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Coronary artery calcium and carotid artery intima-media thickness for the prediction of stroke and benefit from statins

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Abstract

Background: Current guidelines suggest treatment for many individuals who may never develop a stroke. We hypothesized that a combination of coronary artery calcification (CAC) and carotid artery *intima-media thickness* (*CIMT) data* could better individualize risk assessment for ischemic stroke and transient ischemic attack events.

Methods: A total of 4720 individuals from the Multi-Ethnic Study of Atherosclerosis were evaluated for ischemic stroke and transient ischemic attack. Cox proportional hazards models for time to incident ischemic stroke/transient ischemic attack were used to examine CAC and CIMT as ischemic stroke/transient ischemic attack predictors in addition to traditional risk factors. We calculated the 10-year number needed to treat by applying the benefit observed in ASCOT-LLA to the observed event rates within CAC and CIMT strata.

Results: Median follow-up was 13.1 years. Compared with individuals with no CAC and with CIMT $\leq$ 75th percentile, stroke/transient ischemic attack risk increased progressively with each CAC category (0, 1–100, $>$100) among individuals with CIMT $>$ 75th percentile. Among participants eligible for statin therapy based on the 2013 atherosclerotic cardiovascular disease (ASCVD) guidelines (ASCVD risk of $>$5%), 739/2906 (25%) had no CAC and CIMT $\leq$ 75th percentile and an observed ischemic stroke/transient ischemic attack rate of 2.49 per 1000 person-years. The predicted 10-year number needed to treat was 292 for no CAC and CIMT $\leq$ 75th percentile and 57 for CAC $>$ 100 and CIMT $>$ 75th percentile.

Conclusion: The combination of CIMT and CAC could serve to further refine risk calculation for ischemic stroke/transient ischemic attack prevention and may prioritize those in most need of statin therapy to reduce ischemic stroke/transient ischemic attack risk.

Keywords

Carotid artery intima-media thickness, ischemic stroke/transient ischemic attack, coronary artery calcification

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Introduction

Ischemic stroke is one of the most important causes of death and disability in the United States, and primary prevention is crucial. In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) released updated cardiovascular disease (CVD) prevention guidelines expanding the role of risk management for atherosclerotic cardiovascular disease (ASCVD) to include ischemic stroke.[1,2] With these current guidelines, it is clear that many future ASCVD events could be prevented; however, there is a possibility of risk overestimation.[3] The AHA and American Stroke Association (AHA/ASA) also issued a guideline for primary prevention of stroke in 2014 and recommended statin use according to ACC/AHA guidelines.[4] Notably, statins can reduce the number of ischemic stroke and total stroke events; however, it is still uncertain whether the criteria within the 2013 ASCVD guidelines for statin therapy are optimal for preventing ischemic stroke and total stroke.

Coronary artery calcification (CAC) is an independent risk predictor of ASCVD that can improve discrimination for ASCVD in asymptomatic individuals beyond prevalent risk prediction tools.[5] Similarly, CAC could specifically predict stroke;[6] however, its discriminative value for stoke is still controversial.[7] Meanwhile, ischemic stroke is often attributable to carotid artery atherosclerosis, and carotid artery intima-media thickness (CIMT) may predict ischemic stroke.[8] Thus, the combination of CIMT and CAC information may better classify ASCVD risk and thus could indicate eligibility for statin use to reduce ischemic stroke and transient ischemic attack (TIA) risk.

The aim of this study, which used data from the Multi-Ethnic Study of Atherosclerosis (MESA), was to investigate the utility of a combination of CAC and CIMT scores for improving the risk stratification for ischemic stroke/TIA. We also analyzed the potential impact of a combination of CAC and CIMT in determining the eligibility for primary preventive statin therapy.

Methods

Study population of MESA

MESA is a longitudinal epidemiological study aimed at describing the prevalence, progression, and significance of subclinical atherosclerosis. Complete details of the MESA study design have been published previously.[9] In brief, between July 2000 and September 2002, MESA enrolled 6814 participants at six US field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). MESA participants were 38% White, 28% Black, 22% Hispanic, and 12% Chinese. All participants were 45–84 years old and had no known clinical CVD at the time of enrollment. The subset of participants for this study consisted of individuals aged 45–74 years. The MESA study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

Data collection

As part of the baseline examination, clinical staff at each of the six centers collected information about cardiovascular risk factors. Demographics, medical history, and anthropometric and laboratory data for the present analysis were taken from the first examination of the first MESA cohort (July 2000 to September 2002). Diabetes mellitus was defined as fasting glucose $\geq$7.0 mmol/L (126 mg/dL), self-reported diabetes, or use of hypoglycemic drugs. Resting blood pressure was measured three times in the seated position, and the average of the second and third readings was used. Hypertension was defined as untreated systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or use of medication prescribed for hypertension. Current smoking was defined as having smoked a cigarette in the last 30 days. Total and high-density lipoprotein (HDL) cholesterol and triglyceride levels were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein (LDL) cholesterol was measured by the Friedewald equation.

The 10-year risk of ASCVD events was estimated on the basis of age, race, sex, current smoking, diabetes mellitus, systolic blood pressure, use of antihypertensive medication, and total cholesterol and HDL/LDL cholesterol levels from the ACC/AHA Pooled Cohort Equations.[2]

Determination of CAC score

The methods for computed tomography (CT) scanning and interpretation have been published previously.[10] CAC was determined by the Agatston score. Images were interpreted at the MESA CT reading center (Los Angeles Biomedical Research Institute, Torrance, CA, USA) by an experienced physician.

Carotid ultrasonography

High-resolution B-mode ultrasonography was used to image the intima-media layer of the carotid arterial wall of the near and far walls of the left and right common and internal carotid arteries. A standardized method for measuring and interpreting CIMT was reported

previously.[11] The mean maximal IMT of the common carotid artery (CCA) and internal carotid artery (ICA) was obtained by averaging the bilateral maximal measurements from the near and far walls at each projection. In this study, increased CIMT evaluated by ultrasound was defined as either ICA or CCA IMT > 75th percentile for the entire MESA population inclusive of all ages.

Analysis of ischemic stroke and TIA

Participants were followed from baseline examination (2000–2002) to 2016. They were contacted by telephone every 9–12 months to inquire about interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. To verify self-reported diagnoses, information was collected from death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses. Stroke was defined as the rapid onset of documented focal neurological deficit lasting 24 h or until death, or, if the deficit lasted <24 h, a diagnosis of stroke was confirmed if there was a clinically relevant lesion on brain imaging (typically CT or magnetic resonance imaging) and no non-vascular cause. TIA was defined as a focal neurological deficit lasting <24 h without detection of stroke by brain imaging. Ischemic stroke/TIA were adjudicated by a MESA committee that included cardiologists, physician-epidemiologists and neurologists. A detailed description of the adjudication process has been published.[9]

Statistical analysis

Baseline characteristics are presented as the mean ± standard deviation (SD) or as the number of individuals (and percent of the participants). The chi-square test and one-way analysis of variance were used for comparison of variables between groups. We used Kaplan–Meier estimates of cumulative event-free survival to describe the occurrence of ischemic stroke/TIA events over time. Models were adjusted for age, sex, race, diabetes, systolic blood pressure, anti-hypertensive medications, smoking status, body mass index, and total and HDL cholesterol. A 10-year number needed to treat (NNT) for lowering of LDL cholesterol by statins was estimated for ischemic stroke/TIA reduction by applying the hazard ratio associated with atorvastatin use in the ASCOT-LLA[12] (hazard ratio 0.73, 95% confidence interval (CI) 0.56–0.96, $p = 0.024$) to the event rates within each CAC stratum and CIMT category for primary prevention. For this analysis, a 10-year NNT was calculated directly as the reciprocal of the absolute risk difference at the 10-year follow-up of the cohort based on Kaplan–Meier estimates. The categories examined were (1) CAC strata (CAC = 0, CAC = 1–100, and CAC > 100), (2) CIMT category (CIMT ≤ 75th percentile and CIMT > 75th percentile), and (3) a combined CAC/CIMT category encompassing the six possible combinations. $p < 0.05$ indicates statistical significance.

Results

Participant characteristics

The final study population included 4720 participants aged 45–74 years who did not use lipid-lowering medications and had complete lipid-lowering medication data and LDL level and risk factor information. A flowchart of participants included in the study is shown in Supplementary Material Figure 1 online. Among 4720 participants, 38% ($n = 1781$) of patients were in the lowest (<5%) category of 10-year predicted ASCVD risk, with 12% ($n = 588$) having predicted risk of ≥5.0% but <7.5%, and 50% ($n = 2351$) having predicted risk of ≥7.5% or diabetes mellitus or LDL > 190 mg/dL. Baseline characteristics of the study participants according to statin recommendation are shown in Supplementary Material Table 1 online. At baseline, 4674 participants underwent baseline CIMT assessment.

Comparison of CAC score, CIMT category, and a combination of CAC score and CIMT category for predicting ischemic stroke and TIA

Over a median follow-up of 13.1 years, 162 (3.4%) ischemic stroke/TIA events were observed among 4674 individuals. The frequency of ischemic stroke/TIA events, along with the 10-year risk of ASCVD and hazard ratios for this subgroup of MESA individuals who were stratified by CAC score and CIMT category are shown in Table 1. The rate of 10-year ischemic stroke/TIA events increased stepwise according to CAC scores. Similarly, individuals with CIMT > 75th percentile showed a significantly increased risk for having ischemic stroke/TIA as compared with those with CIMT ≤ 75th percentile. When the combination of CAC and CIMT data was considered, individuals with CAC = 0 and CIMT > 75th percentile showed a twofold increase in ischemic stroke/TIA risk relative to individuals with the same CAC score and CIMT ≤ 75th percentile (2.57% *vs.* 1.27%, respectively). Likewise, individuals with CAC > 100 and CIMT > 75th percentile showed a twofold increase in ischemic stroke/TIA risk as compared with those with CAC > 100 and CIMT ≤ 75th percentile (6.56% *vs.* 3.38%, respectively).

The unadjusted Kaplan–Meier estimates of event-free survival relative to ischemic stroke/TIA among

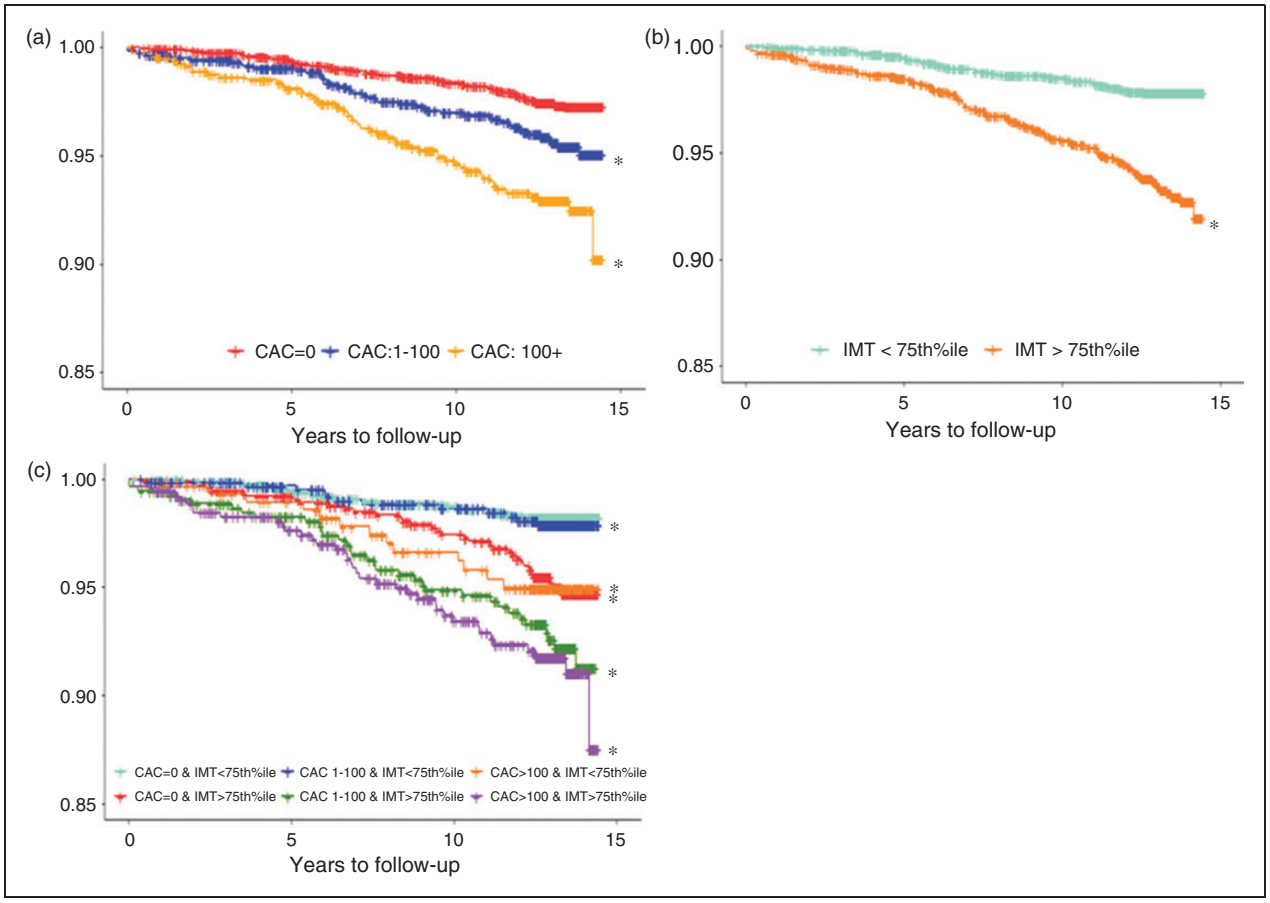

Figure 1. Unadjusted Kaplan–Meier survival curves free of ischemic stroke/TIA according to (a) coronary artery calcification (CAC) score, (b) carotid artery intima-media thickness (IMT) category, and (c) the combination of CAC and CIMT data. $N = 4674$.
*$p < 0.05$, comparing each category with the lowest risk category.

Table 1. The frequency, 10-year risk and hazard ratios of ischemic stroke/transient ischemic attack events.

Category	Number of individuals	Number of events	10-year risk	HR (95% CI)	*p*-value
CAC score					
0	2710	65	1.62%	Reference	
1–100	1190	47	3.07%	1.24 (0.83–1.83)	0.29
>100	820	52	5.49%	1.60 (1.05–2.45)	0.029
CIMT					
CIMT ≤ 75th percentile	2852	57	1.49%	Reference	
CIMT > 75th percentile	1822	105	4.43%	1.88 (1.32–2.67)	<0.001
Combined CAC and CIMT					
CAC = 0, CIMT ≤ 75th percentile	1923	32	1.27%	Reference	
CAC = 1–100, CIMT ≤ 75th percentile	645	12	1.35%	0.88 (0.45–1.72)	0.71
CAC>100, CIMT ≤ 75th percentile	284	13	3.38%	1.92 (0.97–3.78)	0.06
CAC = 0, CIMT > 75th percentile	763	33	2.57%	1.75 (1.05–2.89)	0.03
CAC = 1–100, CIMT > 75th percentile	529	34	5.15%	2.41 (1.42–4.10)	0.001
CAC > 100, CIMT > 75th percentile	530	38	6.56%	2.39 (1.37–4.18)	0.002

CAC: coronary artery calcification; CIMT: carotid artery intima-media thickness; HR: hazard ratio; CI: confidence interval

these participants based on CAC and CIMT data are shown in Figure 1. After adjustment for traditional risk factors, risk of ischemic stroke/TIA increased progressively for each CAC category (0, 1–100, >100) among individuals with CIMT > 75th percentile. In contrast, among individuals with CIMT ≤ 75th percentile, as compared with those with CAC = 0, those with CAC > 100 demonstrated a trend toward increased risk (hazard ratio 1.92, 95% CI 0.97–3.78), whereas those with CAC = 1–100 did not (hazard ratio 0.88; 95% CI 0.45–1.72).

Of participants considered or recommended for statin therapy by the ACC/AHA guidelines (ASCVD risk of >5%), 739/2906 (25%) had both CAC = 0 and CIMT ≤ 75th percentile at baseline and an observed ischemic stroke/TIA event rate of 2.49 per 1000 person-years, contrasting with 4.74 per 1000 person-years in those with both CAC = 0 and CIMT > 75th percentile of 549/2906 (18.9%).

NNT according to CAC score and CIMT strata

Using CAC scores alone, the NNT to prevent one ischemic stroke/TIA incidence over 10 years was 229 for individuals with a CAC = 0, and was 68 for individuals with CAC > 100 (Table 2). Individuals with no CAC and CIMT ≤ 75th percentile showed a twofold increase in the 10-year NNT for statin therapy to prevent one ischemic stroke/TIA event as compared with those with CIMT > 75th percentile (292 *vs.*145, respectively). Moreover, the 10-year NNT for statin therapy to prevent one ischemic stroke/TIA incidence was 57 for those with CAC > 100 and CIMT > 75th percentile, and yet was 110 for those with CAC > 100 and CIMT ≤ 75th percentile.

Table 2. Estimated 10-year NNT for ischemic stroke/transient ischemic attack based on CAC and CIMT data.

Category	Number of individuals	10-year NNT
CAC score		
CAC = 0	2710	229
CAC = 1–100	1190	121
CAC > 100	820	68
CIMT category		
CIMT ≤ 75th percentile	2852	249
CIMT > 75th percentile	1822	84
Combined CAC and CIMT data		
CAC = 0, CIMT ≤ 75th percentile	1923	292
CAC = 1–100, CIMT ≤ 75th percentile	645	275
CAC > 100, CIMT ≤ 75th percentile	284	110
CAC = 0, CIMT > 75th percentile	763	145
CAC = 1–100, CIMT > 75th percentile	529	72
CAC > 100, CIMT > 75th percentile	530	57

NNT: number needed to treat; CAC: coronary artery calcification; CIMT: carotid artery intima-media thickness

Discussion

The present study demonstrated that, for the primary prevention of ischemic stroke/TIA, MESA participants with CAC = 0 and CIMT ≤ 75th percentile had a very low ischemic stroke/TIA event rate and the highest NNT for statin therapy. In contrast, individuals with CAC > 100 and CIMT > 75th percentile had a high ischemic stroke/TIA event rate and the lowest NNT for statin therapy. Moreover, based on the 2013 ACC/AHA cholesterol management guidelines, we found that approximately one-quarter of statin-eligible candidates had both CAC = 0 and CIMT ≤ 75th percentile and showed a very low ischemic stroke/TIA event rate. Hence, a combination of CAC score and CIMT may mitigate the need for statin therapy to reduce ischemic stroke/TIA risk and avoid exposure of low-risk patients to unnecessary treatment-related harm among the ever-growing population of statin-eligible individuals.

In people at moderate total ASCVD risk (i.e. a Systematic COronary Risk Evaluation (SCORE) >1, <5%/10 years), risk estimation could be improved by considering other 'qualifiers' such as CAC, ankle-brachial index and carotid artery scanning. CAC is a stronger predictor of cardiac events, but has been shown to predict strokes and total ASCVD as well.[13] A risk evaluation including CAC score shows a high external validity regarding cardiovascular risk.[14] Within the current guidelines, a CAC score-based risk assessment is considered helpful for treatment decisions regarding ASCVD; in contrast, the recommendation class of CIMT testing is a class 3 recommendation because of the lack of compelling incremental predictive value beyond traditional risk factor models.[2] Regarding ischemic stroke/TIA, previous studies have shown a notable value for both CAC[6,15,16] and CIMT[17] information for predicting ischemic stroke/TIA; however, their discriminative and reclassification power is sometimes insufficient.[6,7,15,16] Our findings indicate that a combination of CAC and CIMT information is promising for more accurate risk assessment of ischemic stroke/TIA, and this approach may identify individuals at low or high risk for ischemic stroke/TIA for statin therapy in primary prevention.

A CAC score of zero is strongly associated with a low risk of coronary heart disease (CHD), CVD, and all-cause mortality.[18,19] The clinical utility of a CAC score of zero on ischemic stroke/TIA has not, however, been fully investigated. We observed a 10-year risk of

ischemic stroke/TIA of 1.62% among individuals with no CAC, which is comparable to the rates seen among the middle-aged general population.[20] Moreover, a combination of CAC score and carotid artery atherosclerosis may provide more accurate risk assessment of ischemic stroke/TIA as well as cardiac events.[21] In particular, our analysis affirmed the twofold increase in ischemic stroke/TIA risk in individuals with CIMT > 75th percentile as compared with those with CIMT ≤ 75th percentile, even among those with CAC = 0. The rate of 10-year ischemic stroke/TIA events was 1.27% in individuals with no CAC and CIMT ≤ 75th percentile, which was lower than that when individuals with no CAC were assessed without consideration of CIMT (1.62%). The combination of CAC and IMT thus seems able to identify a very low risk group (although either measure does fairly well on its own). Thus, those with CAC = 0 and CIMT ≤ 75th percentile could be potentially free from preventive statin therapy for ischemic stroke/TIA, whereas those with CAC = 0 and CIMT > 75th percentile may be considered for preventive statin therapy for ischemic stroke/TIA.

Individuals with a CAC score of >100 are definitely at high risk of ischemic stroke/TIA as well as coronary artery disease.[22] Notably, individuals with CAC > 100 and CIMT > 75th percentile should be considered at high risk of ischemic stroke/TIA. In contrast, our results showed a non-significant increase in ischemic stroke/TIA in individuals with CIMT ≤ 75th percentile among those with CAC >100. A previous report from the BioImage study showed a stepwise increase in the number of major adverse cardiac events according to the carotid plaque burden even among individuals with the highest CAC category.[23] Although individuals with a CAC score of >100 are at high risk, CIMT ≤ 75th percentile may be reassuring for ischemic stroke/TIA.

Meanwhile, among individuals with a CAC score of 1–100, who might also be at relatively high risk of coronary artery disease,[24] an increased hazard ratio was observed only in individuals with CIMT > 75th percentile. Previous reports from MESA[16,25] showed a significant increase in ischemic stroke/TIA for individuals with CAC = 1–100 relative to those with CAC = 0 in a univariate model, but not in multivariate models. Our results suggest that a CAC score of 1–100 can be predictive of ischemic stroke/TIA if CIMT is also >75th percentile.

For primary prevention of ASCVD, guidelines issued by the European Society of Cardiology (ESC) recommend cardiovascular risk stratification to use the Systematic COronary Risk Evaluation (ESC-SCORE) algorithm to predict fatal ASCVD.[26] It could predict cardiovascular events well;[27,28] however, the problem of overestimation is similar with US preventive guidelines.[3,29] A recent investigation has shown that the CAC score could well differentiate the risk for future cardiovascular events in the ACC/AHA Pooled Risk Cohort as well as the ESC-SCORE algorithm.[30] Individuals in these groups with higher CAC scores had a higher CHD and CVD event rate irrespective of statin indication.[30] Regarding ischemic stroke, Hermann et al. demonstrated the significant association between the CAC score and stroke incidence in a German cohort; however, the discriminative power of the CAC score was insufficient in primary screening for ischemic stroke.[6] Although the combination of CAC and CIMT data may be promising for improving discrimination for ischemic stroke/TIA in this current population, further studies in a non-US population are needed to definitively determine the utility of the combined assessment.

The strengths of our study include its large sample size, the multi-ethnic nature of the cohort, the adjudicated ischemic stroke/TIA, and the long follow-up duration. However, some limitations also need to be addressed. First, the number of ischemic stroke/TIA events is relatively small. There were only 12 and 13 ischemic stroke/TIA events in individuals with CAC = 1–100 and CIMT ≤ 75th percentile and those with CAC > 100 and CIMT ≤ 75th percentile, respectively, so these results must be interpreted with caution. Second, there is an uncertainty when applying the relative risk reduction observed in ASCOT-LLA to the current population for the estimation of NNT. For example, it is unclear whether individuals with elevated CAC and CIMT > 75th percentile have a similar benefit with statin therapy compared with those with lower or zero CAC scores and CIMT ≤ 75th percentile, and, thus, our NNT result should be hypothesis generating. NNTs presented are not absolute and there is uncertainty around the point estimates for NNT that is not presented. Third, the study population in this analysis was missing a large number of individuals at high or very high CVD risk because participants on lipid-lowering drugs were excluded; this may limit the external validity of the study. Finally, we used the ASCVD risk score for identifying individuals at low or high risk for ischemic stroke/TIA. Current guidelines for statin use focus on ASCVD events, not just strokes and TIAs, so reviewing ischemic stroke/TIA event reduction alone may be insufficient. However, current AHA/ASA guidelines recommend using the ASCVD risk score for primary prevention of stroke.

In conclusion, addition of CIMT to CAC can further stratify ischemic stroke/TIA risk. Among individuals eligible for statin therapy, those with no CAC and CIMT ≤ 75th percentile had a very low ischemic stroke/TIA event rate and a high NNT for statin therapy,

possibly mitigating the need for statin therapy to reduce ischemic stroke/TIA risk.

Author contribution

KO, MEPT, RN, RLM, MJB, RB, JWM, IC, JHS, and MJB designed the study, and KO, MEPT, RN and RLM wrote the initial draft of the manuscript. MEPT, RLM, JFP, and RLS contributed to the analysis and interpretation of data and assisted in the preparation of the manuscript. All authors contributed to data collection and interpretation and critically reviewed the manuscript.

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Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Matthew J Budoff: National institute of health and general electric.

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