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ORIGINAL RESEARCH

# Interaction Between Statin Use, Coronary Artery Disease Phenotypes, on Computed Tomography Angiography, and Cardiovascular Outcomes

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## ABSTRACT

**BACKGROUND** Although statins are recommended for decreasing cardiovascular risk, their efficacy across different patient phenotypes stratified by coronary artery disease (CAD) remains unclear.

**OBJECTIVES** This study aims to evaluate whether statins decrease major adverse cardiac events (MACE) among CAD phenotypes according to severity, vulnerability and extent categorized by coronary computed tomography angiography (CTA).

**METHODS** The authors analyzed consecutive patients who were referred for coronary CTA at a tertiary center for the assessment of chronic coronary syndrome. The primary endpoint was MACE defined as a composite of all-cause mortality, acute myocardial infarction, or revascularization for unstable angina. Statin use was defined as annualized days on statin therapy (days on statin based on redeemed prescriptions, divided by follow-up time), and analyzed for each 10% increase in statin use over the follow-up period. Interaction analysis, adjusting for risk factors was applied to define treatment benefit across CAD phenotypes.

**RESULTS** Overall, 11,026 individuals (mean age: 58.6 ± 11.9 years, 54.7% male) were analyzed who underwent coronary CTA between January 1, 2013, and December 31, 2020. A 10% increase in statin use was associated with lower risk for MACE the stratified Cox-regression model in patients with CAD (adjusted HR [aHR]: 0.95 [95% CI: 0.92-0.99]; $P = 0.006$), but not in patients without CAD (aHR: 0.95 [95% CI: 0.84-1.07]; $P = 0.370$). In the total population using interaction analysis including CAD phenotypes, a 10% increase in statin use decreased the risk for MACE in the presence of obstructive CAD (aHR: 0.91 [95% CI: 0.85-0.97]; $P = 0.006$), high-risk plaque (aHR: 0.82 [95% CI: 0.68-0.98]; $P = 0.026$), calcium score of ≥400 (aHR: 0.93 [95% CI: 0.87-0.99]; $P = 0.024$), and segment involvement score of >4 (aHR: 0.89 [95% CI: 0.84-0.95]; $P < 0.001$), but not for any CAD (aHR: 0.95 [95% CI: 0.85-1.07]; $P = 0.411$).

**CONCLUSIONS** Statin efficacy to decrease MACE depends on CAD phenotypes and increases with the extent and severity of disease and in the presence of high-risk plaques. Patients without CAD have no benefit from statin therapy regarding MACE. Coronary CTA may play a pivotal role in optimizing statin allocation for personalized treatment decisions to prevent MACE. (JACC Cardiovasc Imaging. 2025;■:■–■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**ASCVD** = atherosclerotic cardiovascular disease

**CAD** = coronary artery disease

**CT** = computed tomography

**CTA** = computed tomography angiography

**HRP** = high-risk plaque

**MACE** = major adverse cardiac events

Statin therapy is the cornerstone of primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD).[1,2] Clinical guidelines consider age, sex, serum cholesterol levels, and risk factors to estimate individual risk when assigning patients to statin therapy.[3] Recent recommendations aimed to establish precise cholesterol cutoff values tailored to various patient groups to mitigate risk effectively. However, the ability of statins to decrease major adverse cardiac events (MACE) could differ across the spectrum of the underlying coronary artery disease (CAD) phenotypes.[4,5] Ensuring appropriate allocation of statins is of paramount importance, given that a significant number of patients may discontinue their medication after comprehensive risk assessment including results from computed tomography (CT) imaging.[6] Moreover, it is crucial to identify individuals with possible benefit from statins based on certain CAD characteristics to further improve outcomes and optimize costs.

Recently published evidence suggested that the extent of CACS (coronary artery calcium score) and nonobstructive CAD on coronary computed tomography angiography (CTA) could identify those who benefit most from statin therapy.[4,7] Nonetheless, reliable monitoring of statin use is challenging because of the unknown exact duration and dosing. Notably, former investigations defined statin use as the presence or absence of ≥1 filled prescription within a certain time period, or incidental statin use reported by the patient or from electronic databases without data on the redemption of the drug or on the duration and intensity of the therapy.[5,8] More precise estimates of statin adherence may help to better understand which CAD phenotypes benefit the most from statin therapy and can describe the effect of coronary CTA on statin allocation.

Therefore, we sought to evaluate whether statin use, defined as the number of days the patient took the medication based on the redeemed prescriptions, may be associated with MACE reduction in a cohort of patients with stable chest pain according to the presence, extent, and vulnerability of CAD as assessed by coronary CTA. We also aimed to identify the treatment threshold for certain CAD phenotypes, determining where statins could provide benefit. Furthermore, we aimed to assess the role of coronary CTA findings on statin allocation before and after coronary CTA.

## METHODS

**STUDY DESIGN AND POPULATION.** The study population included consecutive patients with stable chest pain referred for clinically indicated coronary CTA to assess CAD at our tertiary university center. Inclusion criteria were as follows: >18 years of age at the time of the scan, had at least 1 diagnostic coronary CTA examination at our institute between January 1, 2013, and December 31, 2020. International Classification of Diseases-10th edition (ICD-10) codes and ICPM (International Classification of Procedures in Medicine) were used to identify patients fulfilling the exclusion criteria of prior myocardial infarction or coronary revascularization. The list of ICD-10 and ICPM codes for defining exclusion criteria is summarized in Supplemental Table 1.

The study was approved by the Institutional Ethical Review Board (TUKEB IV/8887-1/2021/EKU) and informed consent was waived due to the retrospective study design. The study was in accordance with local and federal regulations, and the Declaration of Helsinki.

**PHARMACOLOGICAL THERAPY.** The NHIS (National Health Insurance Service) is a nationwide medical care system for the Hungarian population (~10 million people) that stores and manages a database of health care practices, diagnoses, and treatments covering almost 100% of the Hungarian population. The follow-up window lasted from data availability in NHIS (earliest available date in the NHIS records was January 1, 2010) until the occurrence of the outcome (MACE), or the end of follow-up (December 31, 2020). We retrieved all entries for the redemption of a prescription for statin or a combination of statin with ezetimibe (ATC [Anatomical Therapeutic Chemical] classification system: C10AA statins, C10BA statin + ezetimibe). Any statin therapy and annualized days on statin therapy were recorded. The latter was defined as the number of days on statin from the first day of statin prescription redemption up to the given event, or until censoring, divided by the available total follow-up time for a given patient. We report the impact of a 10% increase in annualized days on statin therapy, which corresponds with a proportional 10% increase in statin use during the study period (January 1, 2010, to December 31, 2020).

**CT IMAGE ACQUISITION AND READING.** All patients underwent coronary CTA imaging using a GE Cardiographe (GE HealthCare) or 256-slice Philips Brilliance iCT (Philips Healthcare) scanner (further detailed in the Supplemental Methods).

Obstructive CAD was defined as the presence of at least 1 ≥50% coronary artery luminal diameter stenosis. The SIS (segment involvement score) (sum of all coronary segments affected with plaque) was recorded to quantify total CAD burden. An SIS of >4 was considered indicative of extensive disease.[9] The presence of high-risk plaque (HRP) features was defined as having any coronary segment with a lesion demonstrating low CT attenuation, napkin ring sign or positive remodeling.[10]

CAD phenotypes were categorized using the following parameters derived from CT imaging: any CACS (>0), total CACS >100 or > 400, presence of any CAD, presence of obstructive CAD, SIS of >4, and presence of any HRP feature. Additionally, CACS and SIS were analyzed as continuous variables to define the optimal threshold for initiating statins.

**ENDPOINT DEFINITION.** The primary endpoint was MACE, which was defined as a composite of death from any cause, nonfatal myocardial infarction, and revascularization due to unstable angina.

Mortality data were collected and verified via official NHIS death records to ensure data consistency and accuracy, with no loss to follow-up, because the NHIS comprehensively tracks health care use and outcomes for the entire population. A list of ICD-10 and procedure codes (Hungarian adaptation of the International Classification of Procedures in Medicine [OENO]) for endpoint definitions are detailed in Supplemental Table 2. The follow-up period extended from the earliest available NHIS record (January 1, 2010) until the occurrence of the primary outcome (MACE) or the end of follow-up on December 31, 2020.

**STATISTICAL ANALYSIS.** Categorical variables were compared using chi-square or Fisher's exact tests and presented as frequencies with percentages. Continuous variables are expressed as mean ± SD and were compared between groups using independent 2-sample Student's *t*-test. We created 4 statin treatment groups based on pre- and post-coronary CTA statin treatment (only pre-coronary CTA, only post-coronary CTA, pre- and post-coronary CTA, or no statin intake). We conducted ANOVA (analysis of variance) to identify differences among these groups, followed by independent 2-sample Student's *t*-tests for pairwise comparisons, adjusting *P* values using the Bonferroni correction (adjusted $\alpha$ level 0.0083) to assess differences in risk factors and CAD parameters. Univariable and multivariable models (logistic regression) was used to define predictors (CAD phenotypes based on coronary CTA) of statin initiation after coronary CTA, based on redeemed prescriptions among patients who were not on statins before the procedure. A similar approach was used to define the association between plaque markers and statin discontinuation in patients who were on statins before undergoing coronary CTA but stopped afterward.

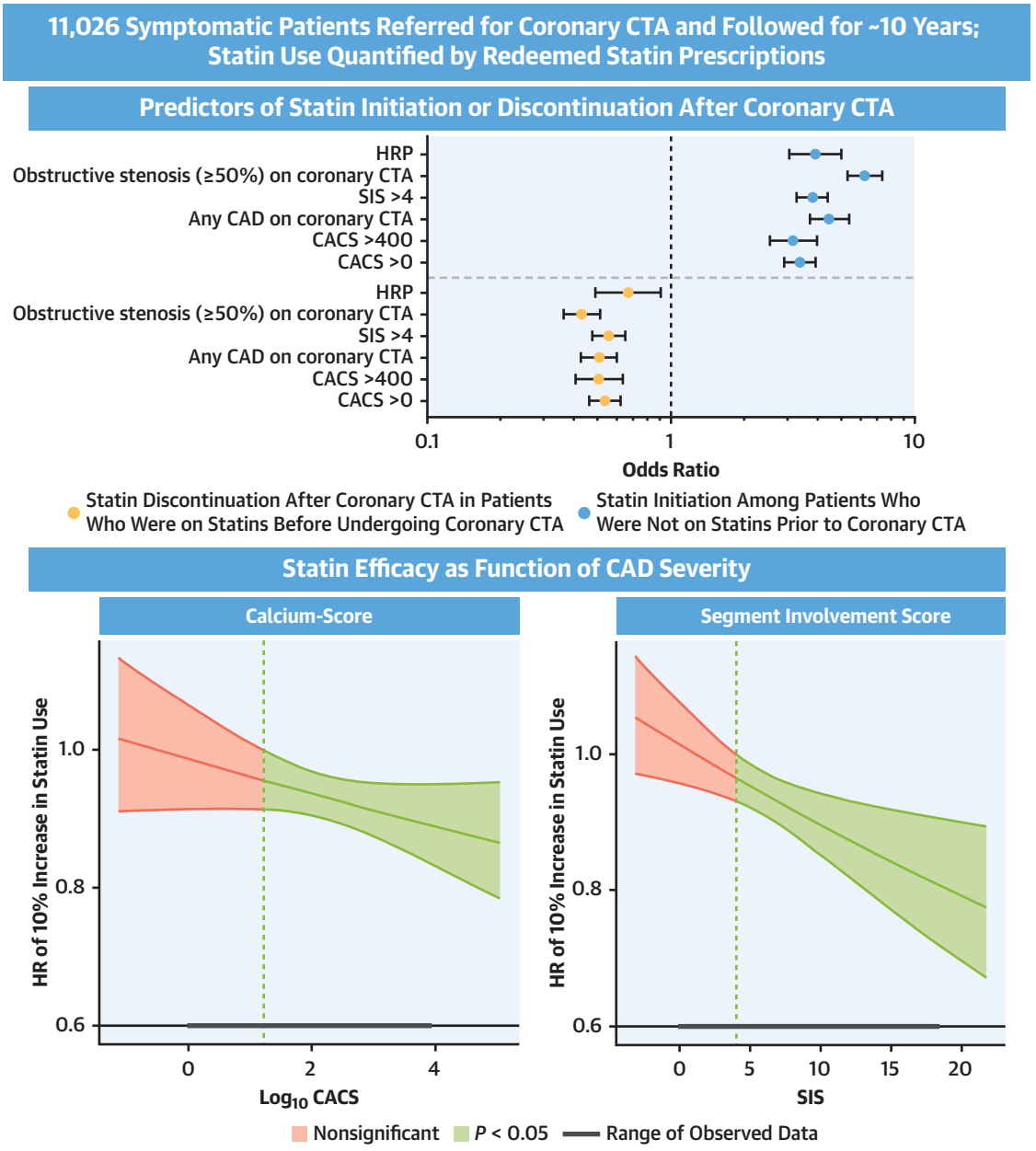
Subsequently, we analyzed the association of statin therapy with the composite endpoint of MACE using Cox proportional hazard models. Univariable models were performed separately by adding traditional risk factors, and any statin therapy or a 10% increase in annualized days on statin therapy as predictors. In all multivariable models, we included the following patient reported risk factors to account for confounding: age, sex, body mass index, hypertension, diabetes, smoking, and aspirin therapy. Furthermore, a prespecified interaction analysis was performed to define the effect of statin on the outcome according to the presence (or absence) of CAD, CACS, obstructive CAD, HRP feature, or CAD extent. We included the annualized days on statin therapy as the primary statin parameter with 10% increase and performed an additional interaction analysis with any statin therapy. Three subanalyses were conducted: 1) stratification by sex with independent interaction analyses for males and females; 2) evaluation of post-coronary CTA statin therapy reflecting management changes based on coronary CTA findings; and 3) assessment of statin benefits on mortality or myocardial infarction alone.

Finally, we generated Johnson-Neyman plots to visualize and determine the ranges of the moderator variable (CACS and SIS) where the predictor (10% increase in statin use) has a significant effect on MACE for the total study period and the restricted time period after coronary CTA (**Central Illustration**). This approach allows for the identification of treatment thresholds across CAD phenotypes and aids the understanding of the moderation effects of statin therapy. CACS values were log transformed because of the skewed distribution. All analyses were performed using R programming language version 4.0.3 (packages: interactions, survival, survminer, tableone, car, stats). Statistical significance was defined as a 2-sided value of $P < 0.05$.

## RESULTS

A total of 11,506 coronary CTA scans were performed between January 1, 2013, and December 31, 2020. After applying our exclusion criteria, 11,026 patients (mean age: 58.6 ± 11.9 years; 54.7% male) were included in the final analysis (Supplemental Figure 1). A total of 66% of the patients (7,245/11,026) were treated with any statins during the entire study period. Further details on patient demographics, risk

**CENTRAL ILLUSTRATION** **Benefits of Statin Therapy on Adverse Cardiovascular Outcomes Across Different CAD Phenotypes as Obtained by Coronary CTA**

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We analyzed 11,026 consecutive patients referred for coronary CTA to assess CAD. The primary endpoint was MACE (a composite of all-cause mortality, acute myocardial infarction, or revascularization for unstable angina). The Forest plot illustrates the odds ratios for the association of CAD parameters with statin use. The upper section (blue) shows the relationship between predictors (CAD phenotypes) and statin initiation after coronary CTA, based on redeemed prescriptions among patients who were not on statins before the procedure. The lower section (orange) depicts the association between plaque markers and statin discontinuation in patients who were on statins before undergoing coronary CTA but stopped afterward. The Johnson-Neyman plots depict the ranges of SIS and CACS where statin was protective for MACE (total study period). CACS = coronary artery calcium score; CAD = coronary artery disease; CTA = computed tomography angiography; MACE = major adverse cardiac events; SIS = segment involvement score.

profile and coronary CTA findings stratified by tertiles according to the primary statin parameter are summarized in **Table 1**.

The median follow-up time was 8.33 years (Q1-Q3: 6.85-10.12 years) from the first available date of statin therapy to the first event or end of follow-up. The median follow-up time was 3.33 years (Q1-Q3: 1.85-4.98 years) from CTA to the first event or end of follow-up. The primary outcome of MACE was detected in 486 of 11,026 patients (4.4%), myocardial infarction alone in 96 (0.9%), and all-cause mortality in 344 (3.1%) patients. Supplemental Tables 3 to 5 compare patient characteristics and CT findings between patients with and without events.

**STATIN THERAPY AND CAD FINDINGS.** Overall, 14% (1,590/11,026) of patients stopped using statins after coronary CTA, 11% (1,261/11,026) initiated statin therapy after coronary CTA, 40% (4,394/11,026) continued statin therapy after coronary CTA, and 34% (3,781/11,026) were not treated with statins at all based on the data regarding redeemed prescriptions. The majority of the cardiovascular risk factors differed between the 4 different statin treatment groups ($P < 0.05$ for all) (Supplemental Table 6).

When analyzing the predictors of statin initiation or discontinuation based on coronary CTA, we found that all assessed plaque parameters consistently demonstrated a significant association with treatment decisions (**Table 2**). Comparing the 4 groups categorized based on statin therapy and coronary CTA date, we detected significantly higher rates of CACS >400, SIS >4, and obstructive CAD among patients on statin therapy after coronary CTA, as compared with patients with statin therapy only before coronary CTA or no statin therapy at all (all $P < 0.001$). Notably, 3.4% of patients with a CACS of >400 did not take statins during the whole study period. Patients who were on statins only before coronary CTA had significantly lower obstructive stenosis rates (16.1% vs 39.3%) and SIS (2.8 ± 2.8 vs 4.2 ± 3.2) as compared with the patients who were treated only after coronary CTA ($P < 0.05$ for all).

**THE ASSOCIATION OF STATIN THERAPY WITH MACE.** In the total patient cohort, statin therapy defined as a 10% increase in statin use was protective against MACE (adjusted HR [aHR]: 0.95 [95% CI: 0.93-0.99]; $P = 0.007$). Conversely, defining statin therapy as any statin use showed that it was not linked with MACE (aHR: 0.86 [95% CI: 0.68-1.08]; $P = 0.180$) after adjusting for risk factors (**Table 3**).

We evaluated the interplay between the presence of any CAD on coronary CTA and statin therapy during the whole study period. 10% increase in statin use reduced the risk of MACE in patients with any CAD (aHR: 0.95 [95% CI: 0.92-0.99]; $P = 0.006$); however, this was not observed in patients without any plaque on coronary CTA (aHR: 0.95 [95% CI: 0.84-1.07]; $P = 0.370$).

**MODERATION OF STATIN EFFECTS BY CAD PHENOTYPES.** Results of the multivariable analysis of interactions between CAD markers and 10% increase in statin use are summarized in **Table 4** and Supplemental Figure 2. An interaction analysis demonstrated that a 10% increase in statin use (proportional statin use of 10%) was protective in the presence of a CACS of ≥400 (aHR: 0.93 [95% CI: 0.87-0.99]; $P = 0.024$), SIS of >4, (aHR: 0.90 [95% CI: 0.84-0.95]; $P < 0.001$), obstructive CAD (≥50%) (aHR: 0.91 [95% CI: 0.86-0.97]; $P = 0.006$), or the presence of HRP (aHR: 0.82 [95% CI: 0.68-0.98]; $P = 0.026$). In the presence of any CACS (>0), a 10% increase in statin use showed a trend toward an improved prognosis (aHR: 0.92 [95% CI: 0.84-1.00]; $P = 0.054$). Univariable results are presented in Supplemental Table 7. Defining statin therapy as any statin use in the interaction analysis showed different results: any statin use was not associated with improved MACE as shown in Supplemental Table 8.

The Johnson-Neyman plot demonstrates the SIS and CACS ranges where statin use achieves significant clinical benefit in terms of reducing MACE (**Figure 1**, **Central Illustration**). The thresholds for achieving beneficial outcomes in terms of reducing MACE with statin (10% increase in statin use) are SIS 4.03 for the total study period. Statin utilization was protective for MACE if a total value of CACS 16.6 was detected in the total study period.

**PROGNOSTIC BENEFIT OF STATINS FOR SECONDARY ENDPOINTS.** Proportional statin use of 10% improved mortality in patients with a SIS of >4 (aHR: 0.92 [95% CI: 0.86-0.99]; $P = 0.036$). Regarding myocardial infarction, statin therapy was protective in the presence of obstructive CAD (aHR: 0.80 [95% CI: 0.68-0.94]; $P = 0.005$). All other CAD phenotypes and outcome analysis resulted in nonsignificant associations ($P > 0.05$ for all) (Supplemental Table 9, Supplemental Figure 3). Additional subanalyses of the association of post-coronary CTA statin use and MACE are presented in Supplemental Table 10 and Supplemental Figure 2.

**SUBANALYSIS DESCRIBING SEX DIFFERENCES IN THE PROTECTIVE VALUE OF STATIN THERAPY.** A total of 242 MACE occurred in the male and 244 in the female population. Statin was protective for

**TABLE 1 Patient Characteristics at the Time of CTA, and CT Findings Stratified by Statin Therapy Tertiles**

| | Without Statin (n = 3,781) | Tertile 1 (n = 2,415) | Tertile 2 (n = 2,415) | Tertile 3 (n = 2,415) | *P* Value |
|---|---|---|---|---|---|
| Demographic data | | | | | |
| Age, y | 52.1 ± 12.0 | 59.8 ± 10.9 | 61.4 ± 10.3 | 64.8 ± 9.1 | <0.001 |
| Male | 2,096 (55.4) | 1,215 (50.3) | 1,290 (53.4) | 1,257 (52.1) | <0.001 |
| BMI | 27.5 ± 4.9 | 28.3 ± 4.8 | 28.8 ± 5.0 | 29.1 ± 4.8 | <0.001 |
| Hypertension | 1,616 (42.7) | 1,472 (61.0) | 1,697 (70.3) | 1,847 (76.5) | <0.001 |
| Diabetes mellitus | 192 (5.1) | 278 (11.5) | 427 (17.7) | 633 (26.2) | <0.001 |
| Dyslipidemia | 480 (12.7) | 804 (33.3) | 1,283 (53.1) | 1,697 (70.3) | <0.001 |
| History of smoking | 1,178 (31.2) | 767 (31.8) | 783 (32.4) | 801 (33.2) | 0.212 |
| Family history of premature CAD | 947 (25.1) | 638 (26.4) | 606 (25.1) | 622 (25.8) | 0.162 |
| Statin therapy | | | | | |
| Percent of days on statin during follow-up | – | 2.32 ± 1.96 | 20.06 ± 8.85 | 66.32 ± 20.18 | – |
| ASA therapy | | | | | |
| ASA use at any time | 675 (17.9) | 924 (38.3) | 1,181 (48.9) | 1,370 (56.7) | <0.001 |
| Coronary CTA findings | | | | | |
| Calcium score >0 | 1,173 (31.0) | 1,374 (56.9) | 1,662 (68.8) | 1,880 (77.9) | <0.001 |
| Calcium score >100 | 391 (10.3) | 638 (26.4) | 910 (37.7) | 1,178 (48.8) | <0.001 |
| Calcium score >400 | 127 (3.4) | 235 (9.7) | 390 (16.2) | 612 (25.3) | <0.001 |
| CACS | 178.5 ± 414.9 | 248.0 ± 456.2 | 335.7 ± 598.9 | 465.9 ± 710.1 | <0.001 |
| Any CAD on coronary CTA | 2,040 (54.0) | 1,851 (76.7) | 2,068 (85.6) | 2,131 (88.2) | <0.001 |
| SIS >4 | 447 (11.8) | 684 (28.3) | 949 (39.3) | 1,114 (46.1) | <0.001 |
| Obstructive stenosis (≥50%) on coronary CTA | 269 (7.1) | 569 (23.6) | 857 (35.5) | 895 (37.1) | <0.001 |
| HRP feature | 115 (3.0) | 146 (6.1) | 239 (9.9) | 160 (6.6) | <0.001 |
| CAD | | | | | <0.001 |
| No | 1,741 (46.1) | 564 (23.4) | 347 (14.4) | 284 (11.8) | |
| Minimal | 1,072 (28.4) | 612 (25.3) | 533 (22.1) | 473 (19.6) | |
| Mild | 699 (18.5) | 670 (27.7) | 678 (28.1) | 763 (31.6) | |
| Moderate | 187 (5.0) | 339 (14.0) | 468 (19.4) | 489 (20.3) | |
| Severe | 67 (1.8) | 182 (7.5) | 326 (13.5) | 323 (13.4) | |
| Occluded | 15 (0.4) | 48 (2.0) | 63 (2.6) | 83 (3.4) | |
| Revascularization rate (CABG or PCI) | 14 (0.3) | 132 (5.5) | 250 (10.4) | 254 (10.5) | <0.001 |

Values are mean ± SD or n (%), unless otherwise indicated. Tertiles were defined based on the distribution of the primary statin parameter (days on statin therapy).

BMI = body mass index; CABG = coronary artery bypass grafting; CACS = coronary artery calcium score; CAD = coronary artery disease; CTA = computed tomography angiography; HRP = high-risk plaque; PCI = percutaneous coronary intervention; SIS = segment involvement score.

MACE in male patients with a SIS of >4 (10% proportional statin use; aHR: 0.83 [95% CI: 0.76-0.92]; $P < 0.001$) or obstructive CAD (≥50%) (aHR: 0.91 [95% CI: 0.82-0.99]; $P = 0.039$) (Supplemental Table 11, Supplemental Figure 4), whereas only borderline significance was observed for the presence of obstructive CAD among females (aHR: 0.92 [95% CI: 0.84-1.00]; $P = 0.058$). All other associations between statin and MACE were not significant.

## DISCUSSION

Analyzing data from >11,000 consecutive stable chest pain patients, we observed that statin therapy decreased MACE in patients diagnosed with CAD on coronary CTA, although it was not associated with events in patients without CAD. Furthermore, coronary CTA influenced the allocation of statin therapy significantly, leading to notable differences across patient subgroups based on their statin treatment. Interaction analyses identified distinct CAD phenotypes including obstructive disease (≥50%), extensive CAD defined as a CACS of ≥400 or SIS of >4 and the presence of HRP where statins proved beneficial. Additionally, we identified the treatment thresholds and ranges for SIS and CACS where statin demonstrated prognostic benefit. Our findings suggest that coronary CTA can provide quantified plaque infor-

**TABLE 2 The Association of CAD Phenotypes on Coronary CTA With Statin Initiation of Discontinuation After Coronary CTA**

| | Statin Discontinuation After Coronary CTA | | Statin Initiation After Coronary CTA | |
|---|---|---|---|---|
| | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| CACS >0 | 0.54 (0.463-0.624) | <0.001 | 3.39 (2.929-3.926) | <0.001 |
| CACS >400 | 0.51 (0.407-0.636) | <0.001 | 3.18 (2.54-3.991) | <0.001 |
| Any CAD on coronary CTA | 0.51 (0.429-0.601) | <0.001 | 4.48 (3.747-5.39) | <0.001 |
| SIS >4 | 0.56 (0.477-0.651) | <0.001 | 3.81 (3.281-4.431) | <0.001 |
| Obstructive stenosis (≥50%) on coronary CTA | 0.43 (0.364-0.514) | <0.001 | 6.26 (5.312-7.377) | <0.001 |
| HRP feature present (excluding spotty calcification) | 0.67 (0.491-0.91) | 0.012 | 3.92 (3.067-5.027) | <0.001 |

Adjustments in this multivariable model set was made for age, sex, BMI, hypertension, diabetes mellitus, any smoking, aspirin therapy.
Abbreviations as in Table 1.

mation to guide statin therapy initiation and thereby facilitating preventive measures and advancing toward CT guided personalized preventive therapies.

**PERSONALIZING STATIN TREATMENT BASED ON CORONARY CTA.** Statins are generally recommended for primary prevention to prevent MACE through the reduction of low-density lipoprotein cholesterol levels.[11] Current major dyslipidemia guidelines underline the importance of tailoring treatment intensity to a patient's risk of developing ASCVD based on strong evidence derived from primary prevention trials. However, the thresholds at which treatment is initiated varies greatly across guidelines.[12] Also, we witnessed a transition from a treat-to-goal strategy (to achieve NCEP ATP III [National Cholesterol Education Program Adult Treatment Panel III] goals) to the identification of certain groups of individuals based on statin therapy's proven benefits.[13,14] A recent analysis from the Copenhagen General Population Study found that the 2021 ESC (European Society of Cardiology) guidelines substantially decreased the number of patients (aged 40-69 years) eligible for statin therapy in primary prevention as compared with the ACC (American College of Cardiology)/AHA (American Heart Association) or the NICE (National Institute for Health and Care Excellence) guidelines, which could lead to early discontinuation of statin therapy in patients who could benefit from statin therapy.[15] Also, the ability of statins to decrease MACE could differ across the spectrum of the underlying CAD phenotypes as detected by coronary CTA.

SCOT-HEART (Scottish COmputed Tomography of the HEART Trial) demonstrated the impact of coronary CTA on patient prognosis,[16] whereas other trials showed that CT-based education can increase new statin therapy recommendations and also improve adherence to lipid-lowering therapy.[6] Our results also strongly reinforce the impact of coronary CTA on patient management. Forthcoming studies (eg, DANE-HEART [Prevention of Heart Disease in Adult Danes Using Computed Tomography Coronary Angiography], SCOT-HEART 2 [Scottish Computed Tomography of the Heart 2]) will explore asymptomatic patients to delineate subclinical disease and establish treatment thresholds, where our findings will be pivotal in guiding future decision-making.[7] An individual's cardiovascular risk is not static, but rather a continuous spectrum, and traditional risk scores might be inaccurate to identify those who require pharmacotherapy. Also, longitudinal studies are essential to deepen our understanding of the

**TABLE 3 Univariate and Multivariable Cox Regression Analysis of Cardiovascular Risk Factors and Different Definitions of Statin Therapy for the Assessment of MACE (N = 11,026)**

| | Cox Regression Univariate | | Cox Regression Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | aHR (95% CI) | *P* Value |
| 10% Increase in statin use | | | | |
| Age | 1.07 (1.06-1.08) | **<0.001** | 1.07 (1.06-1.08) | **<0.001** |
| Sex | 0.94 (0.79-1.13) | 0.526 | 1.02 (0.84-1.22) | 0.872 |
| BMI | 1.02 (1.01-1.04) | **0.035** | 1.01 (0.99-1.04) | 0.158 |
| Hypertension | 1.91 (1.54-2.37) | **<0.001** | 1.12 (0.89-1.40) | 0.348 |
| Diabetes mellitus | 2.12 (1.72-2.61) | **<0.001** | 1.65 (1.32-2.06) | **<0.001** |
| Any smoking | 1.25 (1.04-1.51) | **0.021** | 1.40 (1.16-1.70) | **<0.001** |
| Any ASA therapy | 1.78 (1.49-2.13) | **<0.001** | 1.18 (0.97-1.43) | 0.105 |
| 10% increase in statin use | 1.05 (1.02-1.08) | **<0.001** | 0.96 (0.93-0.99) | **0.007** |
| Any statin therapy | | | | |
| Age | 1.07 (1.06-1.08) | **<0.001** | 1.07 (1.06-1.08) | **<0.001** |
| Sex | 0.94 (0.79-1.13) | 0.526 | 1.01 (0.84-1.22) | 0.911 |
| BMI | 1.02 (1.01-1.04) | **0.035** | 1.01 (0.99-1.04) | 0.175 |
| Hypertension | 1.91 (1.54-2.37) | **<0.001** | 1.10 (0.87-1.38) | 0.419 |
| DM | 2.12 (1.72-2.62) | **<0.001** | 1.59 (1.27-2.00) | **<0.001** |
| Any smoking | 1.25 (1.03-1.51) | **0.021** | 1.39 (1.14-1.69) | **0.001** |
| Any ASA therapy | 1.78 (1.49-2.13) | **<0.001** | 1.16 (0.96-1.42) | 0.133 |
| Any statin therapy | 1.60 (1.31-1.97) | **<0.001** | 0.86 (0.68-1.10) | 0.180 |

**Bold** indicates significant *P* value.
ASA = acetylsalicylic acid; DM = diabetes mellitus; other abbreviations as in Table 2.

**TABLE 4 Prespecified Interaction Analysis of Statin Therapy (10% Increase in Proportional Statin Use) and CAD Phenotypes (N = 11,026)**

| | | | Interaction Term | |
|---|---|---|---|---|
| **Outcome: MACE** | **aHR (95% CI)** | ***P* Value** | **aHR (95% CI)** | ***P* Value** |
| 10% increase in statin use | 1.02 (0.94-1.10) | 0.656 | 10% increase in statin use × CACS >0 | |
| CACS >0 | 2.62 (1.92-3.58) | <0.001 | 0.92 (0.84-1.001) | 0.054 |
| 10% increase in statin use | 0.98 (0.93-1.03) | 0.449 | 10% increase in statin use × CACS >100 | |
| CACS >100 | 2.73 (2.10-3.54) | <0.001 | 0.94 (0.88-1.01) | 0.070 |
| 10% increase in statin use | 0.97 (0.93-1.01) | 0.156 | 10% increase in statin use × CACS >400 | |
| CACS >400 | 3.06 (2.31-4.05) | <0.001 | 0.93 (0.87-0.99) | **0.025** |
| 10% increase in statin use | 1.00 (0.89-1.12) | 0.956 | 10% increase in statin use × any CAD (SIS >0) | |
| Any CAD (SIS >0) | 1.91 (1.31-2.80) | <0.001 | 0.95 (0.85-1.07) | 0.411 |
| 10% increase in statin use | 1.01 (0.96-1.06) | 0.659 | 10% increase in statin use × SIS >4 | |
| SIS >4 | 2.67 (2.07-3.44) | <0.001 | 0.90 (0.84-0.95) | **<0.001** |
| 10% increase in statin use | 0.99 (0.95-1.04) | 0.721 | 10% increase in statin use × obstructive CAD | |
| Obstructive CAD | 3.18 (2.47-4.11) | <0.001 | 0.91 (0.86-0.97) | **0.006** |
| 10% increase in statin use | 0.96 (0.93-0.99) | 0.031 | 10% increase in statin use × HRP | |
| HRP | 1.98 (1.25-3.13) | 0.004 | 0.82 (0.68-0.98) | **0.026** |

**Bold** indicates significant *P* value. The HRs for 10% increase in statin use, the given CAD parameter and the interaction terms (statin therapy × CAD parameter) are reported. Adjustments in this multivariable model set was made for age, sex, BMI, hypertension, diabetes mellitus, any smoking, and aspirin therapy.

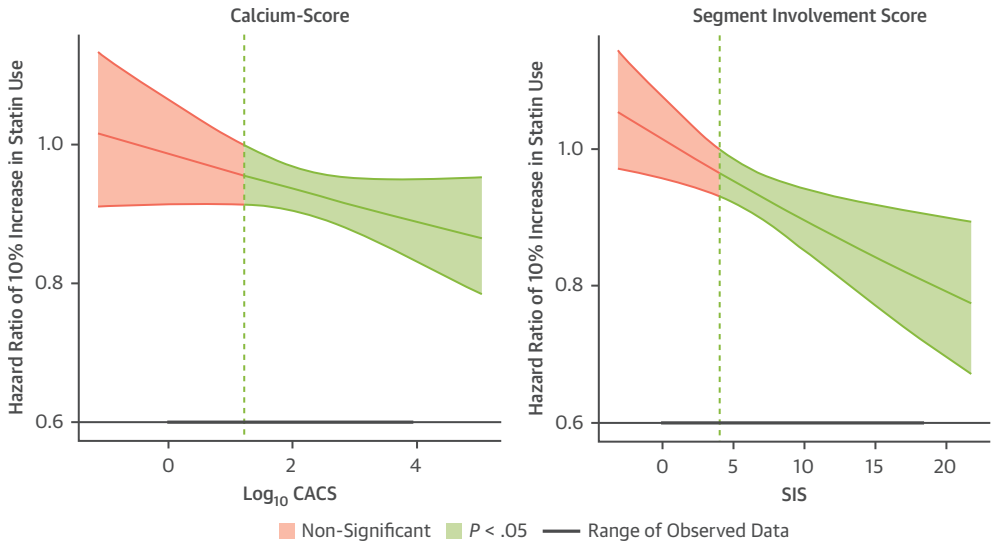
Abbreviations as in Table 1.

relationship between achieved low-density lipoprotein cholesterol or lipoprotein a levels and plaque progression. Such research can clarify how these lipid levels impact atherosclerosis over time, ultimately guiding more effective prevention and treatment strategies in cardiovascular care.[17] Therefore, a more personalized risk assessment has been proposed to prevent ASCVD events involving CAD phenotypes obtained by coronary CTA. Nevertheless, the optimal allocation of statins is a topic of debate as we strive to identify those who would derive the greatest benefit from statin. We found that coronary CTA results substantially influenced statin allocation and could improve prognosis based on CAD phenotyping. Still, large disparities exist in statin prescribing patterns and guidelines are still lacking regarding coronary CTA-based therapy decisions: 3.4% of patients who had extensive calcifications did not take statins in our cohort. This might be explained partially with: 1) adherence to therapy; 2) statin intolerance; 3) use of other type of lipid-lowering medication; and 4) report misinterpretation.

**CACS-BASED PREVENTION.** CACS can improve risk assessment of intermediate risk individuals and improves statin eligibility based on the MESA (Multi-Ethnic Study of Atherosclerosis) trial.[18,19] The use of statins for prevention in patients without detectable coronary calcification does not seem to improve outcomes. The SCCT consensus statement recommended a CAC threshold of 100 for statin treatment in patients with a 5% to 20% ASCVD risk.[20] Mitchell et al[5] followed 13,644 patients with noncontrast CT scans over a median follow-up time of 9.4 years and found that statin use was linked to reduced risk of MACE in patients with a CAC of >0 (aHR: 0.76 [95% CI: 0.60-0.95]; $P = 0.015$), but not in patients with a zero CACS (aHR: 1.00 [95% CI: 0.79-1.27]; $P = 0.99$). The impact of statin use on MACE was significantly influenced by the severity of CAC (interaction $P < 0.0001$).[5] Statin use was defined as a binary variable based on the presence or absence of 1 filled prescription at baseline or within 5 years after the CT, and prolonged statin use (>50% of follow-up period) was also addressed. Our findings showed different benefits for any statin use and the annualized days on statin therapy reflecting length of therapy. Compared with previous investigations, our methodology ensures accurate monitoring of actual drug administration and not just the indication for statin therapy. Statin use (reported as 10% proportional use during follow-up) was protective for MACE if a CACS of ≥16.6 was detected that is lower than current treatment thresholds recommended for initiating statins (Central Illustration). Although days on statin therapy—reflecting total dose taken and duration of therapy—was protective in the presence of extensive CAD (CACS ≥400, SIS >4), obstructive CAD, or HRP, a simplified variable of any statin intake did not seem to mitigate risk for MACE in the presence of these CAD phenotypes.

**BENEFITS OF STATINS BASED ON CAD EXTENT OR VULNERABILITY.** Although CACS and SIS both reflect plaque burden, coronary CTA outperforms CACS to predict MACE.[21] The CAD-RADS (Coronary Artery

**FIGURE 1** **Johnson-Neyman Plot Indicates the Ranges of CACS and SIS, Where Statin Therapy Significantly Affects MACE**




By identifying the specific ranges of calcium score and SIS where statin therapy is effective, the Johnson-Neyman plot provides insights into how the therapeutic impact of statins varies with the extent of CAD and determines therapeutic thresholds for initiating statins. The thresholds for achieving beneficial outcomes in terms of reducing MACE with statin (10% increase in statin use) are SIS ≥4.03 for the total study period. Statin use was protective for MACE if a total value of CACS ≥16.6 was detected in the total study period. CACS = coronary artery calcium score; CAD = coronary artery disease; MACE = major adverse cardiac events; SIS = segment involvement score.

Disease Reporting and Data System) 2.0 recommendation uniquely incorporated SIS categories to guide treatment recommendations.[22] Our interaction analysis demonstrated that statin therapy was protective in the extensive disease (CACS ≥400, SIS >4), obstructive CAD, or in patients with HRP, but not for patients with any CAD per se. This finding indicates that merely having some degree of CAD is insufficient; it must exceed a specific threshold of severity. Therefore, patients exhibiting these CAD markers should be offered statin therapy to improve outcomes. These observations are in line with the findings from previous trials. Moreover, recent advancements in postprocessing techniques may pave the way for an era of fully quantified plaque assessment, allowing for prevention therapy initiation based on plaque volume thresholds.[5,23]

In a large cohort of symptomatic patients with no or nonobstructive CAD on coronary CTA, statin therapy assessed by post-CTA redeemed prescriptions was associated with a risk reduction of MI and all-cause mortality during 3.5 years of follow-up.[23] If we consider statin therapy only after coronary CTA, statin use reduced the risk of MACE in the presence of HRP or an SIS of >4. When analyzing secondary outcomes in our study, we found that statin use (reported as a 10% increase) was associated with improved outcomes in patients with a SIS of >4 regarding mortality, whereas a CACS of >100 and the presence of obstructive CAD regarding myocardial infarction. Health care providers can enhance the effectiveness of preventive strategies in a more individualized approach using these features for statin allocation.

**SEX DIFFERENCES IN OUTCOMES.** The contradictory outcomes regarding the similarities and differences in CAD characteristics between male and female patients warrant further prospective studies.[24-26] It was observed that statin therapy lowered the incidence of CAD in men during primary prevention trials, but no such reduction was evident among women.[27] Notably, there are no data on the efficacy of statins across different CAD categories stratified by sex. We identified substantial sex-specific differences in the efficacy of statins in delivering protective effects. Statin therapy was protective in male patients with an SIS of >4 and obstructive CAD, whereas only borderline significance was observed for the presence of obstructive stenosis among females. We can hypothesize that

this difference might be explained by the overall lower SIS and fewer obstructive lesions among women as compared with men. Also, the efficacy of statin therapy can differ between sexes due to several factors, including differences in hormone levels, metabolism, and genetic predisposition.[28]

**STUDY LIMITATIONS.** Our analysis was constrained by the use of cross-sectional data when analyzing outcome information (first coronary CTA was analyzed). We could not monitor the changes of risk factors during the trial (eg, new onset of diabetes) as this was recorded during the coronary CTA. Also, we did not evaluate the effects of novel lipid lowering therapies including PCSK-9 inhibitors or bempedoic acid; however, these agents were used infrequently in our follow-up period. Furthermore, cholesterol levels were not available. Electronic health records codes often suffer from inaccuracies and miscoding, which can compromise the quality of data used in research and patient care. Prior evidence suggests that low socioeconomic position is significantly associated with nonadherence to statin therapy, with income identified as a key factor influencing this relationship.[29] Additionally, numerous data sets have demonstrated that a low socioeconomic position correlates with an increased risk of cardiovascular events. These findings underscore the importance of addressing socioeconomic disparities to improve medication adherence and decrease cardiovascular risk in vulnerable populations. Also, statin adherence may be associated with better risk factor modification because patients who consistently take their statins are likely to be more engaged in their overall health management. In the current study, we did not evaluate the effect of high-intensity vs non-high-intensity statin use on the outcome. Assessing statin-induced benefits in 10% increments provides a clearer understanding of adherence-related effects, making the results more interpretable and clinically applicable; however, further investigation is needed to determine the optimal scale for measuring statin-induced benefit. Although the use of a timeless statin variable (dividing the time on statin with the overall follow-up time per individual) avoids some complications of time-dependent Cox models, it does not capture the dynamic nature of medication adherence fully. Nevertheless, model assumption analyses indicated no violation of proportional hazards. Although the percent statin use does not depend on specific statin types or doses, the study does not consider potential differences in the effectiveness of various statin medications and dosages. The assumption of equivalence between statin types in the timeless variable may not reflect the varying impacts of different statin regimens fully. Ultimately, there is a pressing need for data on quantitative plaque thresholds to inform the initiation of statin therapy. However, the absence of unified protocols underscores the urgent need for their establishment.

## CONCLUSIONS

Efficacy of statin treatment depends on CAD phenotypes, including severity, extent, or the presence of HRP. Patients without CAD receive no benefit from statin therapy regarding MACE. Based on coronary CTA findings, patients with different CAD phenotypes who are most likely to benefit from statin therapy can be identified, and this approach could pave the way for an allocation of statins based on imaging to improve patient outcomes.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In an analysis of >11,000 stable chest pain patients, statin therapy reduced major adverse cardiovascular events in those diagnosed with CAD by coronary CTA but showed no benefit in patients without CAD. Coronary CTA also significantly influenced statin allocation. Interaction analyses identified specific CAD phenotypes—obstructive disease (≥50%), extensive CAD (calcium score ≥400 or SIS >4), and HRP—where statins were particularly effective.

**TRANSLATIONAL OUTLOOK:** Coronary CT imaging may identify individuals who benefit most from statin therapy and allows for the adoption of a personalized approach to mitigate the risk of adverse events through statin therapy.

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**KEY WORDS** coronary CTA, coronary artery disease, statin therapy, prognosis

**APPENDIX** For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.