.1–19.0)	0.7
Signal-to-noise ratio	13.8 (9.1–16.1)	13.3 (10.2–15.8)	0.7	10.6 (7.9–14.3)	13.1 (10.8–14.4)	0.07	13.3 (9.8–15.1)	12.2 (8.3–15.2)	0.6

Values are expressed as *n* (%), mean ± standard deviations, or median (interquartile range, 25th–75th).
bpm, beats per minute; CCTA, coronary computed tomography angiography; DLP, dose-length product; kV, kilovoltage.

Table 3 Comparison of baseline and follow-up fasting lipid panel and coronary artery calcium scores

	Statin-naïve ($n = 36$)			Statin-commenced ($n = 26$)			Statin-continued ($n = 34$)		
	Baseline	**Follow-up**	***P***	**Baseline**	**Follow-up**	***P***	**Baseline**	**Follow-up**	***P***
Fasting lipid panel, mmol/L									
Total cholesterol	5.02 ± 0.98	5.12 ± 0.97	0.7	5.15 ± 1.18	3.87 ± 0.92	**<0.0001**	4.79 ± 1.54	4.22 ± 1.05	**0.01**
Triglyceride	1.26 ± 0.56	1.32 ± 0.68	0.6	2.03 ± 1.34	1.67 ± 1.21	0.09	1.56 ± 0.85	1.57 ± 0.70	0.9
HDL	1.42 ± 0.42	1.39 ± 0.31	0.6	1.18 ± 0.38	1.20 ± 0.64	0.7	1.29 ± 0.42	1.34 ± 0.33	0.2
LDL	3.03 ± 0.86	3.12 ± 0.83	0.6	2.98 ± 1.03	1.80 ± 0.64	**0.0002**	2.52 ± 0.93	2.12 ± 1.01	**0.009**
Coronary artery calcium score (Agatston units)									
Total	37.91 ± 110.80	102.70 ± 269.40	**0.001**	30.58 ± 95.99	61.04 ± 138.3	**0.002**	38.28 ± 66.57	99.76 ± 160.10	**<0.001**
LAD	20.63 ± 56.81	50.69 ± 139.70	**0.001**	13.63 ± 33.22	31.79 ± 54.70	**0.004**	24.31 ± 45.35	65.17 ± 102.60	**0.002**
LCx	7.06 ± 30.60	21.59 ± 77.87	**0.01**	11.74 ± 46.64	19.32 ± 69.69	0.06	5.79 ± 13.46	17.76 ± 46.17	**0.02**
RCA	10.23 ± 45.20	29.52 ± 98.34	**0.02**	5.16 ± 17.17	9.95 ± 25.86	0.12	8.17 ± 18.13	16.83 ± 34.80	**0.002**

Values are expressed as mean ± standard deviations. Boldface *P*-values indicate statistical significance.
HDL, high-density lipoprotein; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LDL, low-density lipoprotein; RCA, right coronary artery.

Table 4 Conventional coronary plaque characteristics at baseline and follow-up

	Statin-naïve ($n = 64$ lesions)			Statin-commenced ($n = 66$ lesions)			Statin-continued ($n = 66$ lesions)		
	Baseline	**Follow-up**	***P***	**Baseline**	**Follow-up**	***P***	**Baseline**	**Follow-up**	***P***
Plaque composition, *n* (%)									
Non-calcified	18 (28%)	18 (28%)	NS	20 (30%)	7 (11%)	**<0.01**	14 (21%)	12 (18%)	NS
Partially calcified	14 (22%)	15 (24%)	NS	30 (46%)	28 (42%)	NS	17 (26%)	10 (15%)	0.2
Calcified	7 (11%)	31 (48%)	**<0.0001**	13 (19%)	31 (47%)	**<0.01**	17 (26%)	44 (67%)	**<0.01**
Visual luminal stenosis									
<50%	63 (98%)	60 (94%)	0.4	54 (82%)	48 (72%)	0.3	59 (89%)	48 (73%)	**0.03**
≥50%	1 (2%)	4 (6%)	0.4	12 (18%)	18 (27%)	0.3	7 (11%)	18 (27%)	**0.03**
Quantitative plaque metrics									
Total plaque volume, mm^3	132.5 (56.2–308.6)	146.2 (76.5–356.4)	**<0.01**	143.5 (68.6–307.3)	163.2 (83.5–331.5)	**<0.01**	140.2 (62.3–306.6)	155.4 (78.4–342.6)	**<0.001**
Calcified plaque volume, mm^3	8.4 (1.2–21.5)	12.4 (2.2–29.7)	**<0.01**	7.5 (1.6–23.9)	20.3 (7.5–45.6)	**<0.0001**	16.5 (10.3–34.8)	29.1 (17.8–50.2)	**0.001**
Non-calcified plaque volume, mm^3	118.2 (47.1–262.5)	134.6 (68.4–266.7)	**<0.01**	132.2 (62.4–275.8)	129.4 (66.1–280.1)	0.056	130.7 (62.9–276.9)	128.1 (64.7–276.5)	**0.02**
Lesion length, mm	12.1 (6.0–30.6)	14.1 (6.7–30.3)	**<0.001**	13.6 (6.4–31.2)	14.3 (7.2–30.4)	**<0.05**	13.9 (6.2–31.5)	14.4 (6.9–30.6)	**0.03**
Mean plaque burden	0.57 (0.49–0.62)	0.61 (0.52–0.66)	**0.003**	0.56 (0.52–0.63)	0.60 (0.54–0.67)	**0.02**	0.58 (0.55–0.68)	0.61 (0.55–0.69)	**0.01**
Lumen area stenosis (%)	42 (25–53)	47 (32–55)	**<0.001**	41 (27–56)	46 (035–61)	**<0.05**	42 (26–57)	46 (34–62)	**0.03**

Values are expressed as *n* (%) or median (interquartile range, 25th–75th). Boldface *P*-values indicate statistical significance.

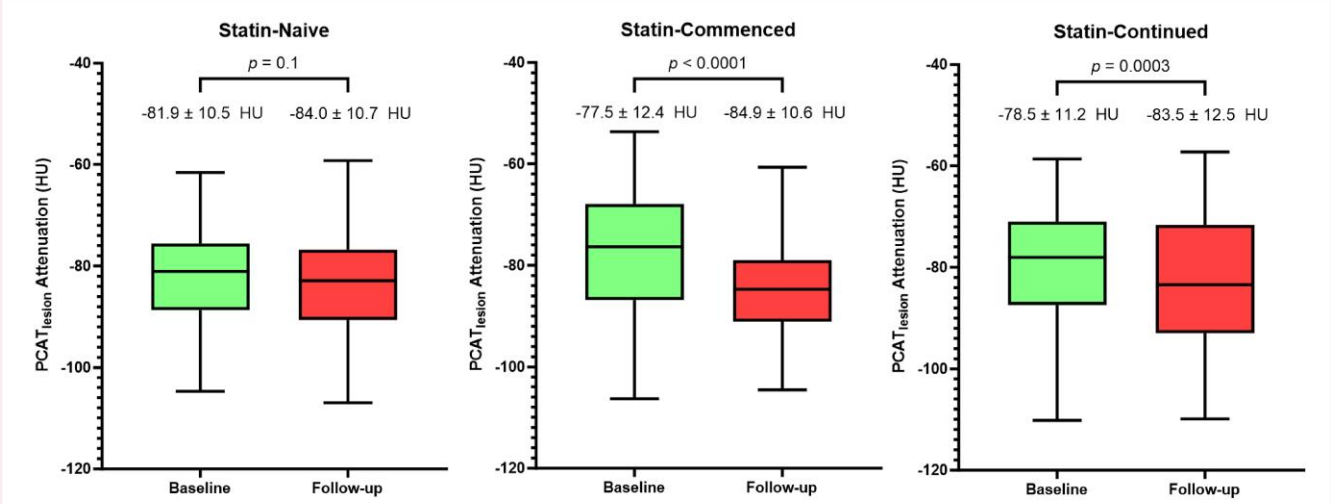


Figure 2 Changes in $PCAT_{lesion}$ attenuation value across the three groups with different statin intake histories. There was significant reduction in $PCAT_{lesion}$ in the statin-commenced (-77.5 ± 12.4 to -84.9 ± 10.6 HU, $P < 0.0001$) and statin-continued groups (-78.5 ± 11.2 to -83.5 ± 12.5 HU $P = 0.0003$). No significant change was seen in the statin-naïve group (-81.9 ± 10.5 to -84.0 ± 10.7, $P = 0.1$).

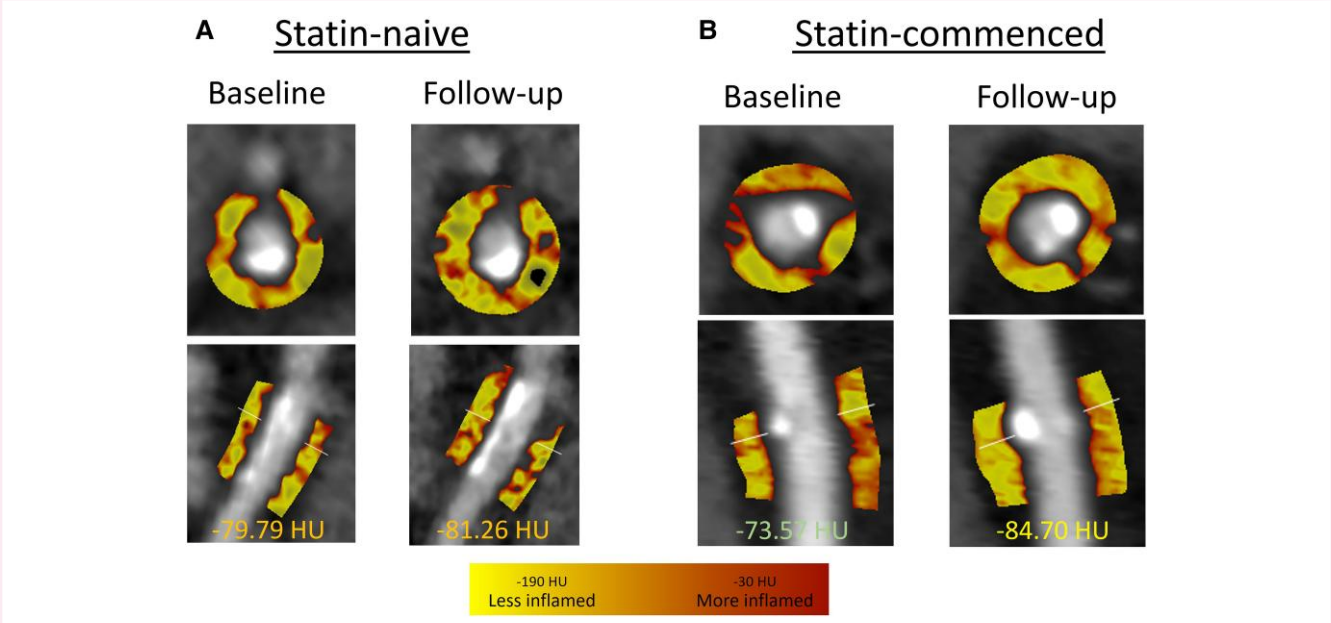


Figure 3 Baseline and follow-up $PCAT_{lesion}$ attenuation maps on CCTA. PCAT around the coronary plaque is shown in cross-section (upper panels) and curved multi-planar views (lower panels) in case examples of patients who are statin-naïve (*A*) and statin-commenced (*B*).

increase in the total plaque volume [143.5 (68.6–307.3) to 163.2 (83.5–331.5), $P < 0.01$] and calcified plaque volume [7.5 (1.6–23.9) to 20.3 (7.5–45.6), $P < 0.0001$]. There was a trend for a reduction in the non-calcified plaque volume [132.2 (62.4–275.8) to 129.4 (66.1–280.1)], but it was not statistically significant ($P = 0.056$).

In the statin-continued group, we observed a significant increase in the calcified plaque count only (26–67%, $P < 0.01$). Similarly, there were significant increase in the total plaque volume [140.2 (62.3–306.6) to 155.4 (78.4–342.6), $P < 0.001$] and calcified plaque volume [16.5 (10.3–34.8) to 29.1 (17.8–50.2), $P = 0.0001$]. In contrast, here, we observed a significant reduction in the non-calcified plaque volume [130.7 (62.9–276.9) to 128.1 (64.7–276.5), $P = 0.02$].

Serial changes of per-lesion and per-patient PCAT attenuation

There was a significant reduction in $PCAT_{lesion}$ in the statin-commenced (-77.5 ± 12.4 HU to -84.9 ± 10.6 HU, $P < 0.0001$)

and statin-continued groups (−78.5 ± 11.2 HU to −83.5 ± 12.5 HU, $P = 0.0003$) (*Figure 2*). Meanwhile, no significant change was seen in the statin-naïve group (−81.9 ± 10.5 to −84.0 ± 10.7, $P = 0.1$). *Figure 3* shows case examples of PCAT attenuation maps on CCTA of statin-naïve and statin-commenced patients at baseline and follow-up. Mixed-effect multivariable linear regression analysis showed statin intensity (β coefficient: 30.877, $P = 0.003$) and LDL change (β coefficient: 3.630, $P = 0.02$) to be independently associated with percentage change of $PCAT_{lesion}$, after correcting for cardiovascular risk factors, changes in body weight, and coronary artery calcium score (*Table 5*).

At the per-patient level, we observed a significant reduction in $PCAT_{RCA}$ in all three cohorts (*Figure 4*). The greatest reduction was noted in the statin-commenced cohort (−75.6 ± 9.5 HU to −84.3 ± 8.5 HU, $P < 0.0001$), followed by the statin-continued cohort (−76.2 ± 9.7 to −80.2 ± 10.2, $P = 0.03$), and with the statin-naïve cohort having the lowest change (−78.8 ± 9.4 HU to −83.3 ± 7.9 HU, $P < 0.01$).

Table 5 Mixed-effect linear regression model assessing predictors of $PCAT_{lesion}$ attenuation percentage change

	β coefficient[a]	95% CI Lower	95% CI Upper	*P*-value
Age, y	−0.17	−0.535	0.196	0.358
Male gender	−2.841	−10.52	4.839	0.464
Hypertension	0.092	−7.648	7.832	0.981
Diabetes	5.734	−3.463	14.931	0.218
Smoker	−6.229	−12.808	0.350	0.063
Weight change, kg	0.350	−0.041	0.74	0.079
Change in total Agatston score	−0.004	−0.018	0.009	0.533
LDL change, mmol/L	3.630	0.583	6.677	**0.02**
Statin intensity	30.877	6.195	55.558	**0.003**

Boldface *P-value* indicates statistical significance.
LDL, low-density lipoprotein; $PCAT_{lesion}$, pericoronary adipose tissue attenuation adjacent to atherosclerotic plaques.
[a]Dependent variable: percentage of $PCAT_{lesion}$ change between the serial CCTAs.

Reproducibility analysis for per-lesion and per-patient PCAT attenuation

There were high intraobserver and interobserver repeatability with both per-lesion and per-patient PCAT attenuation. Interobserver ICCs for per-lesion and per-patient PCAT attenuation were 0.99 (95% confidence interval: −3.4–2.95, $P < 0.001$) and 0.99 (95% confidence interval: −2.63–2.39, $P < 0.001$). Interobserver ICCs for per-lesion and per-patient PCAT attenuation were 0.99 (95% confidence interval: −3.69–3.16, $P < 0.001$) and 0.99 (95% confidence interval: −2.33–2.6, $P < 0.001$).

Discussion

In this retrospective observational study, we evaluated the temporal changes in PCAT attenuation of patients with and without statin therapy. Understanding the natural history of patients free from the influence of statin is essential to help with the design of future clinical trials and informing sample size calculations. Our main finding is that statin therapy was associated with a reduction in $PCAT_{lesion}$ attenuation, while no significant change was observed without statin therapy. Furthermore, statin intensity and LDL change were both independently associated with percentage change of $PCAT_{lesion}$ after correcting for cardiovascular risk factors and changes in body weight and coronary artery calcium scores. We also observed that there is a reduction in NCP volume in the statin-continued group in contrast with an increase in NCP volume in the statin-naïve group.

PCAT attenuation is an established non-invasive imaging biomarker that has been demonstrated to reflect regional atherosclerotic burden and the extent of local inflammation.[4,13,14] Furthermore, elevated PCAT attenuation has been shown to have independent and incremental predictive value for MACE beyond the presence of CCTA-defined high-risk plaques.[5,15–18] This in turn has led to several observational studies to explore the capacity of PCAT attenuation to dynamically

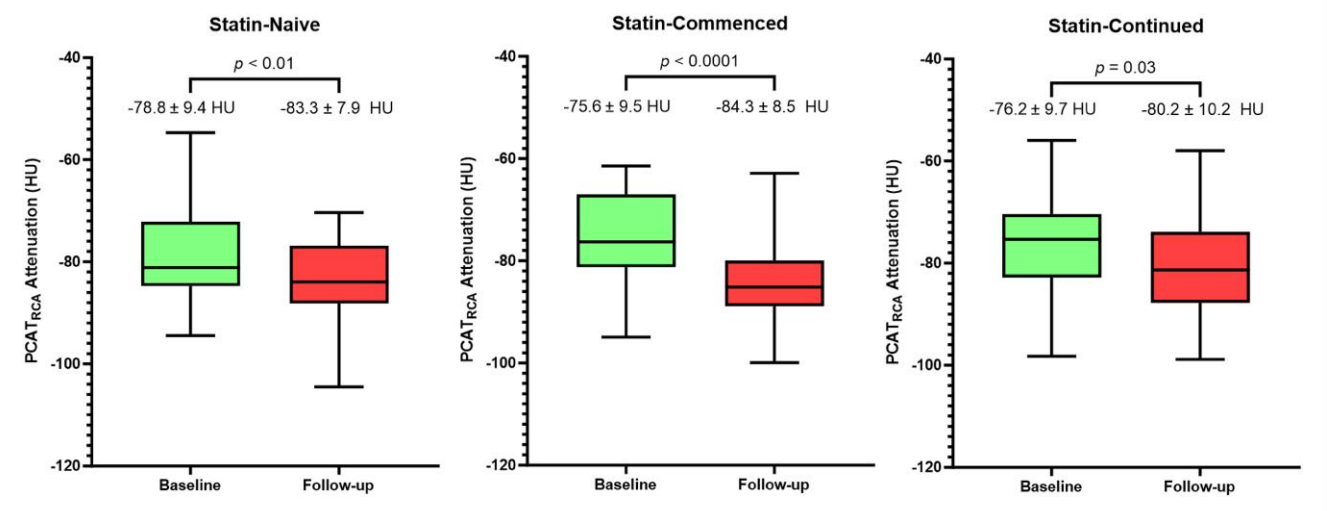


Figure 4 Changes in $PCAT_{RCA}$ across the three groups with different statin intake histories. There was a significant reduction in $PCAT_{RCA}$ in all three cohorts. The statin-commenced cohort has the greatest reduction (−75.6 ± 9.5 to −84.3 ± 8.5 HU, $P < 0.0001$), followed by the statin-continued cohort (−76.2 ± 9.7 to −80.2 ± 10.2, $P = 0.03$), and with the statin-naïve cohort having the lowest change (−78.8 ± 9.4 to −83.3 ± 7.9 HU, $P < 0.01$).

track inflammatory changes within the vasculature, including those induced by therapeutic interventions. In a prospective study of 134 patients with psoriasis who underwent serial CCTA, biologic therapy was associated with a significant decrease in PCAT attenuation at 1-year follow-up, while no change was observed in those not receiving biologic therapy.[19] A retrospective study of 108 statin-naïve patients who were commenced on statin treatment and underwent follow-up CCTA after a mean period of 16.6 months has demonstrated a significant reduction in $PCAT_{lesion}$ (-69.8 ± 9.1 HU to -72.1 ± 8.9 HU, $P < 0.001$).[8] In our study, the statin-commenced cohort underwent a longer mean follow-up period of 43 months and demonstrated a larger reduction in $PCAT_{lesion}$. For the first time in the current literature, we report the natural history of $PCAT_{lesion}$ and $PCAT_{RCA}$ attenuation in patients not treated with statin therapy. Understanding the natural history of PCAT attenuation is an important step in utilizing this non-invasive imaging biomarker for future clinical intervention trials with its design and sample size calculation.

In our statin-naïve cohort, we observed a significant reduction with the $PCAT_{RCA}$ but not with the $PCAT_{lesion}$. This suggests that $PCAT_{lesion}$ offers a more specific marker in monitoring the anti-inflammatory effect of statin. The proximal RCA is the most well-studied and standardized per-patient-level marker of PCAT attenuation, following the landmark study by Antonopoulos *et al.*[3] This is due to the substantial amount of PCAT surrounding the RCA in the atrioventricular groove, along with the absence of confounding non-fatty structures such as major side branches, accompanying coronary veins and myocardium.[3] On the other hand, $PCAT_{lesion}$ has been shown to be increased around plaques with high 18F-sodium fluoride uptake on PET imaging in stable patients with high-risk plaque features, whereas $PCAT_{RCA}$ showed no difference.[20] Furthermore, $PCAT_{lesion}$ has also been shown to be able to distinguish between culprit vs. non-culprit lesions in patients presenting with ACS.[13] We suggest that future studies should include measurement of both $PCAT_{RCA}$ and $PCAT_{lesion}$ to provide a comprehensive understanding of the status of the patient's coronary inflammation. $PCAT_{RCA}$ provides a broader general overall of the inflammatory status of the coronary arteries and would be useful for epidemiological studies or in screening of CAD risk. On the other hand, $PCAT_{lesion}$ offers targeted insight into the local inflammatory environment around the atherosclerotic plaque once the patient has developed CAD which is valuable in evaluating the risk of plaque rupture and the risk of acute coronary events. Therefore, $PCAT_{RCA}$ would be useful for global CVD risk assessment and may guide primary prevention strategies while $PCAT_{lesion}$ is more suited for managing established CAD and preventing acute coronary events.

Evaluation of coronary plaque characteristics on CCTA has been shown to be strongly predictive of patient risk over and above standard clinical data relying on conventional cardiovascular risk factors.[21–24] Specifically, in keeping with current literature, our findings have demonstrated that statin therapy is associated with regression of NPV but a more rapid progression of CPV.[25,26] This is supportive of statin's cardioprotective effect as elevated NPV has been shown to be highly predictive of future ACS.[23] Interestingly, we observed an increase in the total plaque volume, mean plaque burden, and lumen area stenosis regardless of the statin history. Similar changes in plaque composition following treatment with statin therapy have been reported in previous studies.[25,26] Although there is an increase in plaque volume and burden across the three groups, it was driven by a predominant increase in the NPV in the statin-naïve group in contrast to a predominant increase in the CPV in the statin groups. Our observation of reduced $PCAT_{lesion}$ is concordant with the reduction in NCV and is in keeping with prior observation.[4] It has been hypothesized that the increase in coronary calcification represents a healing mechanism of statins, whereby coronary plaques become increasingly stabilized through calcification of the necrotic core.[27] There is also growing evidence linking elevated PCAT attenuation with higher NPV and no correlation with stenosis severity.[28,29] This is supportive of the hypothesis that perivascular inflammation is more related to the adjacent plaque composition, whereas high-grade stenosis may arise due to loco-regionally altered haemodynamic conditions.[30]

In the statin-commenced groups, we observed a significant reduction in $PCAT_{lesion}$ whereas the NPV was trending towards a reduction ($P = 0.056$). This suggests that $PCAT_{lesion}$ may be a more sensitive marker of the early treatment effects of statins. Mechanistically, the reduction in vascular inflammation in response to statin treatment may precede changes in the atherosclerotic plaque.[31] Our findings suggest that $PCAT_{lesion}$ attenuation value could potentially identify patients with early coronary inflammation, thereby allowing for the identification of patients with residual coronary inflammation and assessment of the effect of anti-inflammatory therapy.

Limitations

The study is limited by its retrospective nature and its relatively small sample size with imaging data collected from two CT vendors. Secondly, it is not possible to determine the correlation of PCAT change with major adverse cardiovascular events as the primary endpoint of this study was the change PCAT attenuation and no follow-up was performed after the second CCTA. Hence, future prospective studies with larger sample size and longer follow-up period are warranted to investigate the relationship between PCAT improvement and prognosis.

Conclusion

Statin therapy was associated with a significant reduction in $PCAT_{lesion}$ attenuation while no significant in $PCAT_{lesion}$ attenuation was observed in the absence of statin therapy. PCAT attenuation can be a potential imaging biomarker to monitor the coronary anti-inflammatory response of future therapies.

Trial registration

This study has been prospectively registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12621001018808).

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures in this study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013), International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. The final protocol was reviewed and approved by the Ethics Committees and Institutional Review Boards at each study site and by the Monash Health Human Research Ethics Committee, Melbourne, Australia (HREC/75307/MonH/2021). All participating hospitals/centres were informed and agreed on the study. Informed consent is obtained from the participants in the prospective arm prior to enrolment, and the data and samples are de-identified and managed entirely anonymously.

Conflict of interest: None declared.

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Data availability

The data underlying this article cannot be shared publicly to protect the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

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