Thoracic Aortic Calcium for the Prediction of Stroke Mortality (from the Coronary Artery Calcium Consortium)

Olufunmilayo H. Obisesan, MD, MPH[a], Albert D. Osei, MD,MPH[b], Daniel Berman, MD[c], Zeina A. Dardari, MS[a], S.M Iftekhar Uddin, MBBS,MSPH[a], Omar Dzaye, MD, PHD[a], Olusola A. Orimoloye, MD, MPH[d], Matthew J. Budoff, MD[e], Michael D Miedema, MD MPH[f], John Rumberger, MD, PhD[g], Mohammadhassan Mirbolouk, MD[h], Ellen Boakye, MD, MPH[a], Michelle C. Johansen, MD, PhD[a], Alan Rozanski, MD[i], Leslee J. Shaw, PhD[j], Donghee Han, MD[k], Khurram Nasir, MD, MPH[l], and Michael J. Blaha, MD,MPH[a,*]

Thoracic aortic calcium(TAC) is an important marker of extracoronary atherosclerosis with established predictive value for all-cause mortality. We sought to explore the predictive value of TAC for stroke mortality, independent of the more established coronary artery calcium (CAC) score. The CAC Consortium is a retrospectively assembled database of 66,636 patients aged ≥18 years with no previous history of cardiovascular disease, baseline CAC scans for risk stratification, and follow-up for 12 ± 4 years. CAC scans capture the adjacent thoracic aorta, enabling assessment of TAC from the same images. TAC was available in 41,066 (62%), and was primarily analyzed as present or not present. To account for competing risks for nonstroke death, we utilized multivariable-adjusted Fine and Gray competing risk regression models adjusted for traditional cardiovascular risk factors and CAC score. The mean age of participants was 53.8 ± 10.3 years, with 34.4% female. There were 110 stroke deaths during follow-up. The unadjusted subdistribution hazard ratio (SHR) for stroke mortality in those who had TAC present compared with those who did not was 8.80 (95% confidence interval [CI]: 5.97, 12.98). After adjusting for traditional risk factors and CAC score, the SHR was 2.21 (95% CI:1.39,3.49). In sex-stratified analyses, the fully adjusted SHR for females was 3.42 (95% CI: 1.74, 6.73) while for males it was 1.55 (95% CI: 0.83, 2.90). TAC was associated with stroke mortality independent of CAC and traditional risk factors, more so in women. The presence of TAC appears to be an independent risk marker for stroke mortality. **(Am J Cardiol 2021;148:16−21)**

Thoracic aortic calcium (TAC), the most common form of extracoronary calcification, is an important marker of systemic atherosclerosis with known predictive value for all-cause mortality and 10-year coronary heart disease (CHD) risk, including when used in addition to the more established Agatston Coronary Artery Calcium (CAC) score.[1−3] It can be measured with the same cardiac CT scans used to assess CAC, allowing its assessment without additional exposure to radiation and at no additional cost.[4] Furthermore, TAC can be accurately assessed on all chest CT scans regardless of ECG gating.[5] Although CAC and other extracoronary calcification have been associated with the incidence of stroke,[6,7] there is minimal information on the utility of TAC in estimating stroke outcomes. TAC has been associated with increased inflammatory markers, as well as increased risk of stroke and other cardiovascular events.[8,9] Additionally, the aorta is the main conduit large artery in the body, and is more directly connected to the carotid arteries which provide the bulk of the blood supply of the brain.[10] Thus, TAC might be a better predictor of stroke outcomes than CAC, which is at best, a modest predictor of stroke.[11] We therefore sought to explore the predictive value of TAC for stroke mortality independent of the CAC score. We also explored the association between TAC and stroke mortality by sex.

Methods

The CAC Consortium is a retrospectively assembled database of 66,636 patients aged ≥18 years with no previous history of cardiovascular disease (CVD), who had CAC

[a]Johns Hopkins University School of Medicine, Baltimore, Maryland; [b]Medstar Union Memorial Hospital, Baltimore, Maryland; [c]Cedars-Sinai Medical Center, California, California; [d]Vanderbilt University Medical Center, Nashville, Tennessee; [e]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles, California; [f]Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; [g]Princeton Longevity Center, Princeton, New Jersey; [h]Yale University, New Haven, Connecticut; [i]Division of Cardiology, Mount Sinai St. Luke's Hospital, New York; [j]Weill Cornell Medicine, New York; [k]Department of Imaging, Cedars-Sinai Medical Center, Los Angeles, California; and [l]Houston Methodist Hospital, Houston, Texas. Manuscript received January 11, 2021; revised manuscript received and accepted February 23, 2021.

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*Corresponding author: Tel. 443-287-4960.

E-mail address: mblaha1@jhmi.edu (M.J. Blaha).

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scans done for risk stratification, with long-term follow-up of 12 ± 4 years for mortality outcomes.[12] Participants were recruited from four institutions in the United States: Cedars-Sinai Medical Center, Los Angeles, CA; Preva-Health Wellness Diagnostic Center, Colombus, OH; Harbor-UCLA Medical Center, Torrance, CA; and Minneapolis Heart Institute, Minneapolis, MN.[12] Consent was obtained from all participants at their participation site and IRB approval was obtained from the Johns Hopkins University School of Medicine for coordinating center activities and death ascertainment.[12]

For this study, we restricted our analysis to 41,066 participants with available information on the presence or absence of TAC.

ECG-gated noncontrast scans were performed for each participant using electron bean tomography or multidetector CT. A standard protocol was adapted for each scanner technology used.[12] CAC scans capture a view of the adjacent thoracic aorta, enabling assessment of TAC at no extra cost. TAC was primarily assessed as present or absent. In addition, TAC score was assessed using the Agatston score in 34,024 patients (83% of the total analytical sample). In this subgroup, TAC area was calculated as TAC volume score/2.5 (slice thickness of multidetector CT scanners), and peak TAC density was calculated as TAC score/TAC area.[13]

Patient demographic information, risk factor information and laboratory data were collected during routine clinical visit or at the time of the CAC scan. Hypertension was defined as a history of clinical diagnosis of hypertension or hypertensive medication therapy.[12] Diabetes was defined as a previous clinical diagnosis of diabetes or management on oral hypoglycemic drugs or insulin.[12] Dyslipidemia was defined as a history of clinical diagnosis of primary hyperlipidemia, dyslipidemia, management on any lipid lowering therapy or laboratory data showing LDL-C >160 mg/dl, HDL-C <40 mg/dl in men or <50 mg/dl in women, or fasting triglycerides>150 mg/dl.[12] Smoking status was classified as current, former or never smoking.[12] Family history of CHD was defined as a first degree relative with a history of CHD.[12] CAC groups were defined as CAC = 0, CAC = 1−99, CAC = 100−399, CAC ≥400.[14] Multiple imputation was used to account for any partially missing risk factor data.[12] Mortality status was determined from the Social Security Index Death Master File, and death certificates were obtained from the National Death Index. Causes of death were then categorized using the International Classification of Diseases.[12] The primary outcome of interest in our study was stroke mortality (listed as the primary underlying cause of death).

Demographic characteristics were summarized by TAC category (present/absent). Means and proportions were reported for continuous and categorical data respectively. Differences between categorical variables were tested using chi square statistic, while differences between continuous variables were tested using 2 sample *t* test. The cumulative incidence for stroke mortality by TAC and CAC groups was assessed and cumulative incidence function curves were derived and plotted. To assess the predictive value of TAC for stroke mortality while accounting for competing risks for death from other causes, we utilized Fine and Gray's competing risk regression model. We report the relationship between TAC and stroke mortality risk with subdistribution hazard ratios (SHR) and 95% CI, using four models outlined as follows: Model 1 was unadjusted, Model 2 was adjusted for age and sex, Model 3 was defined as Model 2 plus traditional cardiovascular risk factors (hypertension, hyperlipidemia, cigarette smoking, diabetes, family history of CHD), Model 4 was defined as Model 3 plus CAC score groups.

Based on our findings and *a priori* knowledge of the strong effect of sex on TAC and outcomes, the models were further stratified by sex. We further tested for an effect modification of sex on the relationship between TAC and stroke mortality. Finally, to further assess the discriminatory value of TAC independent of CAC for the prediction of stroke mortality, we assessed the area under reviewer operating curves for fully-adjusted models with and without TAC.

Unlike TAC presence or TAC score, previous research found TAC density to be protective against CHD and CVD events, after accounting for TAC area or volume.[13,15] Thus, in further exploratory analysis within the subset with TAC scores, we assessed the relationship between peak density TAC and stroke mortality.

All analyses were run with Stata model 15.1 SE.

Results

Overall, the mean age of participants was 53.8 ± 10 years and 34.4% were female. Among the 41,066 participants studied, 11,684(28.5%) had TAC. Compared with individuals without TAC, those with TAC were older and more likely to be female, have hypertension, dyslipidemia, diabetes, higher CAC categories, smoke cigarettes, and have higher atherosclerotic cardiovascular disease risk scores (Table 1).

Table 1.
Demographic information of participants by TAC status

Characteristic	Thoracic aortic calcium	
	YES (n = 11,684)	NO (n = 29,382)
Age (years) (Mean± S.D)	61.8 ± 9.6	50.7 ± 8.7
Women	4,340 (37.1%)	9,776 (33.3%)
Hypertension	5,176 (44.3%)	7,183 (24.5%)
Dyslipidemia*	7,101 (60.8%)	14,039 (47.8%)
Diabetes mellitus	1,190 (10.2%)	1,313 (4.5%)
Smokers	1,294 (11.1%)	2,733 (9.3%)
Family history of CHD	4,868 (41.7%)	12,570 (42.8%)
CAC score group		
0	2,286 (19.6%)	17,190 (58.5%)
1-100	3,702 (31.7%)	8,225 (28.0%)
100-400	2,762 (23.6%)	2,653 (9.0%)
>400	2,934 (25.1%)	1,314 (4.5%)
ASCVD risk categories		
<5%	3,380 (28.9%)	20,844 (70.9%)
5-7%	1,673 (14.3%)	3,701(12.6%)
>7.5%	6,631 (56.8%)	4,837 (16.5%)

CHD = coronary heart disease; ASCVD = atherosclerotic cardiovascular disease.

* defined as a history of clinical diagnosis of primary hyperlipidemia, dyslipidemia, management on any lipid lowering therapy or laboratory data showing LDL-C >160 mg/dl, HDL-C <40mg/dl in men or <50 mg/dl in women, or fasting triglycerides >150 mg/dl.

Over a mean follow-up of 10.7 ± 3.0 years, 143 individuals had stroke mortality, of whom 110 (76.9%) had TAC present. At the end of follow-up, the cumulative incidence of stroke mortality for individuals with TAC present was 1.2%, while those without TAC had a cumulative incidence of 0.1% (Figure 1). Among individuals with TAC present, the cumulative incidence of stroke deaths in those with CAC scores of 0, 1−99, 100−399 and ≥400 was 0.6%, 0.7%, 1.0%, and 2.4% respectively, compared with individuals without TAC who had cumulative incidence estimates of 0.1%, 0.2%, 0.1%, and 0.3% for the respective CAC categories (Figure 2).

In an unadjusted model, TAC presence was associated with stroke mortality with a SHR of 8.80 (95% confidence intervcal [CI]: 5.97, 12.98) when compared to individuals without TAC. After adjusting for age, sex, and traditional risk factors, the SHR was attenuated but remained significant (2.41 [95% CI:1.54,3.78]). After additionally accounting for CAC score groups, the SHR was 2.21 (95% CI: 1.39, 3.49).(Table 2) The addition of TAC to the model with age, sex, risk factors, and CAC nominally increased the area under the curve from 0.8598 to 0.8647, however this change was not statistically significant (p = 0.28).

We explored the association between TAC and stroke mortality by sex category, and found that TAC was associated with an increased risk for stroke mortality in women but not in men, with fully adjusted SHRs of 3.42 (95% CI: 1.74, 6.73) and 1.55 (0.83, 2.90), respectively (Table 3). However, there was no evidence of multiplicative interaction between TAC and sex in our dataset (p = 0.1892).

Among the individuals in our dataset, 19,476 had no CAC present (CAC = 0), of whom 2,286 (11.7%) had TAC present and 24 had mortality from stroke. Among these individuals, TAC presence was associated with stroke mortality with an unadjusted HR of 7.65 (95% CI: 3.44, 17.02). After adjusting for age, sex, and traditional risk factors, the association remained significant (2.81 [95% CI: 1.07, 7.45]).

In further exploratory analyses within the subset with Agatston TAC scores, TAC score was associated with stroke mortality in unadjusted analyses, however, it not longer remained significant after full multivariable adjustment. Peak TAC density was associated with stroke mortality after accounting for TAC area, age, sex, and risk factors, with an SHR of 1.53(95% CI: 1.08, 2.17). However, after adjusting for CAC groups in addition, the SHR lost significance (1.44 [95% CI: 0.99, 2.08] ;Supplement Table 1).

Discussion

In this study of over 41,000 individuals with no known baseline CVD, the presence of TAC was found to be associated with stroke mortality independent of CAC and traditional risk factors, particularly in females, with persistent associations in those with baseline CAC = 0. Consistent with previous studies, we found TAC to be associated with increased age, female sex, higher atherosclerotic cardiovascular disease risk, and known cardiovascular risk factors including hypertension, diabetes, dyslipidemia, and smoking.[2,16]

Although women typically have been shown to have lower CAC prevalence, they have been found to have higher prevalence of TAC especially in the absence of CAC,[17] with TAC presence in women indicative of increased all-cause and cardiovascular mortality.[18] In our dataset, we found an association between TAC presence and stroke mortality only in women. Similarly, Iribarren et al found TAC to have potential value for the prediction of ischemic stroke only in women, although this could potentially be due to the limited number of events in both studies.[19] Although men tend to have a higher incidence of stroke, women have been shown to have more severe strokes than men, with a wide array of contrasting evidence for the effect of sex on stroke outcomes.[20,21] If confirmed by other studies, our findings suggest that TAC could

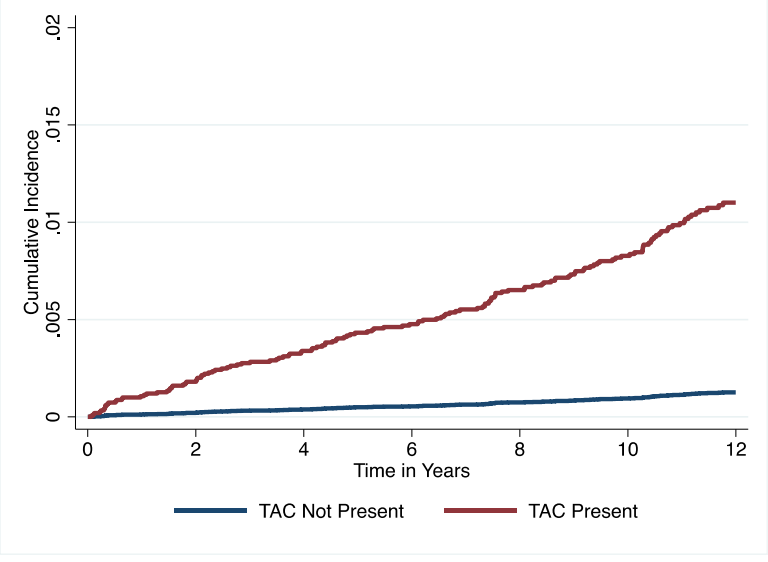

Figure 1. Cumulative incidence function curves for individuals with and without TAC.

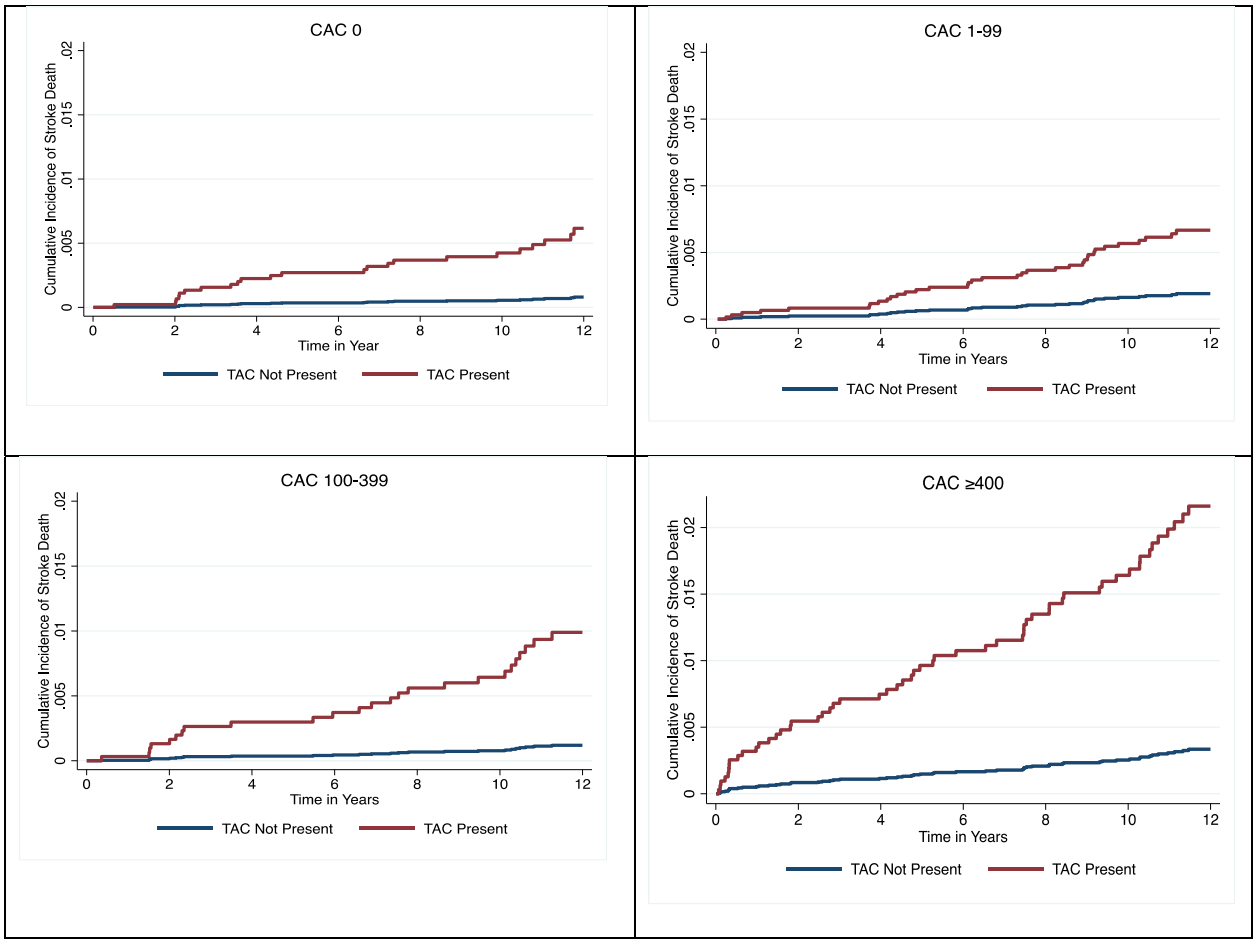

Figure 2. Cumulative incidence function curves for individuals with and without TAC by CAC category.

provide an alternative/additional means of CVD risk prediction in women.

Given that TAC can be easily assessed on ECG-gated CAC scans and on non-gated thoracic CT scans, the incremental value for cardiovascular risk prediction comes at no extra cost and without additional exposure to radiation.[2] For example, In light of the USPTF recommendations for screening thoracic CTs for lung cancer, and SCCT/STR recommendations for the assessment of CAC on all thoracic scans,[22] maximal benefit can be ascertained for each patient if TAC is also considered on these scans, making the assessment of its value in CVD risk prediction all the more important.

CAC has been extensively proven to be beneficial in CVD risk stratification especially among individuals with intermediate CVD risk scores.[22,23] However, the additional benefit of screening for extracoronary artery calcium has not been fully established or validated.[24] In our study, among individuals with high CAC scores, an increase in stroke mortality was observed in those who also had TAC present. Our findings are similar to the observations in the study by Santos et al where higher rates of all-cause mortality were observed with higher CAC categories that had TAC present.[2] Our findings have additional face validity considering the proximity and direct connection between the aorta and the brain (through the carotid arteries),

Table 2.
Multivariable adjusted SHRs and 95%CI for TAC and stroke mortality

Models	Subdistribution HR (95%CI)
1[*]	8.80 (5.97,12.98)
2[‡]	2.64 (1.69,4.14)
3[‡]	2.41 (1.54,3.78)
4[§]	2.21 (1.39,3.49)

[*] Unadjusted.
[†] Adjusted for age and sex.
[‡] Adjusted for Model 2+risk factors.
[§] Adjusted for Model 3+ CAC.

Table 3.
Multivariable adjusted SHRs and 95%CI for TAC and stroke mortality by gender

Models	Females subdistribution HR (95% CI)	Males subdistribution HR (95% CI)
1[*]	11.62 (6.23,21.66)	6.88 (4.15,11.41)
2[†]	3.67 (1.87,7.20)	1.73 (0.94,3.18)
3[‡]	3.42 (1.74,6.73)	1.55 (0.83,2.90)

[*] Unadjusted.
[†] Adjusted for age and risk factors.
[‡] Adjusted for age, risk factors, and CAC.

compared with the coronary arteries.[10] Also, the aorta is a large conduit artery more similar in structure to the carotids compared to the coronary arteries which are small muscular arteries with perhaps a different pathobiology of atherosclerosis, and TAC has been found to be directly associated with carotid stiffness which has been associated with an increased risk for cerebrovascular disease.[7,25,26] Additionally, aortic calcification has been associated with incident and recurrent stroke, with the release of atheroemboli from these plaques suggested as another potential mechanism for the association.[7,9] Thus, there is potential benefit to the routine assessment of TAC on CAC scans to further increase the precision of CVD risk prediction.

Furthermore, the absence of CAC has been proven to have a high negative predictive value for cardiovascular events.[27] Among patients with no CAC in our study, however, TAC remained indicative of stroke mortality. Along this trajectory, Santos et al found TAC to be predictive of all-cause mortality among individuals with CAC = 0, although the limited events in their study sample caused their findings to be statistically insignificant.[2] Hermann et al also found TAC to be predictive of incident stroke among young individuals and individuals with low or intermediate cardiovascular risk determined with the Framingham risk score.[28] If confirmed by other studies, the assessment of TAC in individuals with CAC scores of 0 and low Framingham risk score could further refine CVD risk prediction.

In our exploratory analysis, TAC score appeared to be further predictive of stroke mortality, although this was no longer significant after full adjustment for risk factors. Contrary to other studies which have found TAC density to be inversely associated with coronary heart disease and atherosclerotic CVD,[15,29] in our exploratory analyses, peak TAC density was directly associated with stroke mortality. Additionally, although TAC density did not significantly improve the predictive power of stroke mortality prediction beyond CAC (in addition to traditional risk factors) in our study, other studies found TAC density to significantly improve CVD risk assessment beyond CAC.[30] These variations across studies could be due to the limited number of cases with Agatston TAC scores and therefore limited power available across the study poulations.

While our study provides detailed in-depth assessment of the benefit of TAC for the prediction of stroke mortality, it has a few limitations. First, we had a small number of fatal stroke events in our study which limited our power to detect differences across categories, which could explain the lack of association between TAC and stroke mortality in men. Also, we do not have information on what part of the thoracic aorta was assessed which might limit the reproducibility of our results in other cohorts. Finally, our cohort is a clinical one, consisting of individuals referred by physicians for the CAC scan, limiting the generalizability of our results. However, since the CAC scan is not a screening tool, our results are reflective of the population who would be considered for CAC scans in daily clinical practice. Although we were only able to assess stroke mortality in our dataset, our results provide justification for future studies exploring the utility of TAC for the prediction of nonfatal stroke outcomes.

TAC is associated with stroke mortality independent of CAC and traditional risk factors, especially among females. TAC also remains predictive of stroke mortality among individuals with CAC = 0, who are generally considered to be low risk. Assessment of TAC on routine CAC scans as well as non-gated chest CTs might therefore significantly improve CVD risk prediction, particularly for stroke outcomes, at no additional cost or radiation exposure for individuals.

Author Contributions

Olufunmilayo H. Obisesan, was responsible for the generation and development of the research idea, as well as the drafting of the manuscript and editing of the figures.

Michael J. Blaha contributed to the generation and development of the research idea, obtaining funding and editing the manuscript.

Zeina A. Dardari was responsible for data management and analysis.

Albert D. Osei, Daniel Berman, S.M Iftekhar Uddin, Omar Dzaye, Olusola A. Orimoloye, Matthew J. Budoff, Michael D Miedema, John Rumberger, Mohammadhassan Mirbolouk, Ellen Boakye, Michelle C. Johansen, Alan Rozanski, Leslee J. Shaw, Donghee Han, and Khurram Nasir, were involved in critically appraising and editing the manuscript.

Disclosures

The authors declare no conflict of interest relevant to the content of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.038.

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