Effect of Statin Therapy on Fibrous Cap Thickness in Coronary Plaque on Optical Coherence Tomography

— Review and Meta-Analysis —

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Background: Statin therapy has been shown to result in coronary plaque regression, but the relationship between statin use and stabilization of coronary plaque has not been elucidated. We conducted a systematic review and meta-analysis to evaluate the effect of statin therapy on fibrous cap thickness (FCT) on optical coherence tomography (OCT).

Methods and Results: Nine OCT studies (6 randomized controlled trials and 3 observational studies) were enrolled with a total of 341 patients (390 lesions). Arms of the studies were grouped according to statin type and/or dose. Random effects meta-analysis was used to estimate a pooled mean change in FCT from baseline to follow-up. The overall effect mean FCT change was 67.7 μ m (95% CI: 51.4–84.1, $I^2=95.0\%$, $P<0.001$). All statin groups had an increase in FCT, but the magnitude of the increase differed according to the statin. Two homogeneous subgroups with $I^2=0$ were identified: mean FCT change was 27.8 μ m (for subgroup atorvastatin 5mg and rosuvastatin), and 61.9 μ m (for subgroup atorvastatin 20mg, fluvastatin 30mg, and pitavastatin 4mg). On meta-regression modeling, statin therapy alone explained most of the change in FCT.

Conclusions: Statin therapy induced a significant increase in FCT as assessed on OCT, independent of coronary risk factors and other medications.

Key Words: Fibrous cap thickness; Meta-analysis; Optical coherence tomography; Statin

Coronary plaque with lipid-rich pool covered with thin fibrous cap is referred to as high-risk plaque for rupture.¹ Thin-cap fibroatheroma (TCFA) is recognized as a precursor lesion for plaque rupture.^{2,3} To our knowledge, plaque rupture occurs frequently at the thinnest fibrous cap site and results in acute coronary syndrome (ACS). The fibrous cap usually can be ruptured when it is <160 μ m thick and is easier to be ruptured as the fibrous cap thickness (FCT) becomes thinner.⁴ Intravascular optical coherence tomography (OCT) is an intracoronary imaging modality with a high resolution and enables in vivo visualization of the microstructural characteristics of coronary plaque.⁵

Intensive statin therapy results in the reduction of cardiovascular events and suppresses the progression of atherosclerotic plaques.^{6,7} Further, statin therapy also leads to an increase in FCT on OCT, as shown in several clinical trials.^{7–10} This increase of FCT has a significant correlation with decrease of low-density lipoprotein cholesterol (LDL-C),^{9,10} but no correlation was observed in another study.⁸

Taken together, the results were not consistent across studies, and most of those studies were small in terms of sample size.

Therefore, we performed a systematic review and meta-analysis to evaluate the effect of statin therapy on FCT using OCT, and the relationship between FCT and coronary risk factors and medication.

Methods

Search Strategy

We conducted a literature search of MEDLINE/PubMed and Web of Science up to July 2018. The search terms were “optical coherence tomography”, “fibrous cap”, “coronary artery disease”, and “statin(s) therapy”. Data were abstracted independently by 2 investigators (Y.O. and S.S.B.) in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹

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Table 1. Characteristics of the Included Studies

Study	Year	Study design	Follow-up (months)	Study drug	Statin-dose (mg/day)	Clinical presentation	Study arms	
							Patient (n)	Lesion (n)
Takarada et al ⁷	2009	Non-randomized (statin vs. non-statin)	9	Statin Non-statin	NR —	AMI	23 17	23 17
Imanishi et al ⁸	2010	Non-randomized (statin vs. non-statin)	9	Statin Non-statin	NR —	UAP	25 15	25 15
Hattori et al ¹⁰	2012	Non-randomized (pitavastatin vs. diet therapy)	9	Pitavastatin Diet therapy	4 —	SAP	26 16	26 16
Nishiguchi et al ¹⁶	2018	RCT (early vs. late)	9	Pitavastatin	4 (early) 4 (late)	ACS	25 28	25 28
Nishio et al ¹²	2014	RCT (rosuvastatin vs. rosuvastatin+EPA)	9	Rosuvastatin Rosuvastatin+EPA	3.50±3.25 3.67±2.08	ACS+SAP	15 15	26 23
Habara et al ¹³	2014	RCT (fluvastatin vs. fluvastatin+ezetimib)	9	Fluvastatin Fluvastatin+ezetimib	30 30	SAP	26 31	26 31
Komukai et al ⁹	2014	RCT (atorvastatin 5 mg vs. 20 mg)	12	Atorvastatin	5 20	UAP	30 30	30 30
Hou et al ¹⁴	2016	RCT (atorvastatin 20 mg vs. 60 mg)	12	Atorvastatin	20 60	CAD	19 27	30 36
Wang et al ¹⁵	2016	RCT (atorvastatin 20 mg vs. 60 mg)	12	Atorvastatin	20 60	CAD	9 12	16 15

Data given as mean ± SD or n. ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; EPA, eicosapentaenoic acid; NR, not reported; RCT, randomized control trial; SAP, stable angina pectoris; UAP, unstable angina pectoris.

Selection Criteria

The inclusion criteria were as follows: (1) trials providing coronary FCT assessed using OCT at baseline and follow-up (6–12 months); (2) trials with >1 group of patients receiving statin therapy; (3) clinical studies published in

peer-reviewed journals; and (4) reports in English. The exclusion criteria were: (1) trials analyzing in-stent morphology; and (2) reviews, meeting abstracts, or unpublished literature.

Table 2. Subject Characteristics

Study	Study arm	Age (years)	Male	DM	HTN	DLP
Takarada et al ⁷	Statin	62±10	14 (61)	7 (30)	14 (61)	23 (100)
Imanishi et al ⁸	Statin	66±11	17 (68)	13 (52)	16 (64)	20 (80)
Hattori et al ¹⁰	Pitavastatin	66±7.8	25 (96.1)	9 (34.6)	13 (50)	NR
Nishiguchi et al ¹⁶	Early pitavastatin	66 (63–71)	19 (76)	10 (40)	15 (60)	25 (100)
	Late pitavastatin	66 (62–74)	23 (82)	9 (32)	19 (68)	28 (100)
Nishio et al ¹²	Rosuvastatin	63.8±9.5	13 (86.7)	2 (13.3)	10 (66.7)	NR
	Rosuvastatin+EPA	61.0±12.6	13 (86.7)	5 (33.3)	11 (73.3)	NR
Habara et al ¹³	Fluvastatin	68.8±7.8	26 (83)	13 (41)	18 (58)	NR
	Fluvastatin+ezetimib	69.8±7.8	21 (65)	11 (34)	23 (71)	NR
Komukai et al ⁹	Atorvastatin 5 mg	69 (58–74)	22 (73)	6 (20)	20 (67)	30 (100)
	Atorvastatin 20 mg	63 (58–73)	26 (87)	7 (23)	18 (60)	30 (100)
Hou et al ¹⁴	Atorvastatin 20 mg	54±9.3	13 (68)	9 (47)	12 (63)	NR
	Atorvastatin 60 mg	55±10	17 (63)	11 (41)	15 (56)	NR
Wang et al ¹⁵	Atorvastatin 20 mg	55.1±6.8	5 (55.6)	5 (55.6)	7 (77.8)	1 (11.1)
	Atorvastatin 60 mg	60.3±6.7	5 (41.7)	3 (25)	9 (75)	4 (33.3)

Smoker [†]	Previous MI	Target vessel			Medication			
		LAD	LCX	RCA	ACEI/ARB	β-blocker	CCB	Nitrates
10 (43)	3 (13) [‡]	NR	NR	NR	16 (70)	12 (52)	NR	5 (22)
10 (40)	NR	14 (56)	4 (16)	7 (28)	18 (72)	7 (28)	NR	NR
14 (53.8)	NR	15 (57.7)	0	11 (42.3)	18 (69)	12 (46)	9 (35)	NR
10 (40)	NR	10 (40)	8 (32)	7 (28)	7 (28)	3 (12)	8 (32)	NR
10 (36)	NR	11 (39)	7 (25)	10 (36)	7 (25)	1 (4)	7 (25)	NR
9 (60)	NR	NR	NR	NR	9 (60)	3 (20)	5 (33.3)	NR
12 (80)	NR	NR	NR	NR	10 (66.7)	3 (20)	2 (13.3)	NR
10 (32)	NR	10 (32)	8 (26)	13 (42)	17 (54.8)	2 (7)	14 (45)	6 (19)
7 (21)	NR	9 (28)	15 (47)	8 (25)	10 (31.3)	2 (6)	14 (43)	6 (19)
15 (50)	NR	10 (33)	6 (20)	14 (47)	27 (90)	18 (60)	3 (10)	NR
19 (63)	NR	14 (47)	8 (27)	8 (27)	26 (87)	20 (67)	4 (13)	NR
8 (42)	4 (21)	8 (27)	6 (20)	16 (53)	7 (37)	11 (58)	4 (21)	11 (58)
15 (56)	7 (26)	12 (33)	7 (20)	17 (47)	13 (48)	19 (70)	8 (30)	15 (56)
4 (44.4)	3 (33.3)	4 (25)	3 (18.8)	9 (56.3)	6 (66.7)	6 (66.7)	2 (22.2)	5 (55.6)
5 (41.7)	2 (16.7)	5 (33.3)	4 (26.7)	6 (40)	5 (41.7)	9 (75)	5 (41.7)	6 (50)

[†]Current or previous. [‡]Previous coronary artery disease. Data given as mean±SD, median (IQR), or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CCB, calcium channel blocker; DLP, dyslipidemia; DM, diabetes mellitus; EPA, eicosapentaenoic acid; HTN, hypertension; LAD, left anterior descending; LCX, left circumflex; MI, myocardial infarction; NR, not reported; RCA, right coronary artery.

Data Extraction and Quality Assessment

Two reviewers (Y.O. and S.S.B.) independently evaluated the studies for eligibility and extracted the data. The following variables were entered into a dedicated extraction form: study design, patient characteristics, type and dose of statins, follow-up duration, coronary risk factors, and OCT findings including FCT and lipid arc. Inconsistencies in the extraction of the data were resolved in a consensus meeting looking at the original reports.

The primary endpoint was the change in FCT between baseline and follow-up after statin therapy. FCT was defined as the minimum thickness of the signal-rich band overlying the lipid core, as previously described in the consensus document.⁵ The second outcome was the change in lipid arc after statin therapy.

Statistical Analysis

Random effects meta-analysis was used to assess study heterogeneity and estimate a pooled mean change in FCT from baseline to follow-up. Because the data are paired (change from baseline to follow-up), meta-analysis calculations for comparing 2 independent treatment groups do not apply. The correlation between baseline and follow-up measures for each study is needed to calculate the proper standard error of differences. This is likely not provided in published studies: patient-level data would be needed. Based on patient-level data obtained from 2 of the studies (The EASY-FIT Study and The ESCORT Study), the correlation between baseline and follow-up FCT was 0.70. This was the correlation used to calculate the standard error for paired differences. It is, of course, possible that the correlation would not be the same from study to study. As sensitivity analyses, the standard error was recalculated

Table 3. Lipid Profiles of the Groups Treated With Statin at Baseline and Follow-up

Study	Study arm	TC (mg/dL)		LDL-C (mg/dL)		HDL-C (mg/dL)		Triglycerides (mg/dL)	
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Takarada et al ⁷	Statin	218±16	166±22	144±22	91±12	41±8	45±6	158±50	142±38
Imanishi et al ⁸	Statin	207±47	164±34	129±40	85±25	44±10	49±17	NR	NR
Hattori et al ¹⁰	Pitavastatin	197±46	164±24	134±40	89±23	46±11	58±16	147±48	137±82
Nishiguchi et al ¹⁶	Early pitavastatin	185 (171–199)	140 (123–149)	117 (105–129)	67 (63–78)	40 (38–45)	41 (37–48)	103 (80–156)	116 (92–146)
	Late pitavastatin	190 (177–213)	143 (124–167)	118 (109–135)	76 (56–91)	43 (37–49)	45 (38–54)	95 (84–144)	100 (81–128)
Nishio et al ¹²	Rosuvastatin	196.3±40.3	146.3±20.5	130.3±34.8	83.2±19.6	41.5±7.4	43.6±9.4	146.8±37.4	131.4±47.9
	Rosuvastatin+EPA	207.3±39.1	144.4±36.5	138.0±35.3	80.1±29.7	40.9±12.0	44.9±9.9	161.4±50.4	123.5±42.6
Habara et al ¹³	Fluvastatin	193.8±37.4	177.5±37.2	109.1±30.2	100.8±27.6	48.1±10.2	49.1±11.1	113±60.6	118±27.6
	Fluvastatin+ezetimib	197.8±37.4	160.4±35.4	122.5±33.6	88.5±29.5	49.9±13.0	50.6±12.2	126±50.4	142±81.3
Komukai et al ⁹	Atorvastatin 5 mg	195 (176–216)	159 (130–195)	117 (110–138)	78 (66–108)	42 (34–53)	43 (35–54)	138 (85–169)	128 (96–154)
	Atorvastatin 20 mg	194 (176–220)	143 (128–156)	127 (111–155)	69 (61–80)	43 (34–49)	45 (36–49)	109 (86–176)	96 (78–132)
Hou et al ¹⁴	Atorvastatin 20 mg	NR	NR	115±28	80±32	50±12	50±18	NR	NR
	Atorvastatin 60 mg	NR	NR	114±23	67±21	47±10	41±8.3	NR	NR
Wang et al ¹⁵	Atorvastatin 20 mg	215±42	164.9±51.7	121.2±26.9	93±35.3	52.6±14.1	46.9±19.4	NR	NR
	Atorvastatin 60 mg	198.2±32.6	139.2±24	110.3±25.4	69.3±16.6	49.8±10.8	43.1±14.2	NR	NR

Data given as mean ± SD or median (IQR). EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not reported; TC, total cholesterol.

assuming correlations of 0.2 and 0.5. Given the means and standard deviations of baseline and follow-up data, the standard deviation of baseline to follow-up differences is:

$$SD(\text{baseline} - \text{follow-up}) = \sqrt{\text{variance}(\text{baseline}) + \text{variance}(\text{follow-up}) - 2r * (SD(\text{baseline}) * (SD(\text{follow-up})))}$$

where r is the correlation of the paired differences. The standard error of paired differences is then given by dividing the standard deviation by the square root of the sample size. Thus, the data for the meta-analysis was study mean difference with its estimated standard error. The same issue applies when performing meta-regression of change in lipid levels with change in FCT from baseline to follow-up. Using patient data from the EASY-FIT and ESCORT study, the standard error of the regression was estimated from the total cholesterol (TC), LDL-C, and high-density lipoprotein cholesterol (HDL-C) regressions with the change in FCT.

Arms of the studies were grouped according to similar statins and/or doses (**Supplementary Table**). Random effects meta-analysis was used to obtain a pooled estimate of change in FCT/lipid arc of the statin groups and assess statin group heterogeneity using the I^2 statistic. If I^2 was large, studies were identified with $I^2 < 10\%$ and pooled estimates of change were made.

Linear regression was used to assess the association of statin use with change in FCT and lipid arc (weighting the regression with the number of patients in each arm). Data provided by the studies that could be used in multivariable analysis included age, sex, diabetes, hypertension, smoking, angiotensin-converting enzyme inhibitor/angiotensin-II receptor blocker (ACEI/ARB), and β -blocker use. For each model, the R^2 statistics (and P-value) are provided. Because some of the statin arms were from the same study, “Study” was included in the regression analyses as a random effect. Stata v15 (Stata Corp, College Station, TX,

USA) was used for all analyses.

Results

A total of 113 reports were identified in the search. After excluding duplication and screening the titles and abstracts, 16 studies were retrieved for full-text reviews. Of these 16 studies, 7 were excluded, and 9 studies (6 randomized controlled trials [RCT] and 3 non-randomized placebo controlled studies) met the inclusion criteria. To evaluate the effect of statin therapy on FCT, we included 15 arms in these 9 OCT studies: 13 arms receiving only statin treatment (6 used atorvastatin, 3 pitavastatin, 1 rosuvastatin, 1 fluvastatin, and 2 others a mix of them) and 2 arms receiving combination treatment (rosuvastatin+eicosapentaenoic acid and fluvastatin+ezetimib), in which there was a total of 341 patients with 390 target lesions, in the meta-analysis (**Figure 1**). Of note, all patients were Asian, and, as such, statin dose was given accordingly. The target lesions in all of the studies were non-culprit lesions.

Table 1 summarizes the characteristics of the included studies. Six studies were RCT,^{9,12–16} and the other 3 studies were non-randomized placebo controlled studies.^{7,8,10} **Table 2** lists the baseline patient characteristics of all patients. Patient age range was 54–69 years old, and 41–96% of patients were male. The length of the follow-up period was 12 months in the 3 studies^{9,14,15} and 9 months in the other 6 studies.^{7,8,10,12,13,16} In the 3 studies including the EASY-FIT study, 2 different dosages of atorvastatin were used.^{9,14,15} Two studies compared statin and other lipid-lowering agents (eicosapentaenoic acid and ezetimib) in addition to statin,^{12,13} and the other 3 studies compared with statin and without statin.^{7,8,10} The ESCORT study investigated the effect of the timing of statin (3 or 36 weeks) in patients with ACS.¹⁶ Lipid arc data were provided in 5 of the studies.^{9,12–14,16} The lipid profiles in the included studies are described in **Table 3**.

A **B**

Figure 2. Forest plots of (A) overall studies, comparing change in fibrous cap thickness (FCT) from baseline to follow-up, and (B) the 2 homogenous subgroups identified with $I^2=0$, comparing change in FCT for 2 groups. Positive value indicates increase. EPA, eicosapentaenoic acid.

A **B**

Figure 3. Forest plot of (A) the studies including lipid arc, and (B) the statin groups with $I^2=0$, comparing changes in lipid arc from baseline to follow-up. Negative value indicates decrease. EPA, eicosapentaenoic acid.

The overall ungrouped random effect mean FCT change was 67.7 μm (95% CI: 51.4–84.1, $I^2=95.0\%$, $P<0.001$; **Figure 2A**). Pooling of the 9 studies, however, resulted in considerable heterogeneity (between-study variability [I^2] was 95.0%). Meta-analysis of the statin groups identified 2 homogenous subgroups with $I^2=0$ for both: atorvastatin 5mg and rosuvastatin (mean FCT change, 27.8 μm ; 95% CI: 13.8–41.8) and atorvastatin 20mg, fluvastatin 30mg, and pitavastatin 4mg (61.9 μm , 95% CI: 50.8–72.9). The atorvastatin 60mg and statin groups stood alone with larger mean increases in FCT than any of the other groups and differed from each other as well (**Figure 2B**). Although all statin groups had an increase in FCT, the estimate of the change varied from 27 μm to >100 μm .

On pooling of the 5 RCT with valid lipid arc data (consisting of a total of 246 patients), the random effect mean lipid arc change from baseline to follow-up was -31.5° (95% CI: -38.0 to -25.1 , $I^2=56.2\%$, $P=0.015$, **Figure 3A**). On meta-analysis of the statin groups, the mean change in lipid arc was -32.4° (95% CI: -36.3 to -28.6) with $I^2=0$ (**Figure 3B**).

Statin group accounted for 75.6% of the change in FCT from baseline to follow-up. The covariates that accounted for >10% of the variance were age for 11.1%, male gender for 18.9%, diabetes mellitus for 20.7%, and ACEI/ARB for 11.2% (**Table 4A**). Furthermore, when included with the statin group, only a trivial change in R^2 was observed

(**Table 4B**). In lipid arc change, the statin group accounted for 90% of the change (data not shown). Meta-regression analysis of the change in FCT with the changes in lipid profile after statin therapy is given in **Table 5**. Significant correlations were observed between the change in FCT and the changes in TC ($P=0.025$) and LDL-C ($P=0.012$), but not in HDL-C ($P=0.427$) during follow-up.

The risk of bias in all included studies is shown in **Supplementary Figure**. Most of the studies were judged as having a low risk of bias (reported in green). Six of the 9 studies were randomized,^{9,12–16} and 3 of the nine studies used random sequence generation.^{9,13,16} All of the randomized studies reported details of dropouts or withdrawals and of the inclusion and exclusion criteria.

Discussion

The present meta-analysis reports on the changes in FCT in 6 RCT and 3 non-randomized placebo controlled studies in patients with coronary artery disease (CAD) treated with statin therapy: first, the pooled mean increase from the 9 studies would not be a valid and reliable estimate of the effect of statin on change in FCT because the pooling resulted in considerable heterogeneity (between-study variability [I^2] was >90%). There were, however, statistically significantly different estimates of mean FCT change (27.8 μm for subgroup: atorvastatin 5mg and rosuvastatin; and 61.9 μm for subgroup: atorvastatin 20mg, fluvastatin 30mg, and pitavastatin 4mg) based on the identification of 2 homogeneous subgroups with $I^2=0$. And second, on multivariate modeling, statin therapy was most associated with change in FCT. To the best of our knowledge, this is the first meta-analysis to evaluate the impact of statin therapy on FCT in coronary plaque using OCT, based on combining studies considered as homogeneous.

The FCT is considered a crucial determinant of plaque vulnerability: 1 of the main characteristics of high-risk coronary plaque is the thinning of the fibrous cap. Nowadays, OCT is regarded as the only intracoronary imaging modality that can detect FCT in vivo, due to its high spatial resolution.³ So far, several OCT studies have demonstrated that FCT in coronary plaque could increase with statin therapy.^{7–10,12–16} Most of these OCT studies on the effect of statin on plaque morphology including FCT, however, had small sample sizes and different treatment effects; therefore, we conducted the present meta-analysis to obtain more confirmatory evidence. After pooling the results, we found an increase of 67.7 μm in FCT with statin therapy. Pooling of the 9 studies, however, resulted in considerable heterogeneity ($I^2=95.0\%$, $P<0.001$). Zhen et al reported that statin therapy induced a significant increase of 59 μm in FCT on OCT ($I^2=87.3\%$, $P<0.001$). The observed heterogeneity in this latter report makes it non-interpretable.¹⁷ In other words, large heterogeneity

Table 4. Percent of Variance Accounted for in FCT Change			
Model	R ² (%)	P-value	
(A) Univariate models			
Statin group	75.6	<0.001	
Age	11.1	0.082	
Male	18.9	0.144	
Diabetes	20.7	0.018	
Hypertension	5.0	0.459	
Smoker	3.8	0.280	
ACEI/ARB	11.2	0.020	
β -blocker	1.3	0.629	
(B) 2-factor multivariable models			
Statin group+	75.6	<0.001	
Age	76.5	<0.001	
Male	75.8	<0.001	
Diabetes	75.9	<0.001	
Hypertension	76.0	<0.001	
Smoker	76.8	<0.001	
ACEI/ARB	77.5	<0.001	
β -blocker	78.2	<0.001	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; FCT, fibrous cap thickness.

Table 5. Change in FCT With Change in Lipids After Statin Therapy: Meta-Regression Analysis				
Variable	Regression coefficient	SE	t-value	P-value
Change in TC	−2.263	0.646	−3.50	0.025
Change in LDL-C	−2.251	0.581	−3.88	0.012
Change in HDL-C	−5.120	5.928	−0.86	0.427

FCT, fibrous cap thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

means that the studies are non-“poolable”. We, therefore, investigated the combination of studies for which $I^2=0$, and fibrous cap thickening was observed in each group with homogeneity. A thin fibrous cap overlying a large lipid core, especially with FCT $<65\mu\text{m}$, known as TCFA, is regarded as the precursor lesion for plaque rupture and induces ACS. Tanaka et al reported that plaque with FCT $<160\mu\text{m}$ was at risk for plaque disruption and that it could be easier to rupture as the FCT becomes thinner.⁴ Although statin therapy has been recognized to reduce cardiovascular events and mortality in patients with CAD,^{18,19} the detailed mechanism remains to be fully elucidated. Previous intravascular ultrasound studies have demonstrated that statin therapy may result in plaque stabilization by regressing plaque volume and modifying plaque composition.^{20,21} The present meta-analysis has also shown that statin therapy significantly decreases lipid arc. Plaque stabilization, by fibrous cap thickening and reduction of the lipid component, is a probable mechanism in statin therapy.

Coronary risk factors have been shown to predict cardiovascular events.²² The current study, however, did not confirm a significant relationship between the increase of FCT and age, male gender, and coronary risk factors including diabetes, hypertension, and smoking, beyond statin therapy. Additionally, previous OCT showed that there were no significant differences in FCT between men and women,²³ or between diabetes and non-diabetes.²⁴ A previous meta-analysis that assessed the effect of statin on FCT also similarly reported that an increase in FCT was not associated with coronary risk factors.¹⁷ These findings are consistent with the present report. In contrast to the previous meta-analysis, however, we found a significant relationship between changes in TC and LDL-C and the change in FCT. This was most likely due to the correct analysis of paired data, given that paired analyses are more powerful than analyses of independent groups.

Taken together, the present study suggests that statin therapy induced fibrous cap thickening (i.e., plaque stabilization) as evidenced by the increased FCT on OCT. There were, however, large and statistically significantly different estimates of the treatment effect (change of FCT from baseline to follow-up) based on combining studies for which differences in treatment effect were due to random sampling variability (i.e., $I^2=0$). A potential explanation for this is the dose of statin and statin type. This needs to be further investigated in comparative randomized studies.

Study Limitations

The present study has some limitations. First, in this meta-analysis, we combined the data derived from different studies with different types of statins, follow-up periods, concomitant medication, and clinical presentations (stable angina or ACS). Second, all included studies were from Asian medical centers; strictly all of them were in Japan and China. Thus, there might be a potential selection bias, and hence the external validity is limited. The IBIS 4 study (conducted solely in European countries) has been recently published showing an increase in FCT in patients with ST-segment elevation myocardial infarction taking high-dose rosuvastatin.²⁵ We did not include this in the present report, in order to not increase heterogeneity further. Finally, 3 of the included studies were non-randomized trials.

Conclusions

Statin therapy, more than any other cardiovascular risk factor and medication, induced significant change (i.e., increase) in coronary FCT as assessed on OCT.

Disclosures

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Supplementary Files

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