Relation of Absence of Coronary Artery Calcium to Cardiovascular Disease Mortality Risk Among Individuals Meeting Criteria for Statin Therapy According to the 2018/2019 ACC/AHA Guidelines

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The 2013 American College of Cardiology and the American Heart Association (ACC/AHA) guidelines resulted in broad recommendations for preventive statin therapy allocation in patients without known cardiovascular disease (CVD). Subsequent studies demonstrated significant heterogeneity of atherosclerotic cardiovascular disease risk across the primary prevention population. In 2018/2019, the guidelines were revised to optimize risk assessment and cholesterol management. We sought to evaluate the heterogeneity of risk in statin-recommended patients, using coronary artery calcium (CAC) according to 2018/2019 ACC/AHA guidelines in a primary prevention cohort. We evaluated 5,800 statin-naive patients aged 40 to 75 years without known coronary heart disease from the Cedars-Sinai Medical Center study cohort. All participants underwent clinical CAC scoring for risk stratification and were followed for all-cause and CVD-specific mortality. A total of 181 deaths occurred including 54 CVD deaths over a follow-up of 9.5 years. Overall, 1,939 participants would have been recommended statin therapy, 32% of whom had no detectable CAC. CAC = 0 participants had the lowest all-cause and CVD mortality rates in both statin-recommended and nonrecommended groups (0.2 and 0.4 CVD deaths per 1,000 person-years, respectively). Absence of CAC in statin-naive patients portends an approximately 12-fold lower CVD mortality (0.2% vs 2.4%) in those recommended for statin therapy compared with any CAC present. In conclusion, in a cohort of patients meeting the 2018/2019 ACC/AHA guidelines for statin therapy for primary prevention, there was a marked heterogeneity of CAC scores, with about one-third of the statin recommended population having no detectable CAC (CAC = 0) with a significantly lower CVD mortality compared with CAC>0. **(Am J Cardiol 2020;136:49−55)**

In 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) recommended statin therapy for primary prevention in asymptomatic patients with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk ≥7.5% using the Pooled Cohort Equations (PCE).[1] Several subsequent studies demonstrated, however, that the PCE markedly overestimated 10-year ASCVD risk in contemporary populations.[2−4] In a breakthrough approach to lead efforts toward optimizing statin recommendations, the 2018 Multi-Society Cholesterol Guidelines and the 2019 ACC/AHA Primary Prevention Guidelines recommended coronary artery calcium (CAC) testing to aid decision-making in primary ASCVD prevention.[5,6] To date, however, no studies have examined the utility of CAC testing for risk assessment in patients who are now classified as statin recommended according to the 2018/2019 ACC/AHA guidelines. We thus sought to evaluate the prevalence of subclinical calcified coronary atherosclerosis, using CAC, in statin-naive patients who are classified as being statin recommended and

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nonrecommended in a primary prevention cohort, according to the 2018/2019 guidelines, and assess the prognostic utility of CAC scanning in both groups.

Methods

CAC Consortium represents four participating institutions from three states within the US (California, Minnesota, and Ohio), which contributed data from 66,636 asymptomatic patients spanning years 1991 to 2010.[7] This is an observational retrospective cohort study designed primarily to evaluate the association between CAC and long-term mortality. All CAC scans were clinically indicated and physician-referred in patients without a known history of coronary heart disease (CHD). Further details on study design and patient recruitment methods have been previously published.[7] Consent for participation in research was collected at the patient centers at the time of CAC scanning. Institutional Review Board approval for coordinating center activities including death ascertainment was obtained at the Johns Hopkins Hospital.

The information on cardiovascular risk factors, medication use, and laboratory data was collected at the clinical visit associated with physician referral for CAC scan using a patient reported questionnaire, and/or from established diagnosis recorded in the electronic medical record. Diabetes mellitus was defined as a prior diagnosis of diabetes or treatment with oral hypoglycemic drugs or insulin, or fasting blood glucose >126 mg/dl. Hypertension was considered present if there was a prior diagnosis of hypertension or treatment with anti-hypertensive medication. Information on the current treatment with any lipid-lowering drugs was collected. Smoking status was classified as never, former, or current. Family history of CHD was determined by the presence of a first degree relative with a history of premature CHD (males <55y; females <65y). For the present analysis, PCE-derived 10-year ASCVD risk was categorized into: <5%, ≥ 5% to < 7.5%, ≥ 7.5% to <20%, and ≥ 20% according to the 2018/2019 ACC/AHA guidelines. The details of the ASCVD risk score derivation have been described in the CAC consortium rationale and design.[7]

The following inclusion and exclusion criteria were used to minimize missing data and to eliminate nondedicated CAC scans (i.e., concomitant CT angiography): Inclusion criteria − (1) >18 years of age (2) were asymptomatic (3) no known CHD at the time of the CAC scan, and (4) had a CAC scan with an Agatston score; Exclusion criteria − (1) had a nondedicated CAC scan, (2) had another concomitant non-CAC CT scan, (3) missing complete CAC scan identifiers, (4) had an improbable date of birth, or (5) had an improbable scan date.

Noncontrast cardiac-gated computed tomography (CT) scans for CAC scoring were performed according to a common standard protocol for each scanner technology. Most participants (93%) were scanned using electron beam CT, whereas the more recent baseline CAC scans were obtained using multidetector CT. Previous studies have demonstrated no clinically meaningful differences between CAC score derived from electron beam versus multidetector scanners.[8] CAC was quantified using the Agatston method in all patients.[9]

Low-density lipoprotein cholesterol (LDL-C), a primary determinant of statin eligibility in the 2018/2019 guidelines, was available for participants from the Cedars-Sinai Medical Center site exclusively. For the present analysis, 13,972 asymptomatic patients without known CHD from the Cedars-Sinai Medical Center enrolled between 1998 and 2010 were included.

Participants were identified as statin recommended for the primary prevention of ASCVD based on the following criteria: (1) LDL-C ≥190 mg/dl (≥ 4.9 mmol/L); (2) patients aged 40 to 75 years with diabetes; (3) patients aged 40 to 75 years without diabetes, with LDL-C ≥70 and <190 mg/dl (≥ 1.7 to < 4.9 mmol/L), and ASCVD risk ≥7.5% to <20%; and (4) patients aged 40 to 75 years without diabetes, with LDL- C ≥70 and <190 mg/dl (≥ 1.7 to < 4.9 mmol/L), and ASCVD risk ≥20%.

The 2018/2019 guidelines recommend CAC scoring in patients aged 40 to 75 years without diabetes, with LDL-C ≥70 to <190 mg/dl, and ASCVD risk ≥7.5% to <20% (intermediate risk), if the risk decision regarding statin therapy is uncertain. Accordingly, if

(1) CAC = 0—no statin unless diabetes, smoking, or family history of CHD, (2) CAC 1-99—favors statin (especially after 55 years of age) and, (3) if CAC >100—initiate statin.

Outcomes of interest were all-cause and CVD-specific mortality recorded over a mean follow-up period of 9.5 years. Ascertainment of death was conducted by linkage to the Social Security Death Index Death Master File using a validated algorithm used in a previous study.[10] A complete algorithmic search of the Social Security Death Index Death Master File was conducted for all 13,972 patients (100%). Cause of death was obtained through death certificates from the National Death Index and subsequently grouped using International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9 and ICD-10) codes as previously described.[7] CVD death was defined as death due to CHD, stroke, heart failure, and other circulatory diseases.

The baseline characteristics of the study population were described overall and by statin recommendation groups using number and proportion for categorical variables, and median and interquartile range for continuous variables. These characteristics were compared across statin recommendation groups using chi-squared tests for categorical variables and Wilcoxon 2-sample tests for continuous variables.

We computed annualized all-cause and cardiovascular disease-specific mortality rates by dividing the number of deaths during follow-up by the total follow-up time (in years) and expressed them as a rate per 1,000 patient-years for groups of statin recommendation and CAC scores. Cox Proportional Hazards regression models were used to calculate hazard ratios and 95% confidence intervals (CI) for each of study outcomes comparing CAC>0 to CAC = 0, by statin recommendation groups. Analyses were unadjusted (Model 1) and adjusted for age and gder (Model 2).

A p value <0.05 was considered statistically significant. All statistical analyses were performed with Stata version 14 (Stata Corporation, College Station, Texas).

Results

The study cohort consisted of 13,972 asymptomatic patients without known CHD. Patient selection for the present analysis was determined according to the 2018/2019 ACC/AHA guidelines and is depicted in **Figure 1**. Of 13,972 participants, 3,853 on lipid-lowering medication at the time of baseline CAC scanning were excluded from the present analysis. Of the resulting 10,119 participants, 3,257 missing LDL-C levels were excluded from the analysis. Additional exclusions included participants with LDL-C <70mg/dl (< 1.8 mmol/L), patients with missing information on risk factors, and if age was <40 years or ≥75 years. This yielded a final study cohort of 5,800 participants for the current analysis.

The characteristics of the study population are presented in **Table 1**. Overall, median age was 54 years and 62% were men; 54% participants had CAC = 0, and 18% had a CAC score≥100. A total of 1,939 (33%) participants were considered statin recommended on the basis of 2018/2019 guidelines. Besides containing all the diabetic patients (6% of total cohort), the statin recommended group was substantially older (by a median of 10 years), and had a higher prevalence of ASCVD risk factors, including more patients with hypertension, smoking, and higher body mass index values. Statin recommended participants also had worse lipid profiles, including higher LDL-C and lower high-density lipoprotein cholesterol values, and higher levels of triglycerides, than nonrecommended participants. The frequency of CAC abnormality was higher in the statin recommended compared with nonrecommended participants (68% vs 34%, p = <0.001) **Figure 2**.

Overall, there were 181 deaths from any cause and 54 CVD deaths during a mean follow- up of 9.5 years. The number of deaths and the corresponding death rates per 1,000 person-years by statin groups and further stratified by baseline CAC burden are presented in **Table 2.** In both groups, the frequency of all-cause death was lowest in participants with no detectable CAC (CAC = 0), and higher rates were observed with higher CAC scores. Similar trends were observed for CVD deaths, the rates being lower than

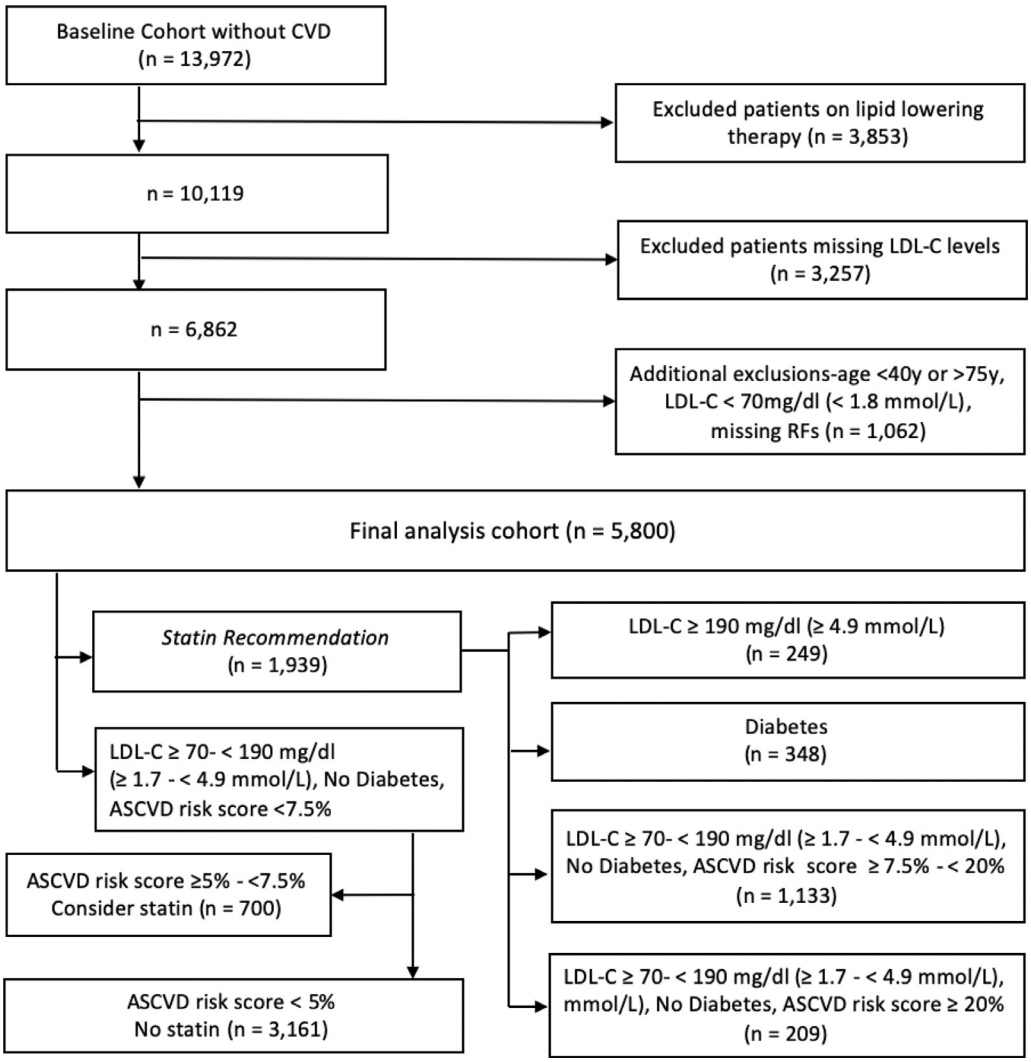

Figure 1. Flow chart of the study population selection meeting criteria for statin recommendation according to 2018/2019 ACC/AHA guidelines. Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; RF = risk factor

Table 1
Baseline characteristics for the overall study cohort and stratified by statin recommendation according to 2018/2019 ACC/AHA guidelines

Variable	Overall	Statin Recommendation		p value
	(n = 5,800)	No (n = 3,861)	Yes (n = 1,939)	
Age (years)	54 (48−60)	51 (46−56)	61 (55−67)	<0.001
Men	3,569 (62%)	2,098 (54%)	1,471 (76%)	<0.001
Diabetes mellitus	358 (6%)	0 (0)	358 (18%)	<0.001
Hypertension	2,120 (37%)	996 (26%)	2,120 (37%)	<0.001
Current smoker	509 (9%)	232 (6%)	277 (14%)	<0.001
Family history of CHD	1,984 (34%)	1,392 (36%)	592 (31%)	<0.001
BMI (kg/m2)	25.3 (23−28.2)	24.9 (22.5−27.6)	26.4 (24.2−29.4)	<0.001
Total cholesterol (mg/dl)	209 (186−234)	208 (185−231)	212 (188−244)	<0.001
LDL cholesterol (mg/dl)	130 (109−152)	128 (108−148)	136 (113−163)	<0.001
HDL cholesterol (mg/dl)	53 (42−66)	56 (45−69)	48 (38−60)	<0.001
Triglycerides (mg/dl)	102 (72−149)	96 (67−136)	118 (81−171)	<0.001
CAC score				<0.001
0	3,153 (54%)	2,530 (66%)	623 (32%)	
1−99	1,585 (27%)	949 (24%)	636 (33%)	
≥ 100	1,062 (18%)	382 (10%)	680 (35%)	

Results are presented as n (%) or median (25th and 75th percentiles)

To convert to SI units, for total cholesterol, low-density lipoprotein cholesterol, and high- density lipoprotein cholesterol, divide mg/dL by 38.6; for triglycerides, divide mg/dL by 88.6. Abbreviations: ACC/AHA = American College of Cardiology/ American Heart Association; BMI = body mass index; CAC = coronary artery calcium; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N = number

those of all-cause death. The lowest CVD death rates were once again observed in CAC = 0 participants from both groups: 0.2 per 1,000 person-years in the statin recommendation group, and 0.4 per 1,000 person-years in the nonrecommended group.

In unadjusted Cox regression analyses, presence of any CAC in statin-recommended patients was associated with an almost three-fold increased risk of death from any cause as compared with CAC = 0 (Table 3) and with a 1.7-fold increased risk of all-cause death in non-recommended patients. In the age- and sex-adjusted analyses, the association with all-cause death remained strong and statistically significant for statin-recommended patients. The associations with CVD death were even stronger in statin-recommended patients. Specifically, presence of detectable CAC was associated an almost 11-fold increased risk of CVD death in analyses adjusted for age and sex. The associations were weaker in nonrecommended participants and the 95% Confidence Intervals were wider.

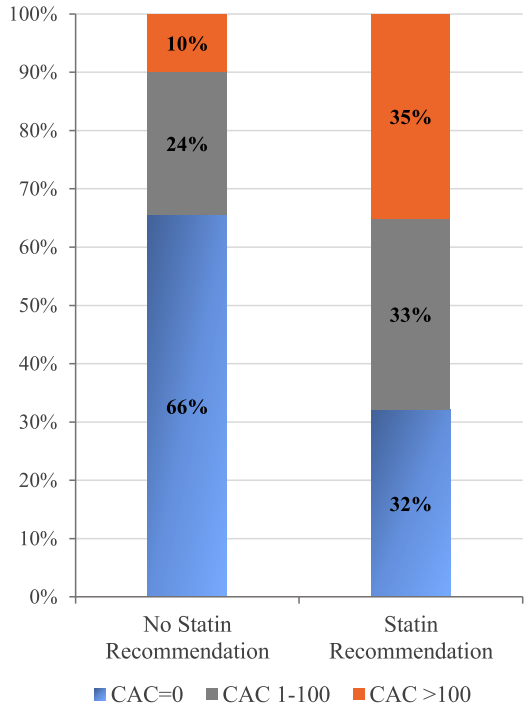

Figure 2. Distribution of CAC scores across statin recommendation groups according to 2018/2019 ACC/AHA guidelines. Abbreviations: CAC = coronary artery calcium

Discussion

Our study demonstrates that CAC scoring substantially differentiates the risk for all-cause and CVD-specific mortality in patients with and without statin recommendation for primary prevention according to the 2018/2019 ACC/AHA guidelines. Overall, in a large cohort of asymptomatic patients who underwent CAC scanning for the evaluation of subclinical atherosclerosis, the all-cause, and CVD-specific mortality rates were much higher in the statin recommended population compared with the nonrecommended population. However, wide heterogeneity of CAC scores was noted in statin recommended patients. Moreover, about one third of the statin recommended population had no detectable CAC and had markedly lower all-cause and CVD- specific death rates. For both end points, the higher the CAC scores, the higher the death rates. The present results provide substantial evidence that CAC testing can enhance decision-making for statin therapy allocation in a primary prevention cohort according to the 2018/2019 guidelines. Overall, these findings can have important implications in terms of reinforcing the clinical utility of CAC = 0 for optimizing statin recommendations, potentially even in those considered at higher risk in the primary prevention settings.

Table 2
Incidence proportions and incidence death rates of all-cause and cardiovascular mortality

Variable	N	All-Cause Mortality		Cardiovascular Mortality	
		Events	Event rate per 1,000 person-years (95% CI)	Events	Event rate per 1,000 person-years (95% CI)
No statin recommendation					
CAC = 0	2,530	33 (1.3%)	1.4 (1.0−2.0)	9 (0.4%)	0.4 (0.2−0.8)
CAC 1-99	949	21 (2.2%)	2.3 (1.5−3.6)	6 (0.6%)	0.7 (0.3−1.5)
CAC ≥ 100	382	11 (2.9%)	3.0 (1.7−5.5)	6 (1.6%)	1.7 (0.7−3.7)
Any CAC present	1,331	32 (2.4%)	2.5 (1.8−3.6)	12 (0.9%)	1.0 (0.5−1.7)
Statin recommendation					
CAC = 0	623	16 (2.6%)	2.9 (1.8−4.8)	1 (0.2%)	0.2 (0.0−1.3)
CAC 1-99	636	37 (5.8%)	6.6 (4.8−9.1)	8 (1.3%)	1.4 (0.8−2.5)
CAC ≥ 100	680	63 (9.3%)	10.4 (8.1−13.3)	24 (3.5%)	4.0 (2.8−5.7)
Any CAC present	1,316	100 (7.6%)	8.6 (7.0−10.4)	32 (2.4%)	2.7 (1.9−3.9)

Abbreviations: CAC = coronary artery calcium; N = number.

Table 3
Associations between coronary artery calcium burden, all-cause and cardiovascular mortality

		All-Cause Mortality		Cardiovascular Mortality	
		HR (95% CI)		HR (95% CI)	
		CAC = 0	CAC > 0	CAC = 0	CAC > 0
No Statin recommendation	Model 1	1.00 (ref)	1.7 (1.1−2.8)	1.00 (ref)	2.4 (1.0−5.7)
	Model 2	1.00 (ref)	1.5 (0.9−2.5)	1.00 (ref)	1.9 (0.8−4.8)
Statin recommendation	Model 1	1.00 (ref)	2.9 (1.7−4.9)	1.00 (ref)	14.9 (2.0−108.7)
	Model 2	1.00 (ref)	2.3 (1.3−3.9)	1.00 (ref)	10.8 (1.5−80.5)

Model 1: Unadjusted; Model 2: Adjusted for age and sex
Abbreviations: CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio.

A wealth of evidence from prior studies has demonstrated significant CVD, all-cause, and CVD mortality benefits with statin therapy in higher-risk patients without clinically overt ASCVD.[11−13] Subsequently, the 2013 ACC/AHA guidelines broadened the criteria for statin use based on PCE-derived 10-year ASCVD risk estimates and relatively low estimated ASCVD risk thresholds, expanding the population eligible for statin therapy.[1,14] In 2016, Yeboah et al[15] reported that CAC score provided superior risk classification beyond that provided by PCE. Nasir et al[16] demonstrated in MESA that CAC improved risk classification for ASCVD events in statin-recommended patients according to the 2013 guideline criteria. In 2018, Mitchell et al used data from 13,644 patients from the Walter Reed Army Medical Center and observed that statin therapy for primary prevention purposes was associated with a reduced risk of major adverse cardiovascular events in patients with detectable baseline CAC over a mean follow-up of 10 years, but did not significantly reduce the already low event rates observed in patients with CAC = 0.[17] The findings of these studies likely informed the updated statin allocation thresholds recommended in the 2018/2019 guideline updates.

In the current study, a wide heterogeneity of CAC scores is noted in patients with statin recommendation.Approximately 70% of the statin recommended population (n = 1,342) is identified based on the 10- year ASCVD risk score ≥ 7.5 patients without diabetes and LDL-C ≥70 and <190 mg/dl ([≥ 1.7 to < 4.9 mmol/L]). The 2018/2019 guidelines recommend CAC scoring for patients at intermediate risk if the decision about statin use is uncertain and note that CAC may also be considered in borderline risk patients, with an estimated 10-year ASCVD risk ≥5% to <7.5% who have factors that increase ASCVD risk. Also, prior studies have reported superior risk factor control and a higher rate of statin adherence associated with CAC testing.[18−20]

As compared with the 2013 guidelines, in which CAC testing had an IIb recommendation, the 2018/2019 upgraded this to an IIa recommendation based on a wealth of observational studies demonstrating improved risk prediction with CAC. There is a growing great interest in evaluating CAC-based prevention strategies in randomized trial settings.[21] If eventually funded, such trials will provide extremely valuable insights regarding whether an even stronger recommendation should be considered.

Our study has several limitations. First, all the patients included in this study underwent a clinically indicated CAC scan for assessment of subclinical atherosclerosis following physician referral and clinical indication for cardiovascular risk stratification. Therefore, the incidence of CAC in this population referred for testing would be expected to be higher than in general population. Nonetheless, these results provide relevant prognostic information even beyond the most updated 2018/2019 guideline recommendations in patients who were deemed to benefit from CAC scoring in a large US center. Second, information on cardiovascular risk factors and medication use were limited by

self-reporting of patient. Third, the study was limited to a single-center population, which was predominantly white, and the baseline prevalence of diabetes and obesity was relatively low. Substantiation of our findings in other racial and ethnic groups is therefore needed. Finally, morbidity data was not collected, and may not reflect the full impact of CV disease impact of treatment versus nontreatment since CV mortality would be a low rate compared with CV morbidity. Future studies evaluating non-fatal CV outcomes are needed to fully understand the prognostic implications of CAC = 0 in statin-recommended patients according to the 2018/2019 guidelines.

Declaration of Competing Interest

The authors report no conflicts of interest to disclose relevant to the content of this manuscript.

Author contribution

Tanuja Rajan: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, validation, interpretation of data, writing – original draft, Writing- review and editing. **Alan Rozanski:** Conceptualization, data curation, formal analysis, investigation, methodology, visualization, validation, interpretation of data, writing – original draft, Writing- review and editing, Supervision. **Miguel Cainzos-Achirica**: Writing – original draft, writing- review and editing. **Gowtham R. Grandhi:** Writing- review and editing. **Zeina A. Dardari:** Data curation, methodology, validation, project administration. **Mouaz H. Al-Mallah:** Writing- review and editing. **Ron Blankstein:** Writing- review and editing. **Michael D. Miedema:** Writing- review and editing, **Leslee J. Shaw:** Writing- review and editing. **John A. Rumberger:** Writing- review and editing. **Matthew J. Budoff:** Writing- review and editing. **Michael J. Blaha:** Conceptualization, data curation, writing – original draft, writing- review and editing. **Daniel Berman**: Conceptualization, formal analysis, investigation, methodology, visualization, validation, interpretation of data, writing – original draft, writing- review and editing, supervision. **Khurram Nasir:** Conceptualization, formal analysis, investigation, methodology, visualization, validation, interpretation of data, writing – original draft, writing- review and editing, supervision.

All the authors have approved the final version of the manuscript.

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