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A cross-sectional survey of coronary plaque composition in individuals on non-statin lipid lowering drug therapies and undergoing coronary computed tomography angiography

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ABSTRACT

Introduction: Non-statin therapy (NST) is used as second-line treatment when statin monotherapy is inadequate or poorly tolerated.

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Non-statin therapy
Ezetimibe
Fibrate
Niacin

Objective: To determine the association of NST with plaque composition, alone or in combination with statins, in patients undergoing coronary computed tomography angiography (coronary CTA).
Methods: From the multicenter CONFIRM registry, we analyzed individuals who underwent coronary CTA with known lipid-lowering therapy status and without prior coronary artery disease at baseline. We created a propensity score for being on NST, followed by stepwise multivariate linear regression, adjusting for the propensity score as well as risk factors, to determine the association between NST and the number of coronary artery segments with each plaque type (non-calcified (NCP), partially calcified (PCP) or calcified (CP)) and segment stenosis score (SSS).
Results: Of the 27,125 subjects in CONFIRM, 4,945 met the inclusion criteria; 371 (7.5%) took NST. At baseline, patients on NST had more prevalent risk factors and were more likely to be on concomitant cardiac medications. After multivariate and propensity score adjustment, NST was not associated with plaque composition: NCP (0.07 increase, 95% CI: −0.05, 0.20; p = 0.26), PCP (0.10 increase, 95% CI: −0.10, 0.31; p = 0.33), CP (0.18 increase, 95% CI: −0.10, 0.46; p = 0.21) or SSS (0.45 increase, 95% CI: −0.02,0.93; p = 0.06). The absence of an effect of NST on plaque type was not modified by statin use (p for interaction > 0.05 for all).
Conclusion: In this cross-sectional study, non-statin therapy was not associated with differences in plaque composition as assessed by coronary CTA.

1. Introduction

Prior to the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, non-statin therapy (NST) for lipid lowering such as ezetimibe, bile acid resins, niacin and fibrates were often added to statins in patients with suboptimal cholesterol levels. The 2017 focused update on the American College of Cardiology (ACC) expert consensus recommends consideration of NST for primary or secondary prevention in patients for whom high-intensity statin therapy does not adequately reduce low-density lipoprotein (LDL) levels for cardiovascular risk reduction.[1] Statins have proven efficacy for prevention of cardiovascular events, while NST have generally not exhibited benefit, except for a recent long-term trial of ezetimibe.[2–6]

Imaging studies have provided insights into possible mechanisms of statin benefit, with not only decreased plaque progression, but also altered coronary plaque composition, through an increase in calcified plaque volume with a corresponding decrease in non-calcified volume which may represent plaque stabilization.[7–11] On the other hand, no study has examined the correlation between NST and coronary plaque composition as assessed by coronary computed tomography angiography (coronary CTA). Given the minimal clinical benefit of NST within the context of primary prevention, it is plausible that NST have minimal impact on coronary plaque composition. The aim of this study was to evaluate the independent association of NST with extent of noncalcified (NCP), partially calcified (PCP), and calcified plaque (CP) in patients without known coronary artery disease (CAD) undergoing coronary CTA due to suspected CAD.

2. Methods

The CONFIRM registry is a prospective, international, multicenter registry of 27,125 patients who underwent coronary CTA between 2005 and 2009 for clinically indicated reasons. Clinical, procedural, and follow-up data were collected from 12 centers in 6 countries, including Canada, Germany, Italy, Korea, Switzerland, and the United States. The rationale, design, site-specific patient characteristics, and follow-up data have been previously published.[12]

Patient charts were reviewed for baseline risk factors. Usage of statin and/or NST was collected by patient self-report as a binary response at the time of coronary CTA. The specific type or dosage of statin or NST was not recorded at the time of enrollment. NSTs that were available during the enrollment period were ezetimibe, niacin, fibrates and bile acid resins, but not PCSK9 and cholesterylester transfer protein (CETP) inhibitors. Statin indication was calculated using the 2013 AHA/ACC guidelines with imputation for categorical risk factors such as hypertension, and patients were categorized as not recommended for statin, statin-considered, and statin-recommended.[13] LDL was measured at the time of enrolment. Downstream changes in medications and LDL values were not collected.

All sites received approval from their 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.

2.1. Study patients

From 27,125 consecutive individuals undergoing coronary CTA, we excluded patients with prior known CAD, defined by previous myocardial infarction and/or coronary revascularization, and patients who lacked data on coronary risk factors, body mass index (BMI), serum lipid profiles, statins, and use of other lipid lowering therapy. A total of 4,945 individuals comprised the study population, of whom 4,923 patients had follow-up for all-cause mortality.

2.2. Non-invasive coronary artery analysis by coronary CTA

Coronary CTA images were obtained by at least 64-slice scanners, following the Society of Cardiovascular Computed Tomography guidelines. Presence of plaque and plaque composition were evaluated by an experienced reader, and assigned locations based on the 16-segment American Heart Association model. Segment stenosis score (SSS) was calculated as a measure of overall coronary artery plaque extent and severity as described previously.[14]

Coronary artery plaques were defined as tissue > 1 mm^2 that was present within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or vessel lumen. Plaques were visually classified as noncalcified plaques (NCP) containing no calcification, partially calcified plaques (PCP) containing both calcified and non-calcified plaque, or calcified plaques (CP), containing only calcification. The primary outcome was the number of segments of each plaque type: NCP, PCP and CP respectively. The secondary outcome was the SSS. High-risk plaque and atherosclerotic plaque characteristics were not evaluated in the CONFIRM cohort.

2.3. Statistical analysis

Categorical variables were presented as frequencies with percentages, and were compared using the Pearson Chi-square test. Continuous variables were presented as mean ± 1SD or median (interquartile range) and evaluated using the student unpaired *t*-test or the Mann–Whitney *U* test, as appropriate.

Comparisons were made between those on and off NST, with subgroup analysis based on concurrent statin use. In order to account for

baseline differences in patients on and off NST, a propensity score for being on NST was created from the predicted probabilities of a logistic regression model predicting NST usage and comprised of the following clinical variables: age, gender, BMI, typical angina, dyspnea, hypertension, diabetes, smoking status, lab values (total cholesterol, high-density lipoprotein (HDL), LDL and statin eligibility; the balancing property of the resulting propensity score was verified to be satisfied.[15] Subsequently, stepwise multivariate mixed effects linear regression, where hospital site was modeled as a random effect, adjusting for the propensity score as well as risk factors, was used in order to determine the association between NST and the number of coronary artery segments with each plaque type (NCP, PCP or CP). Backward stepwise selection was used to determine which covariates were associated with the number of segments of each plaque type and therefore entered in multivariable models along with propensity score. Candidate variables included statin indication, LDL cholesterol level, and individual risk factors such as age, sex, BMI, symptoms, diabetes mellitus, hyperlipidemia, smoking status, anti-hypertensive medications and laboratory values. Overfitting was assessed and absence of it verified. Differences in all-cause mortality were visualized using risk-adjusted Kaplan Meier curves and assessed using Cox Proportional hazards regression analysis. The proportional hazards assumption for Cox models was assessed using Schoenfeld residuals. Finally, a sensitivity analysis excluding statin users was performed for both associations with plaque characteristics as well as survival. Statistical significance was accepted for 2-sided p-values < 0.05. All calculations were performed using STATA version 14 (College Station, TX).

3. Results

A total of 4,945 patients (371 on and 4,574 not on NST) met the inclusion criteria for this study, and were followed for a mean duration of 2.6 ± 1.2 years (Table 1 supplement for a comparison between included and excluded participants). The mean age of the study cohort was 58.7 ± 11.5 years and 52.7% were male. As expected, patients on NST were significantly more likely to be statin-recommended or statin-considered ($p < 0.01$). Patients on NST had more prevalent comorbid conditions with lower LDL (108.7 vs. 113.1, $p < 0.01$) but also lower HDL levels (49.4 vs. 51.0, $p = 0.02$, Table 1).

In univariate analysis, NST was associated with higher numbers of involved segments for all plaque types except non-calcified plaque (Table 2). In univariate regression, NST was associated with increased extent of NCP (0.15 more segments, 95% CI: 0.03, 0.28, $p = 0.02$), PCP (0.29 more segments, 95% CI: 0.09, 0.50, $p < 0.01$), and CP (0.50 more segments, 95% CI: 0.20, 0.80, $p < 0.01$), as well as increased SSS (1.15 increase in score, 95% CI: 0.65, 1.66, $p < 0.01$, Table 3). There were statistically significant interactions between statin and NST therapy across all subtypes of plaque composition and SSS in univariate analysis ($p < 0.05$ for all, Table 3).

After adjusting for clinical variables including the propensity to being on NST, NST use was no longer independently associated with a specific plaque composition type: NCP (0.07 increase in segments, 95% CI: −0.05, 0.20, $p = 0.26$), PCP (0.10 increase in segments, 95% CI: −0.10, 0.31, $p = 0.33$) or CP (0.18 increase in segments, 95% CI: −0.10, 0.46, $p = 0.21$). NST was not associated with increased SSS (0.46 increase in score, 95% CI: −0.02, 0.93, $p = 0.06$). Further, results were unaffected after performance of sensitivity analysis with exclusion of patients on statin therapy (results not shown). Statin use, on the other hand, exhibited significant independent association with PCP, CP, and SSS: PCP (0.26 increase in segments, 95% CI: 0.18, 0.34, $p < 0.01$), CP (0.34 increase in segments, 95% CI: 0.24, 0.45, $p < 0.01$) and SSS (0.69 increase in score, 95% CI: 0.50, 0.88, $p < 0.01$). The interaction between statin and NST on plaque composition became non-significant in multivariate analysis ($p > 0.05$ for all), which is likely a reflection of the inherently different cohorts of individuals receiving either therapy since in clinical practice higher risk individuals are more likely to be on combination therapy with lower target LDL values than lower risk individuals.

Finally, in an exploratory analysis stratified by statin use, there was no difference in survival between the NST users and non-users after adjusting for baseline cardiovascular risk ($p = 0.61$ and 0.46 respectively, Fig. 1). Furthermore, in risk-adjusted Cox regression analysis, NST did not result in a significant difference in all-cause mortality (HR 0.64, 95% CI 0.15–2.68, $p = 0.54$) while statins were associated with improved survival (HR 0.51, 95% CI 0.30–0.87, $p = 0.01$, Table 4). The absence of an association between NST and all-cause mortality was not altered with the exclusion of concurrent statin users (HR 0.57, 95% CI 0.14–2.44, $p = 0.45$). Finally, there was no evidence of an interaction between statins, NST and mortality ($p = 0.44$).

4. Discussion

In the present cross-sectional study, non-statin therapy was not independently associated with differences in qualitative plaque composition as assessed by coronary CTA. Additionally, there was no evidence of an independent interaction between NST and statins on atherosclerotic plaque composition. Similar to previous investigations, statin use was associated with the presence of PCP, CP and SSS, and was associated with lower all-cause mortality in the short follow-up period of the study cohort.

To our knowledge, this is the first observational study to investigate the association between NST and coronary plaque composition on coronary CTA. Studies of NST by intravascular ultrasound (IVUS) imaging have generally demonstrated overall plaque regression with no

Table 1
Baseline clinical characteristics.

	No Non-statin Therapy (n = 4,574)	Non-statin therapy (n = 371)	P value
Demographics			
Age (yrs, mean ± SD)	58.6 ± 11.5	60.6 ± 10.6	< 0.01
Male, n (%)	2,386 (52.2)	218 (58.8)	0.01
BMI (Kg/m^2, mean ± SD)	26.4 ± 5.1	26.6 ± 4.1	0.57
Typical chest pain, n (%)	601 (13.5)	48 (13.2)	0.86
Dyspnea, n (%)	664 (14.9)	56 (15.4)	0.82
PMH			
Hypertension, n (%)	2,449 (53.5)	215 (58.0)	0.10
Diabetes mellitus, n (%)	717 (15.7)	93 (25.1)	< 0.01
Hyperlipidemia, n (%)	2,879 (62.9)	287 (77.4)	< 0.01
Current smoking, n (%)	625 (13.7)	42 (11.3)	0.20
Former smoking, n (%)	215 (31.2)	11 (32.4)	0.88
Medications			
Statins, n (%)	1,725 (37.7)	225 (60.7)	< 0.01
ACE-I/ARB, n (%)	1,399 (30.6)	128 (34.5)	0.12
Beta-blocker, n (%)	1,379 (30.2)	138 (37.2)	< 0.01
Aspirin/Clopidogrel, n (%)	2,280 (49.9)	251 (67.7)	< 0.01
Other antihypertensives, n (%)	1,581 (34.6)	147 (39.6)	0.049
Labs			
Total Cholesterol (mg/dL, mean ± SD)	183.3 ± 37.7	184.3 ± 44.4	0.83
LDL (mg/dL, mean ± SD)	113.1 ± 34.3	108.7 ± 40.3	< 0.01
HDL (mg/dL, mean ± SD)	51.0 ± 14.0	49.4 ± 13.6	0.02
Statin Eligibility, n (%)			Overall < 0.01
Recommended	2,831 (61.9)	256 (69.0)	< 0.01
Considered	907 (19.8)	84 (22.6)	0.19
Not recommended	836 (18.3)	31 (8.4)	< 0.01

Abbreviations: BMI: body mass index; PMH: past medical history; ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blocker; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 2
Number of segments with coronary plaque composition by non-statin therapy.

	No Non-statin Therapy (n = 4574)	Non-statin Therapy (n = 371)	P value
NCP (mean ± SD)	0.3 ± 0.8; 0 (0-0)	0.3 ± 0.8; 0 (0-0)	0.07
PCP (mean ± SD)	0.6 ± 1.3; 0 (0-0)	0.7 ± 1.4; 0 (0–1)	< 0.01
CP (mean ± SD)	1.1 ± 1.9; 0 (0–1)	1.5 ± 2.1; 1 (0–2)	< 0.01
Total plaque number (mean ± SD)	1.9 ± 2.6; 1 (0–3)	2.6 ± 2.7; 2 (0–4)	< 0.01
SSS (segment stenosis score) (mean ± SD)	1.9 ± 3.2; 0 (0–3)	2.6 ± 3.5; 1 (0–4)	< 0.01

Abbreviations: NST: Non-statin lipid-lowering drug therapy; NCP: non-calcified plaque; PCP: partially calcified plaque; CP: calcified plaque; SSS: segment stenosis score; IQR: interquartile range.

effect on plaque composition. For example, patients enrolled in the OCTIVUS trial were started on atorvastatin plus ezetimibe versus atorvastatin monotherapy after the first myocardial infarction (MI). No association was found between ezetimibe use and necrotic core volume as assessed by IVUS.[16] The HEAVEN study was a single center study of 89 patients with stable angina and randomized to aggressive dual lipid lowering therapy (atorvastatin and ezetimibe) or standard of care statin monotherapy. IVUS and virtual histology IVUS (VH-IVUS) were performed after 12 months of therapy and assessed for plaque regression, as well as changes in plaque composition such as fibrous, fibrous-fatty, dense calcium, and necrotic core volumes).[17] LDL levels between aggressive and standard therapy groups were not significant (LDL 119.9 mg/dL vs. 104.4 mg/dL, p = 0.17). The investigators found that aggressive dual lipid lowering therapy resulted in plaque regression without changes in plaque composition. In the PRECISE-IVUS trial, patients undergoing percutaneous coronary intervention for acute coronary syndrome (ACS) were randomized to atorvastatin plus ezetimibe or atorvastatin monotherapy, with serial volumetric IVUS studies performed at 9–12 months.[18] The addition of ezetimibe to statins showed greater plaque regression compared to statin monotherapy (absolute change in percent atheroma volume −1.4%; 95% CI: −3.4% to −0.1% vs. −0.3%; 95% CI: −1.9%–0.9%, respectively; p < 0.01). More recently, Puri and colleagues found that statin therapy was associated with coronary atheroma calcification, independently of their plaque regressive effect, in participants undergoing serial IVUS evaluation.[11] Our study generalizes the plaque composition findings of IVUS to whole heart evaluation past the proximal coronary tree, and to lower risk patients without indications for invasive coronary angiography. As our study was cross-sectional rather than the serial design of the IVUS studies, we could not evaluate plaque progression.

Large-scale trials looking at the effect of NST in combination with statins, specifically ezetimibe, have shown benefit in terms of a reduction in major adverse cardiovascular events in certain high-risk subgroups. In the IMPROVE-IT trial, patients with recent ACS received ezetimibe plus statin or statin alone.[6] Patients who received a combination of ezetimibe and simvastatin had a statistically significant 2% lower absolute risk in the primary composite end point after 7 years of follow up. In the SHARP trial, patients with chronic kidney disease and no known history of CAD were randomized to receive simvastatin plus ezetimibe or placebo, and those on combination therapy had significantly fewer major atherosclerotic events after 5 years of follow up.[19] Fibrates, on the other hand, have been shown to have a beneficial effect both in a primary and a secondary prevention setting (primary prevention risk ratio (RR) 0.84, 95% confidence interval (CI) 0.74–0.96; participants = 16,135; studies = 6 vs. RR 0.88, 95% CI 0.83–0.94; participants = 16,064; studies = 12).[20,21] On a parallel line, other non-statin therapies such as niacin and bile acid sequestrants have shown benefit in select situations. For instance, there has been a lot of discussion surrounding the role of niacin therapy, with the AIM-HIGH trial showing no benefit with the addition of niacin therapy to statin therapy in patients with atherosclerotic cardiovascular disease and LDL values less than 70 mg/dL.[22] A recent meta-analysis of thirteen trials (N = 35,206) showed that niacin use was not associated with lower all-cause mortality (RR 0.99; 95% CI 0.88–1.12) but was associated with a trend toward lower risk of cardiovascular mortality (RR 0.91; 95% CI 0.81–1.02), coronary death (RR 0.93; 95% CI 0.78–1.10), nonfatal MI (RR 0.85; 95% CI 0.73–1.0), revascularization (RR 0.83; 95% CI 0.65–1.06), and stroke (RR 0.89; 95% CI 0.72–1.10).[23] Finally, three randomized controlled trials have shown inconclusive results when evaluating the efficacy of the first generation bile acid sequestrant cholestyramine for cardiovascular prevention.[24–26] Given the inherent limitations of the data available within the CONFIRM database, the present investigation had all non-statin therapies grouped under one subcategory, with no information available on timing, dosage and duration of therapy which prohibits performance of drug-specific analysis in the present investigation.

The lack of relationship between NST and plaque composition contrasts with the strong association for statins within the same cohort. Such a finding could be attributed to the fact that the difference in mean LDL levels between the NST and no-NST groups was 4.4 mg/dL,

Table 3
Association between lipid lowering therapy and number of segments with each plaque type.

Plaque type	Any non-statin therapy (n = 371)	p-value	Any Statin (n = 1950)	p-value	Interaction	p-value
	Number of segments (95% Confidence Interval)		Number of segments (95% Confidence Interval)		Number of segments (95% Confidence Interval)	
Univariate						
Non-Calcified Plaque	0.154 (0.030, 0.279)	0.02	0.112 (0.067, 0.156)	< 0.01	−0.187 (−0.349, −0.025)	0.02
Partially Calcified Plaque	0.294 (0.088, 0.500)	< 0.01	0.515 (0.441, 0.589)	< 0.01	−0.410 (−0.678, −0.141)	< 0.01
Calcified Plaque	0.504 (0.204, 0.805)	< 0.01	0.815 (0.707, 0.923)	< 0.01	−0.538 (−0.930, −0.146)	< 0.01
SSS	1.152 (0.647, 1.658)	< 0.01	1.616 (1.434, 1.798)	< 0.01	−1.359 (−2.019, −0.700)	< 0.01
Multivariate*						
Non-Calcified Plaque	0.071 (−0.053, 0.195)	0.26	0.028 (−0.021, 0.076)	0.26	−0.114 (−0.275, 0.046)	0.16
Partially Calcified Plaque	0.101 (−0.104, 0.306)	0.33	0.263 (0.183, 0.344)	< 0.01	−0.215 (−0.480, 0.050)	0.11
Calcified Plaque	0.179 (−0.100, 0.458)	0.21	0.344 (0.239, 0.450)	< 0.01	−0.083 (−0.444, 0.278)	0.65
SSS	0.455 (−0.023, 0.932)	0.06	0.692 (0.504, 0.879)	< 0.01	−0.555 (−1.173, 0.063)	0.08

*Propensity-adjusted for likelihood of taking non-statin therapy (NST), and risk-adjusted from backward stepwise model selection with individual risk factors such as age, sex, symptoms, diabetes mellitus, smoking status, family history, hypertension or anti-hypertensive medications, and high-density lipoprotein (HDL). Statin and NST indication, low-density lipoprotein (LDL) level, and propensity score were forced into the model.

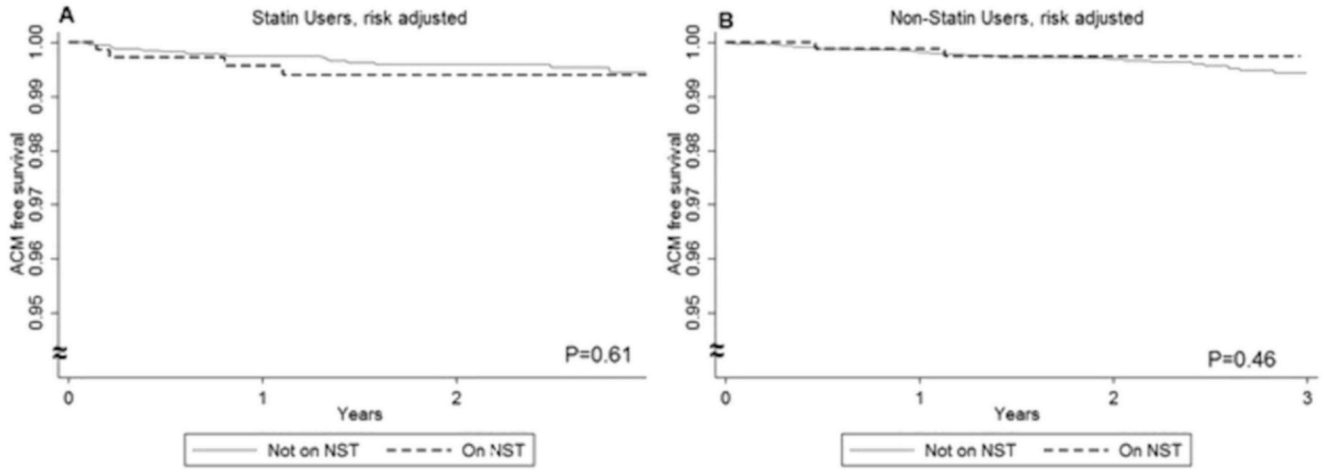

Fig. 1. Kaplan Meier survival for ACM by non-statin therapy. Stratified by patients with (A) and without (B) concurrent statin use, there is no propensity- and risk-adjusted difference in survival for patients taking non-statin therapy. The risk adjustment was based on model selection such as in Tables 3 and 4.
Abbreviations: ACM: all-cause mortality; NST: non-statin therapy.

Table 4
Association between NST and statin therapy on all-cause mortality using Cox Regression.

	Unadjusted HR		Risk-adjusted HR*	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Non-statin Therapy	0.81 (0.20–3.36)	0.78	0.64 (0.15–2.68)	0.54
Statin	0.91 (0.55–1.52)	0.71	0.51 (0.30–0.87)	0.01
Interaction	1.51 (0.26–8.92)	0.65	2.03 (0.34–12.06)	0.44

*Propensity and risk-adjusted from stepwise model selection. Statin and NST indication, LDL level, geographic region, and propensity score were forced into the model. Model adjusted by geography, statin indication, low-density lipoprotein (LDL), propensity score, age, beta-blocker use, BMI, and dyspnea.

since current evidence suggests that benefit is directly proportional to the degree of LDL lowering. On the other hand, although calcified plaque has been established as a prognostic indicator of adverse cardiovascular events, it has been hypothesized that increased calcified plaque secondary to statins may represent more stable coronary plaque less prone to rupture.[27] Statin therapy has been shown to increase calcified plaque volume, with a greater impact in individuals with lower LDL levels.[10] Additionally, coronary CTA and IVUS studies have shown that statins can slow progression of noncalcified coronary plaque, and may also reduce necrotic core volume.[7–9,28] Our study highlights an approach to understanding the mechanistic impact of different cholesterol-lowering drugs on atherosclerosis burden as well as plaque characteristics. In addition, the availability of noninvasive and comprehensive plaque imaging modalities coupled with an improved understanding of atherosclerotic plaque physiology, through elucidation of noninvasively determined surrogates of high-risk plaque, could provide the ability to evaluate the effect of such therapies on the natural progression of coronary artery disease prior to the onset of adverse cardiovascular events.

It is possible that our simple qualitative evaluation of calcification cannot capture the atherosclerotic plaque changes that would result from NST. Qualitative high-risk plaque features on coronary CTA, such as spotty calcification, low-attenuation plaque, positive remodeling and the napkin ring sign, and quantitative plaque composition such as necrotic core volume and non-calcified plaque volume may better capture small changes in plaque and risk.[29,30] Future studies should examine specific NSTs, including PCSK9, for the impact on qualitative and quantitative high-risk features, since PSCK9 may have the potential to directly affect lipid-rich plaque via LDL receptor.[31] Current generation coronary CTA analysis may be a tool that is more convenient for serial studies than IVUS, given its non-invasive nature and its ability to perform whole-heart plaque evaluation.

The results of this study should be considered in the context of its limitations. First, information on the type or dosage of NST (e.g. ezetimibe, fibrate or niacin) was not available, thus conclusions could not be made about any one particular NST. It is possible that there are class-specific effects on plaque composition that cannot be distinguished. Additionally, the effects of NST on plaque composition were only assessed at the time of the initial coronary CTA scan, and longitudinal changes in plaque composition were not assessed. Because history of statin and NST use were unavailable, results may have been influenced by variation in dosing and duration of therapy. In an observational cohort of coronary CTA, there may be unmeasured confounding and referral bias. For instance in clinical practice, higher risk individuals are more likely to be treated aggressively with the addition of non-statin therapies. We have attempted to account for complex confounding with propensity adjustment, multivariate risk adjustment, and incorporation of statin therapy recommendation into the multivariate model, but there are factors beyond those accounted for by clinical indication that could have influenced therapy selection, such as statin intolerance. Another limitation is that new coronary CTA reporting guidelines have specified vulnerable plaque characteristics that were not standardized at the time of CONFIRM.

In conclusion, the results of the present observational study show that in patients without known CAD, non-statin therapy was not independently associated with differences in plaque composition as assessed by coronary CTA. Further, there was no evidence of an interaction between NST and statins on plaque composition. The results of the present study could provide a platform for subsequent longitudinal studies for different lipid lowering therapies on coronary plaque characteristics as well as incident cardiovascular events.

Author contribution statement

Dr. Al'Aref and Dr. Su have equally contributed to the manuscript.

Disclosure

Dr. James K. Min receives funding from the Dalio Foundation, National Institutes of Health, and GE Healthcare, serves on the scientific advisory board of Arineta and GE Healthcare, and has an equity interest in Cleerly. All other authors have reported that they have no

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jcct.2019.01.015.

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