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Abstract

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Conflicts of interest

All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Objective—The effect of statins on coronary artery plaque features beyond stenosis severity is not known. Coronary CT angiography (CCTA) is a novel non-invasive method that permits direct visualization of coronary atherosclerotic features, including plaque composition. We evaluated the association of statin use to coronary plaque composition type in patients without known coronary artery disease (CAD) undergoing CCTA.

Methods—From consecutive individuals, we identified 6673 individuals (2413 on statin therapy and 4260 not on statin therapy) with no known CAD and available statin use status. We studied the relationship between statin use and the presence and extent of specific plaque composition types, which was graded as non-calcified (NCP), mixed (MP), or calcified (CP) plaque.

Results—The mean age was 59 ± 11 (55% male). Compared to the individuals not taking statins, those taking statins had higher prevalence of risk factors and obstructive CAD. In multivariable analyses, statin use was associated with increased the presence of MP [odds ratio (OR) 1.46, 95% confidence interval (CI) 1.27–1.68), $p < 0.001$] and CP (OR 1.54, 95% CI 1.36–1.74, $p < 0.001$), but not NCP (OR 1.11, 95% CI 0.96–1.29, $p = 0.1$). Further, in multivariable analyses, statin use was associated with increasing numbers of coronary segments possessing MP (OR 1.52, 95% CI 1.34–1.73, $p < 0.001$) and CP (OR 1.52, 95% CI 1.36–1.70, $p < 0.001$), but not coronary segments with NCP (OR 1.09, 95% CI 0.94–1.25, $p = 0.2$).

Conclusion—Statin use is associated with an increased prevalence and extent of coronary plaques possessing calcium. The longitudinal effect of statins on coronary plaque composition warrants further investigation.

Keywords

Statin; Plaque composition; Coronary CTA; Coronary artery disease; Lipid profile

1. Introduction

Recent randomized controlled trials have established statin therapy as a successful method for reducing rates of adverse coronary artery disease (CAD) events [1]. While associated reductions in low density lipoprotein (LDL) levels have been posited as one mechanism by which statins exert favorable benefit, numerous other pleiotropic properties of statins—such as modulation of inflammation within the arterial wall or stabilization of endothelial function—may contribute to their beneficial clinical effect [2,3]. The phenotypic effects of statins on coronary atherosclerotic plaque characteristics has been described, but has been limited to invasive studies in small patient cohorts and have primarily focused on the ability of statins to retard coronary plaque progression [4–6].

Coronary computed tomographic angiography (CCTA) has recently emerged as accurate non-invasive method for the detection of coronary atherosclerosis and exclusion of obstructive coronary artery disease (CAD) [7]. Further, CCTA permits direct visualization of numerous coronary atherosclerotic characteristics beyond luminal diameter stenosis, including graded measures of coronary plaque composition. As compared to coronary artery calcium scoring (CCS), contrast-enhanced CCTA confers the added ability to visualize non-calcified plaques (NCP) that represent a mixed group of plaques comprised of fibrous, lipoid or fibrolipoid components. In recent study, NCP by CCTA has been shown to exhibit

important clinical ramifications, with increased NCP associated with incident adverse CAD events, myocardial ischemia and the presence of “vulnerable” coronary plaque features such as thin cap fibroatheroma [8–10].

To date, limited data exists to relate the effect of statin use to coronary plaque features beyond stenosis severity. The aim of this study was to evaluate the association of statins to coronary artery plaque composition inpatients without known CAD undergoing CCTA.

2. Methods

2.1. Design overview

The CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry is an international, multicenter, observational registry collecting clinical, procedural, and follow-up data on patients who underwent ≥64-detector row CCTA between 2005 and 2009 at 12 centers in 6 countries (Canada, Germany, Italy, Korea, Switzerland, and the United States). The rationale, design, site-specific patient characteristics, and follow-up durations have been described [11].

Before the initiation of the scan, we prospectively collected information on the presence of categorical cardiac risk factors in each individual. Systemic arterial hypertension was defined as a documented history of high blood pressure or treatment with antihypertensive medications. Diabetes mellitus was defined by diagnosis of diabetes made previously by a physician and/or use of insulin or oral hypoglycemic agents. A current smoker was defined as current smoking or cessation of smoking within 3 months of testing. Family history of CAD was defined as myocardial infarction, coronary revascularization, or sudden cardiac death in a first-degree male relative <55 years old or female relative <65 years old. Symptom was classified into 5 categories: asymptomatic, nonanginal chest pain, atypical chest pain, typical chest pain, or dyspnea.

All sites had approval of respective institutional review boards, and were compliant with the Health Insurance Portability and Accountability Act where applicable. Patient consent or a waiver of informed consent (as per recommendations of each institutional review board) was obtained at each site in keeping with site-specific regulations. The study was consistent with the principles of the Declaration of Helsinki.

2.2. Study patients

From 27,125 consecutive individuals undergoing CCTA, we excluded individuals with prior known CAD (as defined by previous myocardial infarction and/or coronary revascularization), with unknown statin use or unavailable serum lipid profile. A total of 6673 individuals (2413 on statin therapy and 4260 not on statin therapy) comprised the study population.

2.3. Noninvasive coronary artery analysis by CCTA

Experienced level III equivalent readers evaluated the presence of any plaque and plaque composition (number, stenosis and characteristics) on CCTA images as performed by scanners with 64-slices or more in accordance with Society of Cardiovascular Computed

Tomography guidelines [12]. Detected plaques were assigned locations according to a modified 16-segment American Heart Association coronary tree model [13]. Coronary plaque was defined as any tissue >1 mm^2 within or adjacent to the lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or lumen; and identified in ≥2 planes. Detected plaques were visually classified as NCP (containing no calcification), mixed plaques (MP, containing calcification and noncalcified plaque), or calcified plaques (CP, containing only calcification). CAD severity was classified for three groups; none (0% luminal stenosis), nonobstructive (1–49% luminal stenosis) and obstructive stenosis (≥50% luminal stenosis). For per-vessel analysis, we employed four categorizations: nonobstructive, obstructive (≥50% luminal stenosis) with 1-vessel, 2-vessels, and 3-vessels or left main disease. NCP, MP and CP scores were defined as number of coronary artery segments having each plaque. As previously described [14], a segment stenosis score (SSS) was calculated as a measure of overall coronary artery plaque extent and severity. Each individual coronary segment was graded as having no to severe plaque (i.e., scores from 0 to 3) based on extent of obstruction of coronary luminal diameter. Then the extent scores of all 16 individual segments were summed to yield a total score ranging from 0 to 48.

2.4. Statistical analysis

Categorical variables are presented as frequencies with percentages and evaluated using the Pearson Chi-square test. Continuous variables are presented as mean ± 1SD or median (interquartile range) and were evaluated using a Student unpaired *t* test or a Mann–Whitney *U* test, as appropriate. Comparisons were made between those on statin therapy versus those not on statin therapy. We used logistic and ordinal logistic regression to assess patient risk factors, and SSS in predicting the presence and number of plaques of specific composition (NCP, MP or CP). Ordinal logistic regression was used to assess the number of coronary artery segments with each plaque type, with the latter subjected to none, 1–2 segments, ≥3 segments. Since there is huge geographical variation in the data collected (North America, Europe and Asia), we have included this geographical information in the multivariable model. In secondary analyses, the association between lipid levels and plaque types was examined, when stratified by statin therapy versus no statin therapy. Comparisons were made between those with high versus low LDL (≥130 vs. <130 mg/dl), low versus normal high density lipoprotein (HDL, <40 vs. ≥40 mg/dl), and elevated versus non-elevated total cholesterol (TC, ≥200 vs. <200 mg/dl) based on the recommendations of the National Cholesterol Education Program/Adult Treatment Program (NCEP/ATP) III guidelines [15]. Statistical significance was accepted for 2-sided *p*-values <0.05. All calculations were performed using STATA version 11 (StataCorp, College Station, Texas).

3. Results

3.1. Clinical characteristics of the study cohort

The mean age of the study group was 59 ± 11years and 55% of subjects were male. Clinical characteristics based upon use or non-use of statin are shown in Table 1a. Compared to individuals not on statin therapy, individuals who were taking statins were older and had higher body mass index (BMI), risk factors, lower LDL (111 ± 39 vs. 121 ± 34 mg/dl, $p <$

0.0001), lower TC (185 ± 43 vs. 195 ± 41 mg/dl, $p = 0.0001$), lower HDL (52 ± 14 vs. 53 ± 15 mg/dl, $p = 0.0001$).

3.2. CCTA findings

As compared with individuals not taking statins, those taking statins possessed a significantly higher prevalence of obstructive CAD, as well as higher numbers of vessels with obstructive CAD (Table 1b). In univariable analyses, statin use was each associated with a significantly higher prevalence of NCP, MP and CP (Table 1b). In multivariable analyses adjusting for age, gender, BMI, hypertension, diabetes, current smoker, family history of CAD, symptoms, geography and SSS, statin use was associated with increased presence of MP [odds ratio (OR) 1.46, 95% confidence interval (CI) 1.27–1.68, $p < 0.001$] and CP (OR 1.54, 95% CI 1.36–1.74, $p < 0.001$], but not NCP (OR 1.11, 95% CI 0.96–1.29, $p = 0.1$) (Table 2).

Similarly, in multivariable models adjusting for age, gender, BMI, hypertension, diabetes, current smoker, family history of CAD, symptoms, geography and SSS, statin use was associated with increasing numbers of coronary segments possessing MP (OR 1.52, 95% CI 1.34–1.73, $p < 0.001$) and CP (OR 1.52, 95% CI 1.36–1.70, $p < 0.001$), but not increasing numbers of coronary segments possessing NCP (OR 1.09, 95% CI 0.94–1.25, $p = 0.2$) (Table 3).

We have additionally analyzed the data separately for each country (North America, Europe and Asia), and all results are consistent across the countries (data not shown).

3.3. Subgroup analysis of patients taking statins who have achieved cholesterol “goal”

In multivariable analyses, for patients taking statin medications, successful lipid control—as defined by LDL < 130, TC < 200 or HDL ≥ 40 mg/dl—was not associated with increasing or decreasing numbers of coronary segments possessing NCP (Table 4). However, successful LDL control<130 and TC control <200 mg/dl were associated with higher numbers of coronary segments possessing CP.

In the subgroup of individuals with successful lipid control, statin use was associated with increasing numbers of coronary segments possessing MP and CP but not associated with increasing numbers of coronary segments possessing NCP (Table 5).

4. Discussion

In this large cross-sectional multinational study of individuals undergoing CCTA, we identified a strong association of statin use to coronary artery plaque features. Statin use was associated with a higher frequency of severe coronary artery stenoses as well as numbers of coronary vessels with obstructive CAD. Further, statin use was associated with a differentially increased prevalence and extent of MP and CP but not NCP.

Monitoring atheroma progression using serial intravascular ultrasound (IVUS) has been used to characterize the natural history of atherosclerosis and the effect of anti-atherosclerotic therapies. Serial IVUS studies have demonstrated that reduction in LDL

cholesterol levels by statins may slow the rate of atherosclerotic disease progression [4,5] and may induce very small amounts of coronary atherosclerosis regression if “goal” LDL cholesterol levels are achieved [16]. Collectively, these studies show a strong linear relationship between the degree of LDL cholesterol lowering and change in atheroma volume [16]. Further, limited studies specifically examining coronary plaques by composition have demonstrated a slowing of non-calcified plaque progression in a manner that is out of proportion to the slowing of the overall atherosclerotic process. Statin treatment increases plaque hyperechogenicity by grey-scale IVUS without significant decrease in plaque volume [17], suggesting an effect of statins to affect coronary artery plaque composition. By virtual histology IVUS—employing spectral analysis of radiofrequency ultrasound backscatter signals—statin treatment has been associated with altered coronary artery plaque composition by significantly reducing the degree of the fibro-fatty intraplaque constituents and increasing intraplaque CP composition.

These findings may reflect a differential effect of statins on plaque progression by composition type, or alternatively, may represent a conversion of NCP to CP composition. Germane to the latter, we noted that the use of statins and, in particular, the effectiveness of statins (as surrogate determined by achieving goal cholesterol levels), was associated with increasing presence and numbers of coronary segments with CP components. Whether this finding relates to a stabilization of coronary plaque that is exerted by statin medications requires longitudinal study, and these types of studies now appear warranted. In a previous report by our laboratory, in patients without known CAD in whom coronary artery plaque was detected on CCTA, we observed that statin therapy at the time of CCTA was positively associated with the number of partially calcified plaques while statin therapy was not associated with the number of NCP [18]. In the current cross-sectional prospective multicenter international study, we identified similar findings in patients who were taking statin treatment at the time of CCTA.

Early CCTA single center studies of small patient cohorts have attempted to examine the relationship of lipoproteins to statin use and coronary artery plaque. As an example, Burgstahler et al., observed a significant reduction in the measured NCP volume on CCTA in 27 patients 1 year after initiating statin therapy [19]. Another preliminary study revealed that statin treatment results in reduction of total and NCP volume by serial CCTA assessment [20]. More recently, low-density noncalcified coronary atherosclerotic lesions were observed to be less common in patients with stable coronary atherosclerosis after 6 months of intensive statin treatment than in patients on moderate or no statin treatment [21]. Our study findings should be considered as directly extending these prior early studies, the large number of study individuals, and the multicenter international scope of the study population.

Prognostically, while CP portends risk, the relationship of coronary plaque composition and prognosis is as yet not fully understood. While large body of evidence for non-contrast CCS has definitively determined a prognostic significance to the presence and extent of CPs, five recent prospective studies by CCS have observed that statin therapy does not, in fact, result in regression of coronary calcium and progression of coronary calcium continues regardless of statin treatment [22,23]. Whether this is related to statin effects or native atherosclerosis

progression is unknown. If related to the former, numerous potential explanations exist to account for such findings. When the coronary arterial endothelium is injured by inflammation, complex interactions among monocytes, endothelial cells, smooth muscle cells, and oxidized LDL result in the formation of lipid-laden macrophages, fibrous remodeling, and a necrotic lipid core [24]. All these components can appear as NCP on CCTA, likely contributing to the elevated coronary event risk associated with partially calcified plaque and NCP [25]. More recent studies with CCTA have described several "vulnerable" plaque features, most notably low attenuation plaques (LAP), which correlate to lipid-rich necrotic cores by IVUS [26,27] and which are independent predictors of future acute coronary syndromes [28]. In this regard, the presence, extent and severity of NCP may simply represent a greater overall intra-individual prevalence of plaques with LAP or necrotic cores. Future correlative studies with CCTA and IVUS performed longitudinally in patients taking or not taking statins would be helpful to further elucidate these relationships.

Prior studies examining the effect of lipid levels on coronary artery calcium have observed progression of CCS despite adequate statin on-treatment LDL cholesterol levels, and have not identified a strong relationship between lipoproteins, statin use and coronary artery calcium [22,23]. Our study differed from these prior investigations—particularly given the large sample size—and we noted a significant relationship to the statins, particularly in those who achieved "good" control. Given the prior reported literature coupled with the present study results, one potential unifying hypothesis is that rather than regression of coronary plaque, statins may contribute to the conversion of coronary plaque constituents, perhaps by conversion of NCP to plaque possessing calcium. While beyond the scope of the present study, these findings raise the possibility that serial performance of CCS may not be sufficient to monitor disease progression in patients actively treated with statins. Future longitudinal studies should be performed to examine the direct effects of statins on plaques stratified by composition type. Importantly, these results are cross-sectional and, given that increasing coronary calcium score is associated with higher rates of cardiovascular events, the recommendations of statins for primary prevention should be continued until longitudinal assessments of the effect of statins on plaque composition types can be evaluated.

5. Limitations

This study is not without limitations. Novel CT technology developments—including spectral imaging by dual energy CT—may enhance discrimination of these plaques subtypes, but evaluation of these new technologies is in its early stage, and this technology was not available at the time of study performance. Further, we only examined the effects of statin therapy on plaque composition in patients at the time of the CCTA scan. Importantly, information regarding the use of other lipid-lowering therapies (i.e., Niacin, fibrates, ezetimibe) was not uniformly available and, as such, potential confounder effects from adjuvant therapies cannot be fully accounted for. The information on the duration and dose of statins were not available in the current study, and it is possible that the present study findings are affected to some degree by ascertainment bias. Thus, the ability to relate the present study findings to the serial association of plaque composition type to the longitudinal effects of statins was not addressed. Future study examining the interaction between statin

medications and plaque composition now appear warranted. Finally, most importantly, given the greater prevalence of obstructive CAD in statin-treated individuals, the present study findings may be confounded by a treatment bias towards preferential statin therapy inpatients with higher lipid values when they were statin naïve or "sicker" individuals. However, we prospectively collected statin use information before the CCTA was performed, and adjustments for CAD stenosis severity and extent.

6. Conclusion

Statin use is associated with an increased prevalence and burden of coronary plaques possessing calcium. The longitudinal effects of statin therapy on coronary plaque composition warrant further investigation.

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Table 1a

Clinical characteristics (n = 6673).

	No statin n = 4260	**Statin n = 2413**	***p* value**
Age	57 ± 12	62 ± 10	<0.0001
Male	55%	56%	0.2
BMI	26.3 ± 4.7	26.8 ± 4.9	<0.0001
Hypertension	44%	55%	<0.001
Diabetes	10%	21%	<0.001
Current smoker	14%	14%	0.7
Family history of CAD	22%	26%	<0.001
Symptoms	–	–	<0.001
Asymptomatic	33%	35%	–
Nonanginal chest pain	4%	4%	–
Atypical chest pain	45%	38%	–
Typical chest pain	11%	14%	–
Shortness of breath	7%	9%	–
Geography	–	–	<0.001
North America	34%	41%	
Europe	25%	15%	
Asia	41%	44%	

BMI, body mass index; CAD, coronary artery disease.

Table 1b

CCTA findings.

	No statin *n* = 4260	**Statin *n* = 2413**	***p* value**
CAD severity	–	–	<0.001
None	56%	32%	–
Non-obstructive	31%	44%	–
Obstructive	13%	24%	–
# Vessels with obstructive CAD			<0.001
0-vessel	88%	76%	
1-vessel	9%	16%	
2-vessel	3%	6%	
3-vessel	1%	2%	
# Segments with NCP	–	–	<0.001
0-segments	84%	79%	–
1-segment	9%	13%	–
2-segments	4%	5%	–
≥3-segments	3%	3%	–
# Segments with MP	–	–	<0.001
0-segments	81%	67%	–
1-segment	9%	12%	–
2-segments	5%	8%	–
≥3-segments	5%	13%	–
# Segments with CP	–	–	<0.001
0-segments	67%	49%	–
1-segment	13%	16%	–
2-segments	8%	10%	–
≥3-segments	12%	25%	–

NCP, noncalcified plaque; MP, mixed plaque; CP, calcified plaque.

Table 2

Relationship between statin use and the presence of each plaque type.

	Adjusted OR (95% CI) for statin use	*p* value
NCP	1.11 (0.96–1.29)	0.1
MP	1.46 (1.27–1.68)	<0.001
CP	1.54 (1.36–1.74)	<0.001

Each model (NCP, CP) was adjusted by age, gender, BMI, hypertension, diabetes, current smoker, family history of CAD, symptoms, geography, SSS.

OR, odds ratio; CI, confidence interval.

Table 3

Relationship between statin use and the number of segments of each plaque type.

	Adjusted OR (95% CI) of statin use	*p* value
NCP	1.09 (0.94–1.25)	0.2
MP	1.52 (1.34–1.73)	<0.001
CP	1.52 (1.36–1.70)	<0.001

Each model (NCP, CP) was adjusted by age, gender, BMI, hypertension, diabetes, current smoker, family history of CAD, symptoms, geography, SSS.

Table 4

Relationship between good lipid control and the number of segments with plaque types in patients with taking statin medications.

	Adjusted OR (95% CI) for NCP	*p* value
NCP		
LDL < 130 mg/dl	0.85 (0.67–1.08)	0.2
TC < 200 mg/dl	0.92 (0.73–1.15)	0.5
HDL ≥ 40 mg/dl	0.91 (0.70–1.17)	0.5
MP		
LDL < 130 mg/dl	0.94 (0.76–1.17)	0.6
TC < 200 mg/dl	0.98 (0.80–1.20)	0.9
HDL ≥ 40 mg/dl	0.77 (0.61–0.96)	0.02
CP		
LDL < 130 mg/dl	1.34 (1.10–1.62)	0.003
TC < 200 mg/dl	1.21 (1.01–1.45)	0.04
HDL ≥ 40 mg/dl	1.08 (0.87–1.34)	0.5

Each model (LDL < 130, TC < 200, HDL ≥ 40 mg/dl) was adjusted by age, gender, BMI, hypertension, diabetes, current smoker, family history of CAD, symptoms, geography, SSS.

LDL, low density lipoprotein; TC, total cholesterol; HDL, high density lipoprotein.

Table 5

Relationship between statin use and the number of segments with plaque types in patients with good lipid control.

	Adjusted OR (95% CI) of statin use	*p* value
NCP		
LDL < 130 mg/dl	1.06 (0.89–1.27)	0.5
TC < 200 mg/dl	1.15 (0.96–1.39)	0.1
HDL ≥ 40 mg/dl	1.14 (0.97–1.34)	0.1
MP		
LDL < 130 mg/dl	1.60 (1.37–1.88)	<0.001
TC < 200 mg/dl	1.70 (1.44–2.01)	<0.001
HDL ≥ 40 mg/dl	1.47 (1.27–1.71)	<0.001
CP		
LDL < 130 mg/dl	1.61 (1.41–1.85)	<0.001
TC < 200 mg/dl	1.58 (1.37–1.82)	<0.001
HDL ≥ 40 mg/dl	1.56 (1.37–1.76)	<0.001

Each model (LDL < 130, TC < 200, HDL ≥ 40 mg/dl) was adjusted by age, gender, BMI, hypertension, diabetes, current smoker, family history of CAD, symptoms, geography, SSS.