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ORIGINAL INVESTIGATIONS

Impact of Statins on Cardiovascular Outcomes Following Coronary Artery Calcium Scoring

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ABSTRACT

BACKGROUND Compared with traditional risk factors, coronary artery calcium (CAC) scores improve prognostic accuracy for atherosclerotic cardiovascular disease (ASCVD) outcomes. However, the relative impact of statins on ASCVD outcomes stratified by CAC scores is unknown.

OBJECTIVES The authors sought to determine whether CAC can identify patients most likely to benefit from statin treatment.

METHODS The authors identified consecutive subjects without pre-existing ASCVD or malignancy who underwent CAC scoring from 2002 to 2009 at Walter Reed Army Medical Center. The primary outcome was first major adverse cardiovascular event (MACE), a composite of acute myocardial infarction, stroke, and cardiovascular death. The effect of statin therapy on outcomes was analyzed stratified by CAC presence and severity, after adjusting for baseline comorbidities with inverse probability of treatment weights based on propensity scores.

RESULTS A total of 13,644 patients (mean age 50 years; 71% men) were followed for a median of 9.4 years. Comparing patients with and without statin exposure, statin therapy was associated with reduced risk of MACE in patients with CAC (adjusted subhazard ratio: 0.76; 95% confidence interval: 0.60 to 0.95; $p = 0.015$), but not in patients without CAC (adjusted subhazard ratio: 1.00; 95% confidence interval: 0.79 to 1.27; $p = 0.99$). The effect of statin use on MACE was significantly related to the severity of CAC ($p < 0.0001$ for interaction), with the number needed to treat to prevent 1 initial MACE outcome over 10 years ranging from 100 (CAC 1 to 100) to 12 (CAC >100).

CONCLUSIONS In a largescale cohort without baseline ASCVD, the presence and severity of CAC identified patients most likely to benefit from statins for the primary prevention of cardiovascular diseases. (J Am Coll Cardiol 2018;72:3233–42)

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ABBREVIATIONS AND ACRONYMS

ARR = absolute risk reduction

ASCVD = atherosclerotic cardiovascular disease

aSHR = adjusted subhazard ratio

CAC = coronary artery calcium

CI = confidence interval

ICD-9 = International Classification of Disease-9th Revision

MACE = major adverse cardiovascular event(s)

MDR = Military Data Repository

MI = myocardial infarction

NNT = number needed to treat

Current guidelines rely on age and traditional cardiovascular risk factors to estimate an individual's risk for incident atherosclerotic cardiovascular disease (ASCVD) events to guide the use of statin therapy for primary prevention (1,2). Coronary artery calcium (CAC) scoring, a noninvasive measure of coronary artery atherosclerotic plaque burden, improves the accuracy of contemporary risk scores for predicting ASCVD outcomes (3,4), and has been suggested as a means to optimize patient selection for statin therapy (5,6). Patients with no detectable CAC are at very low risk for ASCVD outcomes, suggesting that the use of statins may not be warranted in these individuals (7). However, the relative impact of statin treatment stratified by CAC results is unknown, and current guidelines do not recommend widespread CAC testing, citing a lack of evidence regarding the relationship of CAC results on changes in preventive treatments and subsequent long-term ASCVD outcomes (8).

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The sole study to date assessing the effect of statin therapy following CAC scoring, the St. Francis Heart Study, investigated the addition of atorvastatin 20 mg daily to aspirin in a randomized, placebo-controlled study of 1,005 asymptomatic subjects with severely elevated CAC relative to age (>80th percentile) (9). At a mean follow-up of 4.3 years, there was a trend in the statin group to reduced combined major adverse cardiovascular events (MACE) (6.9% vs. 9.9%; $p = 0.08$), with a significant reduction in MACE in the subset of patients with CAC >400 in a post hoc analysis (8.7% vs. 15.0%; $p = 0.046$). Limitations of the study included an 18.4% dropout rate and a 14% crossover rate to statin therapy from the control arm, as well as the inclusion of coronary revascularizations in the primary endpoint.

Randomized controlled trials assessing CAC-guided prevention in a broad screening population have not been performed, likely due to concerns over trial size, costs, and the inherent difficulty establishing equipoise to withhold statins from patients at high risk for cardiovascular events due to a significantly elevated CAC score. We therefore performed a retrospective analysis of a large CAC registry to determine the effect of statin treatment on cardiovascular events.

METHODS

STUDY POPULATION AND DATA COLLECTION. We identified 16,996 consecutive patients who underwent initial dedicated CAC testing by electron beam computed tomography between April 2002 and August 2009 at Walter Reed Army Medical Center (Washington, DC). All subjects were >18 years of age at the time of CAC scanning. Baseline comorbidities were extracted using International Classification of Disease-9th Revision (ICD-9) codes from the Military Data Repository (MDR) for any inpatient or outpatient diagnoses entered before the date of CAC scoring, as previously described (4). Baseline medications were extracted for the 6-month period before the CAC score. Initial entry into the military health system and date of last encounter were determined for each patient.

Patients were excluded if they were foreign military members (n = 275) or lacked any of the following: 1) 12 months in the military health care system before their initial CAC scan (n = 282); 2) follow-up after their CAC scan (n = 87); or 3) prescriptions filled during the study period (n = 102). Patients were also excluded if they had pre-existing coronary artery disease, myocardial infarction (MI), stroke or cerebral revascularization, peripheral vascular disease, or malignancy (n = 2,606) as identified using standard ICD-9 codes (Online Table 1). There were 13,644 patients analyzed. The local institutional review board approved the study, and informed consent was not required due to the retrospective study design.

CALCIUM SCORING. For the measurement of CAC, electron beam computed tomography was performed with Imatron C-150 and C300 LXP scanners (Imatron Corp., South San Francisco, California) and CAC scored per the Agatston method as previously described (10,11). Coronary calcium tests were conducted at the discretion of the ordering provider, and results were reported in the electronic health record, per routine clinical care. Patients were classified as having no CAC (CAC 0) or positive CAC (CAC >0), with further subdivision into CAC groups of 0, 1 to 100, 101 to 400, and >400 (12).

MILITARY DATA REPOSITORY. The MDR contains comprehensive administrative and medical care claims information (e.g., demographics, diagnoses, diagnostic and treatment procedures, prescriptions, and vital status) for active duty military, retirees, and other Department of Defense health care beneficiaries and their dependents. The database includes both inpatient and outpatient services that are provided either at military treatment facilities worldwide or at

civilian facilities paid by the Department of Defense. Complete pharmacy data are available since October 1, 2001.

OUTCOME MEASURES AND FOLLOW-UP. Subjects were assessed for a primary combined MACE outcome of cardiovascular mortality, (ICD-10 codes I00 to I78), incident MI (ICD-9 code 410), or stroke (ICD-9 codes 430, 431, 433.x1, 434.x1, and 436), as previously described (4). Codes for stroke were limited to the primary diagnosis, and codes for MI were limited to the first 2 positions, consistent with prior studies by the Food and Drug Administration (13,14). These definitions are associated with a ≥90% positive predictive value for adjudicated stroke and MI outcomes in prior administrative claims databases (15–18). Among patients with >1 incidence of MACE, only the first was used in the analysis.

Death data, including cause of death, were extracted for all patients from the MDR and National Death Index and cross-referenced to the Veterans Affairs Beneficiary Identification Records Locator Subsystem as well as the Social Security Death Index (19). Patients were followed until they no longer actively filled medications within the military health system, otherwise exited the system, or died, or until December 31, 2014, whichever was sooner.

STATIN USE. Statin use was classified as a binary variable by the presence (or absence) of at least 1 filled statin prescription at baseline or within 5 years after the CAC score and before a primary event or end of follow-up. To account for induction and latent periods (20), we used a 1-month lag for the initial statin prescription for statins initiated after the CAC score. In a sensitivity analysis, we classified statin users as those with filled prescriptions within 2 years, instead of 5 years, from their CAC score.

INVERSE PROBABILITY OF TREATMENT WEIGHTING. To reduce the impact of potential confounding variables, an inverse probability of treatment weighting (IPTW) method was used. First, a nonparsimonious, multivariable logistic regression model was created to obtain the probability of receiving statin treatment at baseline. The inverse of the probability of statin assignment was then used to create a weight for each patient (21). Independent variables for the logistic regression model were the presence of CAC; year of CAC score; the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and aspirin (all assessed at baseline); the Charlson comorbidity score (22); male sex; age; baseline hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and tobacco dependence; and all 2 × 2 interactions. The presence of hypertension, hyperlipidemia, and diabetes mellitus was determined both by administrative codes as well as the baseline use of antihypertensive agents, lipid agents, or diabetes medications, respectively (Online Table 2). The presence of atrial fibrillation and current or history of tobacco use were determined by codes alone (Online Table 2), and the year of CAC score was included to account for changing practice patterns over time.

Variables were balanced between statin users and nonusers over the entire study cohort. When evaluating statin use within CAC subgroups, all covariates were forced back into the multivariable time-to-event model alongside the propensity treatment weighting to limit residual confounding. The interaction of statin therapy among CAC subgroups was tested by inserting a CAC group*statin term in the model. The Fine-Gray model was used to account for the competing risk of noncardiovascular death when assessing MACE-free survival (23). Cumulative incidence curves were obtained from the models by applying overall marginal frequencies and mean values for covariates. To determine the ability of the CAC score to risk stratify patients for statin therapy, an incident MACE rate per 1,000 person-years and 10-year number needed to treat (NNT) were derived from the cumulative incidence function extracted at 10 years for each of the CAC groups (24).

ADDITIONAL SENSITIVITY AND SUBGROUP ANALYSES. To assess the impact of prolonged use of statin therapy and medication compliance, we determined the proportion of time a patient was taking statin therapy during the follow-up period and before the outcome of interest. The total number of pills filled during this period was divided by the number of days in the follow-up period. A threshold of >50% was used to indicate medication compliance (25). Patients with overlapping fills were limited to an on-hand-supply not exceeding 180 pills at time of dispensing (26). Compliant patients were subsequently compared with patients not on any statin therapy after applying IPTW to balance covariates as in the primary analysis.

To account for variation in statin use over time and adjust for immortal time bias (27,28), statin therapy was further analyzed using a time-varying covariate in a Cox regression model. Patients were considered on statin treatment after a prescription fill date for the number of days equal to their on-hand-supply plus a 28-day lag period (20,29,30). Covariates included in the model were identical to those used in the propensity analysis, but without all 2 × 2 interactions.

A separate sensitivity analysis also explored the relationship between statin intensity and MACE in a

TABLE 1 Baseline Demographics, Comorbidities,* and Medications for Patients Stratified by Statin Use After CAC Score and Before 5 Years or MACE

	No Statin (n = 6,758)	Statin (n = 6,886)	Absolute Standardized Difference†	
			Before IPTW	After IPTW
Age, yrs	48.1 ± 7.6	51.1 ± 8.9	0.36	0.03
Year of CAC score	2005 (2003–2007)	2005 (2003–2007)	0.08	<0.01
Charlson score	0.02 ± 0.14	0.03 ± 0.21	0.09	<0.01
Male	4,459 (66.0)	5,173 (75.1)	0.20	0.01
Diabetes mellitus	241 (3.6)	687 (10.0)	0.26	0.01
Hypertension	1,538 (22.8)	3,105 (45.1)	0.49	0.01
Hyperlipidemia	1,585 (23.5)	5,163 (75.0)	1.20	0.01
Any tobacco use	359 (5.3)	612 (8.9)	0.14	<0.01
Atrial fibrillation	53 (0.8)	100 (1.5)	0.06	0.01
Race‡			0.07	0.06
White	4,855 (77.8)	4,826 (75.2)		
Black	945 (15.1)	1,081 (16.8)		
Native American	25 (0.4)	24 (0.4)		
Asian	180 (2.9)	179 (2.8)		
Other	236 (3.8)	312 (4.9)		
CAC score			0.68	0.05
0	5,618 (83.1)	3,742 (54.3)		
1–100	944 (14.0)	1,933 (28.1)		
101–400	154 (2.3)	800 (11.6)		
401+	42 (0.6)	411 (6.0)		
Baseline medications				
Aspirin	476 (7.0)	1710 (24.8)	0.50	<0.01
Antihypertensive	995 (14.7)	2,346 (34.1)	0.46	0.01
ACE inhibitor	383 (5.7)	1,203 (17.5)	0.38	0.03
ARB	139 (2.1)	376 (5.5)	0.18	0.03
Beta-blocker	256 (3.8)	639 (9.3)	0.22	0.01
Calcium-channel blocker	189 (2.8)	436 (6.3)	0.17	0.01
Diuretics	495 (7.3)	1,174 (17.1)	0.30	<0.01
Insulin	7 (0.1)	66 (1.0)	0.12	0.01
Non-insulin diabetic therapy	43 (0.6)	338 (4.9)	0.26	0.07
Fibrate or niacin	82 (1.2)	259 (3.8)	0.16	0.08
Statins§, median dose	–	3,298 (47.9)		
Atorvastatin, 20 mg	–	504 (7.3)		
Rosuvastatin, 10 mg	–	13 (0.2)		
Fluvastatin, 40 mg	–	3 (0.0)		
Lovastatin, 20 mg	–	10 (0.1)		
Pravastatin, 20 mg	–	83 (1.2)		
Simvastatin, 20 mg	–	2,685 (39.0)		
Follow-up, yrs	9.4 (7.2–11.2)	9.4 (7.3–11.1)		

Values are mean ± SD, median (interquartile range), or n (%). *Associated ICD-9 codes for comorbid disorders are listed in the Online Appendix. Diabetes mellitus, hypertension, and hyperlipidemia defined as prior ICD-9 diagnosis or baseline diabetic, anti-lipid, or anti-hypertensive medical therapy. †Absolute standardized difference = difference in means or proportions divided by standard error; imbalance defined as absolute value >0.20 (small effect size). ‡981 patients without race data. §Individual statin information based on most recent prescription before CAC score.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAC = coronary artery calcium; ICD-9 = International Classification of Disease-9th Edition; IPTW = inverse probability of treatment weighting; MACE = major adverse cardiovascular event(s).

Cox proportional hazards model after classifying statins into low, medium, and high intensity according to current lipid guidelines (2) (Online Appendix). In a post hoc, subgroup analysis, we also conducted a propensity-weighted analysis restricted to patients with diabetes at baseline (Online Appendix, Online Table 3). We further evaluated the impact of statin therapy by baseline use (prescription before or after CAC score) as well as comparing patients with >50% statin exposure to patients with <50% statin exposure (Online Appendix, Online Tables 4 and 5).

Finally, in a post hoc, exploratory analysis, we estimated each patient's baseline ASCVD risk using the pooled cohort equation (8) by entering assumed values for systolic blood pressures and lipid profiles on the basis of the presence (or absence) of hypertension and hyperlipidemia, and whether or not the patient was receiving treatment with antihypertensive agents or antilipid therapy (Online Appendix). Patients were categorized into low ASCVD risk (<5%), intermediate risk (5% to 20%), and high risk (>20%). After IPTW within each group, hazards of MACE were compared across ASCVD risk category in patients with CAC 0, CAC 1 to 100, and CAC >100.

Baseline characteristics and CAC scores were compared between statin users and nonusers using standardized mean differences. A standardized mean difference <0.1 is considered a negligible difference between groups (31). For other comparisons, a 2-tailed value of $p < 0.05$ was considered significant. Statistics were computed using SAS version 9.4 (SAS Institute, Cary, North Carolina). Additional methods and results can be found in the Online Appendix.

RESULTS

STUDY PATIENTS. After applying exclusion criteria, there were 13,644 consecutive patients (mean age 49.6 ± 8.4 years; 71% male) who underwent CAC screening from April 2002 to August 2009. They had a low burden of traditional ASCVD risk factors, and 9,360 (69%) had no detectable CAC (**Table 1**). Approximately one-half of the patients (n = 6,886; 50.5%) were treated with statins at baseline or following their CAC score. Of these, 3,298 (47.9%) were prescribed statins in the 6 months before their CAC score. Of all statin prescriptions before first MACE or end of follow-up, 15.1% were of low intensity, 65.7% were of medium intensity, and 19.3% were of high intensity. Patients prescribed statins were on therapy for a median of 5.5 years, or 67.0% of their follow-up period. Patients prescribed a statin during the study were significantly more likely to be older, be male, have comorbidities including hypertension, hyperlipidemia, diabetes, and tobacco use, have a higher CAC score, and be on aspirin therapy at baseline. After IPTW, the groups were appropriately balanced on all variables (**Table 1**).

OUTCOMES. Over a median follow-up of 9.4 years (interquartile range: 7.2 to 11.2 years), there were 532

patients (3.9%) who had a MACE, including 191 with MI (1.4%), 342 with stroke (2.5%), and 42 (0.3%) who had cardiovascular death. There were 209 deaths (1.5%) from any cause.

Patients with CAC who were prescribed a statin within 5 years of their CAC testing had a significantly lower risk of MACE (adjusted subhazard ratio [aSHR]: 0.76; 95% confidence interval [CI]: 0.60 to 0.95; p = 0.015), whereas patients without CAC had no MACE reduction with statin use (aSHR: 1.00; 95% CI: 0.79 to 1.27; p = 0.99) (**Figure 1**). The effect of statin use on MACE was significantly related to the severity of CAC (p for interaction <0.001) (**Central Illustration, Table 2**), with patients having CAC >100 associated with the most benefit. Using a 2-year cutoff for statin prescription in a sensitivity analysis yielded similar results (Online Appendix, Online Table 6).

In the 10-year NNT analysis, there was no significant effect of statins among patients without any CAC. Patients with a CAC of 1 to 100 had a trend toward benefit (NNT = 100; p = 0.095), whereas patients with a CAC >100 derived significant benefit with a NNT of 12 (p < 0.0001) (**Table 3**). These differences in observed benefit can also be visualized by the comparative incident MACE rate derived through 10 years of follow-up (Online Figure 1).

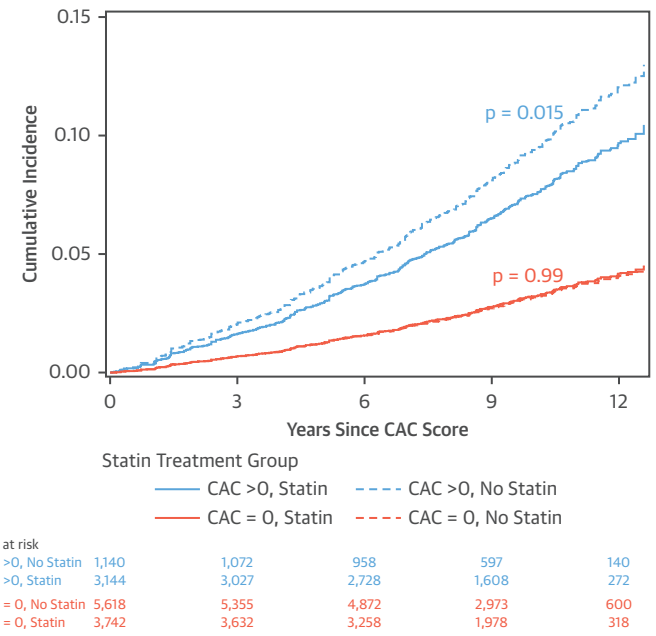
STATIN COMPLIANCE. In a sensitivity analysis, patients with >50% compliance during follow-up (n = 4,415) were compared with patients with no statin treatment (n = 6,758). The groups were appropriately balanced on all variables after IPTW (Online Table 7). Adjusting for the competing hazard of noncardiovascular death, statin treatment was associated with reduced MACE for the entire study subgroup (aSHR: 0.56; 95% CI: 0.45 to 0.69; p < 0.0001) (**Table 2**). The benefit of statin therapy was related to CAC severity (p = 0.028); patients with CAC >100 had a greater reduction in MACE (aSHR: 0.61; 95% CI: 0.40 to 0.93; p = 0.021) compared with patients with CAC <100.

TIME-DEPENDENT ANALYSIS. As a time-dependent variable, statin therapy was an independent predictor among all patients for reduced MACE in the Cox proportional hazard model (aSHR: 0.64; 95% CI: 0.52 to 0.78; p < 0.0001). There was no significant interaction between statin treatment and CAC group. Multivariable predictors of increased MACE in the Cox model were increasing CAC, increasing age, use of beta blockers at baseline, hyperlipidemia or tobacco use at baseline, and earlier CAC screening year (Online Table 8).

STRENGTH ANALYSIS. In a separate sensitivity analysis, statin intensity was an independent predictor of improved MACE-free survival in the multivariable Cox regression model across all patients (p = 0.0012) (Online Table 9). Compared with CAC <100, patients with CAC >100 had greater reduction in MACE from the highest strength tercile of statin compared to no statin (p = 0.03) (see Online Appendix and Online Table 10 for additional results).

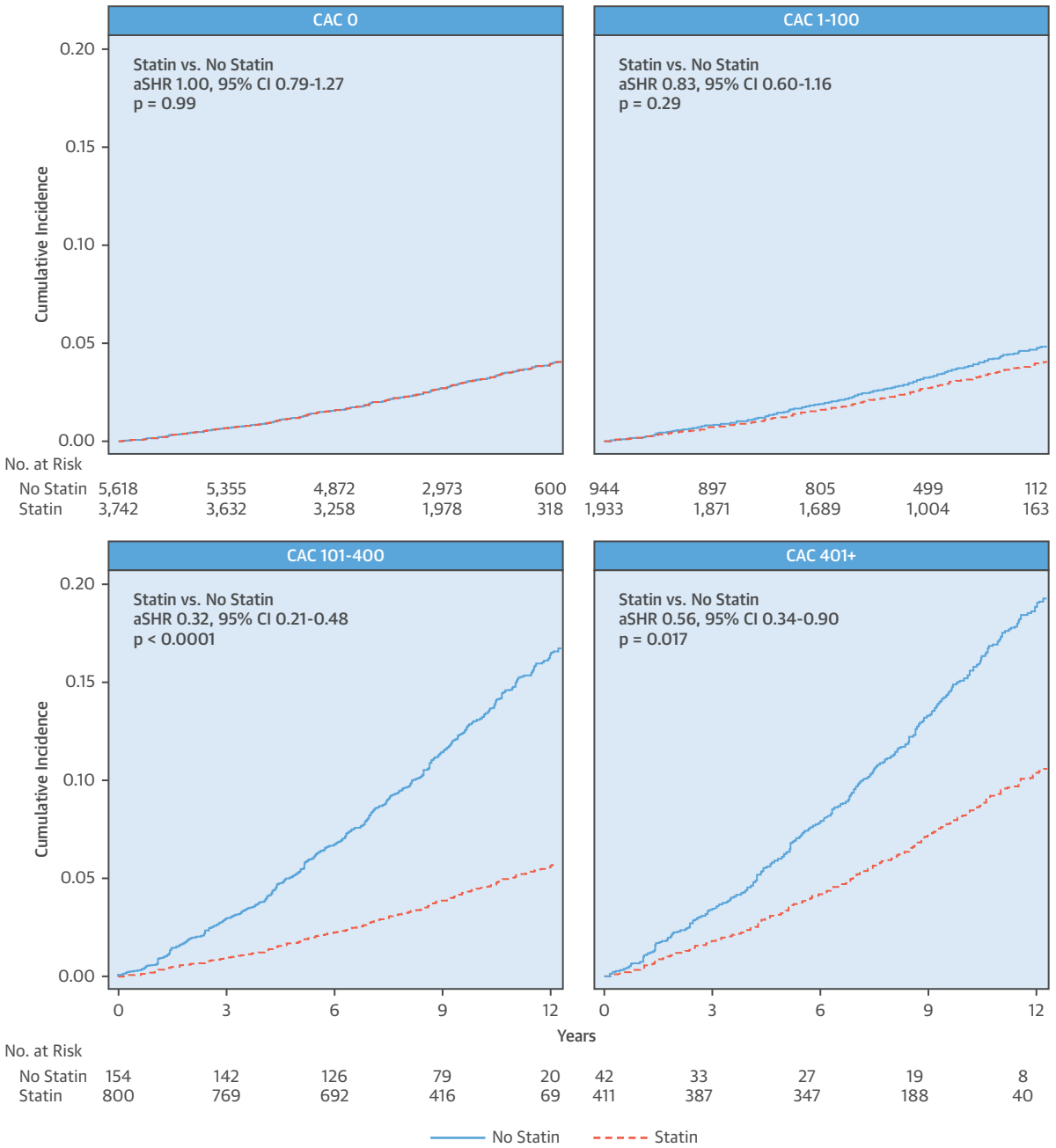
BENEFIT ACROSS ASCVD RISK CATEGORIES. In a post hoc, exploratory analysis using estimated values for the systolic blood pressure and lipids as detailed in the Online Appendix, patients with no CAC and otherwise high ASCVD risk (>20%) had a 74% relative reduction in the hazard of MACE with statin therapy (aSHR: 0.26; 95% CI: 0.11 to 0.61; p < 0.01), but there was no benefit of statin therapy in patients with no CAC and low or intermediate baseline ASCVD risk (Online Appendix, Online Figures 2 and 3). Conversely, patients with CAC >100 had a 64% to 71% relative reduction in the hazard of MACE even with low (<5%; aSHR: 0.29; 95% CI: 0.16 to 0.52; p < 0.0001) or intermediate (5% to 20%; aSHR: 0.36; 95% CI: 0.24 to 0.53;

FIGURE 1 Cumulative Incidence of MACE Stratified by Statin Treatment and CAC Presence



Patients with CAC who were prescribed a statin had a significantly reduced risk of MACE (aSHR: 0.76; 95% CI: 0.60 to 0.95; p = 0.015), whereas patients without CAC had no associated MACE reduction (aSHR: 1.00; 95% CI: 0.79 to 1.27; p = 0.99). p = 0.097 for interaction between statin treatment and CAC presence. aSHR = adjusted subhazard ratio; CAC = coronary artery calcium; CI = confidence interval; MACE = major adverse cardiovascular event(s).

CENTRAL ILLUSTRATION **Cumulative Incidence of MACE Stratified by Statin Treatment and CAC Severity**



Mitchell, J.D. et al. J Am Coll Cardiol. 2018;72(25):3233–42.

Benefit of statin therapy was significantly related to CAC group ($p < 0.0001$ for interaction), with benefit in patients with CAC >100, but not in patients with CAC <100. aSHR = adjusted subhazard ratio; CAC = coronary artery calcium; CI = confidence interval; MACE = major adverse cardiovascular event(s).

$p < 0.0001$) ASCVD risk (Online Figure 2). There was no observed benefit for statins in patients with elevated CAC (101+) and high ASCVD risk (n = 185), but the relatively low number of patients in the nonstatin group limited the analysis (23 not on statins, 162 on statins). On the basis of the overall trend of the data, it does appear that this group is likely an outlier. These results should be interpreted with

caution given the reliance on assumed variable values.

DISCUSSION

In this large observational study, the presence and severity of CAC identified patients most likely to derive long-term benefit from statin treatment. Among this relatively lower-risk cohort, CAC >100 was consistently associated with a greater reduction in the hazard for MACE with statin therapy relative to CAC <100 (**Central Illustration**). Patients without any CAC had no benefit from statin treatment in the primary propensity analysis. To our knowledge, our study is the largest to evaluate the effectiveness of statin treatment in patients with CAC, and the only study to directly compare the direct benefit of statin use between CAC groups. Many have argued for the potential use of CAC to help identify patients with increased benefit from statins (5,6) and improve shared decision making (32), although lack of direct data showing the utility of CAC in selecting patients for statin treatment has prevented widespread use or a stronger recommendation in clinical guidelines. Our study helps provide valuable information on the effect of statin therapy in a real-world population without known ASCVD who underwent CAC scoring.

PRIOR PRIMARY PREVENTION TRIALS AND ESTIMATES. Prior studies and models have attempted to estimate the benefit of statin treatment in patients stratified by CAC (32–34). An analysis of 5,534 MESA (Multi-Ethnic Study of Atherosclerosis) participants found that CAC >100 identified patients with highest risk for cardiovascular events, potentially selecting patients most likely to benefit from statin therapy (33). Using a subgroup of the MESA cohort (n = 4,085) that would have qualified for 1 of 7 previous statin randomized controlled trials, mathematical models estimated the 10-year NNT for MACE for CAC 0, 1 to 100, and 101+ as 87, 37, and 19, respectively (32), based on an average relative risk reduction of 30% for statin therapy in the referenced primary prevention trials (35,36). The 30% reduction reflected inclusion of revascularization in the combined endpoint, whereas the relative risk reduction was 25% (absolute risk reduction [ARR] 2.9%) when limiting the endpoint to nonfatal and fatal cardiovascular disease in the Cochrane meta-analysis (35). From the MESA data, a CAC level >100 was chosen to be an appropriate discriminator to select patients with the greatest ARR, and thus the greatest benefit, from statin therapy.

TABLE 2 Subhazard Ratios for MACE Among CAC Groups

	Statin vs. No Statin*		>50% Compliance†	
	aSHR (95% CI)	p Value	aSHR (95% CI)	p Value
CAC = 0	1.00 (0.79–1.27)	0.99	0.66 (0.49–0.88)	0.0046
CAC >0	0.76 (0.60–0.95)	0.015	0.76 (0.59–0.98)	0.031
CAC 1–100	0.83 (0.60–1.16)	0.29	0.78 (0.53–1.15)	0.21
CAC 101–400	0.32 (0.21–0.48)	<0.0001	0.32 (0.20–0.51)	<0.0001
CAC 401+	0.56 (0.34–0.90)	0.017	0.59 (0.35–0.99)	0.044
CAC >100 vs. CAC <100	0.46 (0.31–0.67)	<0.0001	0.61 (0.40–0.93)	0.021

Groups compared after IPTW and adjusting for competing hazard of noncardiovascular death. *Presence or absence of statin prescription within 5 years of CAC before MACE or end of follow-up. †>50% compliance with statin therapy during follow-up period versus patients with no statin exposure.

aSHR = adjusted subhazard ratio; CI = confidence interval; other abbreviations as in Table 1.

CAC AND STATIN EFFECT MODIFICATION. Although these previous estimates were based on a stable relative risk reduction across all patients, our study found that the presence of CAC was associated with varying statin impact. Patients with no CAC showed no benefit from statin therapy in our primary propensity-weighted analysis, whereas patients with any CAC had an associated 24% reduction in MACE, which is comparable to the Cochrane meta-analysis (35). The ARR for nonfatal and fatal CVD was 2.9% in the Cochrane study, which fell between the ARR for the CAC 1 to 100 (ARR 1%) and CAC >100 groups (ARR 9%) in our study. As with previous estimates, a CAC threshold >100 continued to be a discriminator for selecting patients most likely to benefit from statin therapy. Patients with CAC of 1 to 100 only had a trend toward statin benefit, though our study was likely underpowered for this subgroup analysis given their low MACE rate. Taken in total, our study may be the first to show the ability of a screening test to potentially tailor a statin treatment strategy.

No previous study has supported the ability of a biomarker or test to discriminate patients that will or will not benefit from statin therapy (37), and it has generally been assumed that statins provide a

TABLE 3 NNT to Prevent First Occurrence of MACE Through 10 Years

CAC Score	Therapy	N	MACE	CIF*	ARR, %	NNT (NNH)	aSHR†	p Value
0	No statin	5,618	114	0.0295	−0.03	(3,571)	1.01	0.94
	Statin	3,742	100	0.0298				
1–100	No statin	944	32	0.0401	1.00	100	0.75	0.095
	Statin	1,933	76	0.0301				
101+	No statin	196	32	0.1409	8.53	12	0.38	<0.0001
	Statin	1,211	123	0.0556				

*Cumulative incidence of MACE at 10 years, calculated at observed marginal differences for covariates (means). †aSHR calculated at 10 years.

ARR = absolute risk reduction; CIF = cumulative incidence function; NNH = number needed to harm; NNT = number needed to treat; other abbreviations as in Tables 1 and 2.

consistent relative risk reduction across the general population. CAC, theoretically, is an ideal candidate as a potential discriminator, because it directly measures coronary atherosclerosis resulting from the patient's entirety of previous exposures and risk factors. It is therefore plausible that a patient with no CAC would not show the same benefit in cardiovascular event reduction as a patient with proven atherosclerosis. Certainly, a CAC of 0 has repeatedly been shown to confer a very low annualized risk of MACE, including the Walter Reed cohort (4).

PROLONGED STATIN THERAPY. In our sensitivity analysis, we did observe a potential benefit with prolonged statin therapy (statin therapy for >50% of follow-up period) even in the group without CAC (aSHR: 0.66; 95% CI: 0.49 to 0.88). Time-dependent analysis also showed benefit with statin therapy across all groups in the multivariate model without propensity weighting. Thus, a modest benefit of prolonged statin therapy may still exist among patients with a CAC of 0, but the absolute benefit would be small given that their cumulative incidence of MACE (after accounting for noncardiovascular death) was only 3.0% at 10 years. Statins may still be warranted in certain subpopulations in the absence of CAC when other compelling risk factors are present (e.g., very high low-density lipoprotein cholesterol), and patients with no CAC but high baseline ASCVD risk (>20%) did benefit from statin therapy in our post hoc exploratory analysis using estimated risk variables.

STUDY LIMITATIONS. Given the retrospective design, patients were not pre-assigned to statin therapy. We used propensity weighting to attempt to adjust for baseline covariates, though we cannot rule out residual confounding. Because patients were included in the statin treatment group if they received a prescription in the initial interval following CAC screening, their post-baseline assignment introduces some artifact into the cumulative incidence function curve. Reassuringly, results were consistent in our sensitivity analysis using 2 years instead of 5 years as the cutoff for statin assignment.

As with any large observational study using administrative claims data, there also remains a risk of inaccurate covariate or outcomes assessment. For the outcome of MACE, ICD-9 codes for MI and stroke have been shown to have ≥90% positive predictive value for representing adjudicated clinical MI and stroke events (15,16), though the risk of imprecise outcome accounting remains. Although all deaths and their causes were ascertained using the National Death Index, it is possible that some deaths may have been misclassified (cardiovascular vs. noncardiovascular).

Coding for covariates are inherently less sensitive, and to attempt to partially address this limitation, we did utilize baseline medication data to augment ICD-9 coding for diagnosis of applicable comorbid disorders of hypertension, hyperlipidemia, and diabetes mellitus. Tobacco dependence is often undercoded (38), though the addition of smoking status only had a marginal effect on the efficacy of statin therapy in another population (39). Although we used a propensity score, we cannot fully eliminate confounders and selection bias, and were unable to account for the relative severity of comorbid disorders or calculate ASCVD risk scores because the Walter Reed CAC Cohort does not contain measured blood pressure and lipid values.

As in any prevention study, we cannot rule out a healthy user bias (40), whereby a patient that is more likely to receive preventive therapy may also be more likely to engage in other healthy activities that reduce their chance for MACE, such as exercise or a healthy diet. In our study, all patients were willing to undergo CAC scoring as preventive testing, though some patients may still have been more likely to agree to statin therapy. The related healthy adherer effect may have also influenced the results of our sensitivity analysis looking at prolonged statin therapy (40). Finally, it should be noted that the study population was from a single tertiary medical center and involves subjects with broad, comprehensive access to medical care, which may limit generalizability.

IMPLICATIONS AND PATH FORWARD. Overall, these results support the guidance of the recent Society of Cardiovascular Computed Tomography consensus statement using a CAC threshold of 100 for treatment (5), though further studies are still needed for confirmation of these results. Until we have further studies, a threshold of 100 does appear to be an appropriate cutoff to select patients at greatest benefit for statin therapy from the general population. Providers should consider the Society of Cardiovascular Computed Tomography statement, along with the overall patient risk profile, in patient shared decision making.

CONCLUSIONS

In this large, long-term, retrospective analysis of the Walter Reed cohort, increasing severity of CAC was associated with increased benefit from statin treatment for the prevention of MACE, with greatest

benefit in patients with CAC >100. In our primary, propensity-weighted analysis, patients with CAC 0 had no benefit from statin therapy in a mean follow-up of nearly 10 years. Calcium scoring, therefore, shows significant potential to help select patients most likely to benefit from statin therapy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Measurement of the CAC score by CT imaging can identify patients who gain uncertain (CAC = 0) or substantial (CAC >100) benefit from statin therapy.

TRANSLATIONAL OUTLOOK: Additional research is needed to confirm the utility of CT screening to guide selection of patients for statin therapy for prevention of coronary events.

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KEY WORDS atherosclerotic cardiovascular disease, calcium score, cardiovascular risk, primary prevention, screening

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