Association of coronary artery calcification and thoracic aortic calcification with incident peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Aims
The association of subclinical atherosclerotic disease in the coronary arteries and thoracic aorta with incident peripheral arterial disease (PAD) is unknown. We investigated the association between coronary artery calcium score (CACs) and thoracic aortic calcium score (TACs) with incident clinical and subclinical PAD.

Methods and results
The Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6814 men and women aged 45–84 from four ethnic groups who were free of clinical cardiovascular disease at enrolment. Coronary artery calcium score and thoracic aortic calcium score were measured from computed tomography scans. Participants with a baseline ankle-brachial index (ABI) < 0.90 or > 1.4 were excluded. Abnormal ABI was defined as ABI < 0.9 or > 1.4 at follow-up exam. Multivariable logistic regression and Cox proportional hazards models were used to test the associations between baseline CACs and TACs with incident abnormal ABI and clinical PAD, respectively. A total of 6409 participants (female: 52.8%) with a mean age of 61 years were analysed. Over a median follow-up of 16.7 years, 91 participants developed clinical PAD. In multivariable analysis, each unit increase in log (CACs + 1) and log (TACs + 1) were associated with 23% and 13% (P < 0.01 for both) higher risk of incident clinical PAD, respectively. In 5725 (female: 52.6%) participants with an available follow-up ABI over median 9.2 years, each 1-unit increase in log (CACs + 1) and log (TACs + 1) were independently associated with 1.15-fold and 1.07-fold (P < 0.01 for both) higher odds of incident abnormal ABI, respectively.

Conclusion
Higher baseline CACs and TACs predict abnormal ABI and clinical PAD independent of traditional cardiovascular risk factors and baseline ABI.
Introduction

In 2015, peripheral arterial disease (PAD) was estimated to affect more than 236 million adults ≥25 years of age globally. Peripheral arterial disease is a common manifestation of atherosclerosis, which is associated with coronary heart disease (CHD), all-cause mortality, and limb-threatening complications. Peripheral arterial disease progresses over time, but the majority of patients remain asymptomatic or have atypical symptoms until advanced stages of the disease. Given the high prevalence and insidious progression of PAD, it is of utmost importance to recognize the risk markers associated with incident PAD in order to identify population at risk.

Atherosclerosis is a systemic disease and the presence of atherosclerotic plaques in one vessel is often a marker of atherosclerosis in other vascular beds. The pathogenesis of atherosclerosis initiates with endothelial damage and inflammation and continues with the deposition of lipid particles and calcium in the intima layer of the artery. The quantity of calcification correlates highly with the extent of atherosclerosis burden. Both thoracic aortic and coronary artery calcifications measured by cardiac computed tomography (CCT) are established markers of subclinical atherosclerosis in the aorta and coronary arteries, respectively. On the other hand, the ankle-brachial index (ABI) is a validated non-invasive diagnostic test with high sensitivity and specificity to detect subclinical PAD. Previous cross-sectional studies have shown an association between both coronary artery and abdominal aortic calcifications with a low ABI. Increased abdominal aortic calcification was associated with higher likelihood of ABI < 0.9 in a subgroup analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) participants. In contrast, the previous study did not show any significant association between aortic arch calcification detected in chest X-ray and incident PAD. Despite these findings, little is known regarding the longitudinal association between coronary artery calcium score (CACs) and thoracic aortic calcium score (TACs) measured by CCT with incident PAD. Therefore, we aimed to investigate the association between CACs and TACs with incident abnormal ABI and clinical PAD in a multi-ethnic cohort of participants without prior cardiovascular disease (CVD).

Methods

Study population

The design of the MESA has been published previously. Briefly, MESA is a prospective observational population-based cohort study, consisting of 6814 men and women aged 45–84 years who were free of clinically apparent CVD at enrolment (Exam 1: July 2000–August 2002). Participants were recruited from six US field centres (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY;
and St Paul, MN) and self-identified their ethnicity as Caucasian, African American, Chinese American, and Hispanic. Study protocols were reviewed and approved by the institutional review boards of each participating field centre and all participants gave written informed consent.

**Measurement of covariates**

Standard questionnaires were used at Exam 1 to obtain demographics, medical and family history, medication use, smoking status (current, former, or never smoker), and highest education level. The MESA Typical Weekly Physical Activity Survey was used to gather information regarding self-reported intentional physical activities (walking for exercise, dancing, sport, and conditioning activities). The duration of each intentional activity (minutes per week) was multiplied by the metabolic equivalent (MET) level. Physical activity was recorded as MET-minutes per week of total intentional physical activities. Body mass index (BMI) was defined as weight (kg) divided by the square of height (m²). Resting blood pressure was measured three times in a seated position and the average of the last two was recorded. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation was used to estimate glomerular filtration rate (eGFR). Serum blood glucose, triglycerides, total, and high-density lipoprotein (HDL) cholesterol were measured from blood samples after 12 h of fasting. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or use of any glucose lowering medications.

**Coronary artery calcium and thoracic aortic calcium measurement**

The acquisition and interpretation methods of CCT scan in MESA have been published previously. Electron-beam computed tomography (CT) (three sites) or multi-detector CT (three sites) were used to quantify CACs. All participants underwent two consecutive scans over a calibration calcium phantom at Exam 1. All CT images were transferred to the MESA central CT reading centre (Los Angeles Biomedical Research Institute, Torrance, CA, USA) and were read by a trained physician. The Agatston method was used to quantify CACs. For each participant, the mean of two consecutive scans was recorded after calibration with the calcium phantom. Cardiac computed tomography images were also used to quantify TACs by the same method. Ascending thoracic aortic calcium score (ATACs) and descending thoracic aortic calcification score (DTACs) were quantified from the aortic annulus to the lower edge of the pulmonary artery and from the lower edge of the pulmonary artery to the cardiac apex, respectively. Thoracic aortic calcium score (TACs) is the sum of ATACs and DTACs. Aortic arch calcification could not be computed.

**Ankle-brachial index measurement**

The details of ABI measurement protocol in MESA have been reported in the past. Ankle-brachial index was measured for MESA participants in Exam 1, Exam 3 (March 2004–September 2005) and exam 5 (April 2010–February 2012). Resting systolic blood pressure in left and right brachial, dorsalis pedis and tibialis posterior arteries were measured in a supine position using a 5-mHz Doppler ultrasound probe. The leg-specific ABI was calculated as the higher systolic pressure (dorsalis pedis or tibialis posterior arteries) from that leg divided by the mean of right and left brachial systolic pressure. If the difference between bilateral brachial pressure was ≥10 mmHg, the higher brachial pressure was chosen as ABI denominator. The lower of the leg-specific ABIs (right or left) was recorded for data analysis. In this study, we excluded participants with a history of PAD, missing baseline ABI, baseline ABI <0.90 or >1.4 (non-compressible arteries). Incident abnormal ABI was defined as ABI <0.90 or >1.4 in follow-up exam. In participants with two follow-up ABI measurements (Exam 3 and Exam 5), the most recent one was used for data analysis.

**Clinical peripheral arterial disease**

Every 9–12 month, a telephone interviewer called each participant to investigate any interim hospitalizations, cardiovascular outpatient diagnoses, or procedures. MESA requested copies of death certificates and all inpatient and outpatient medical records to verify self-report diagnoses. Two cardiologists or cardiovascular physician epidemiologists reviewed and classified the clinical events independently. Full review committee made the final classification in case the two reviewers disagreed on the classification.

Peripheral arterial disease was classified as probable if a physician made the diagnosis in a symptomatic patient. Peripheral arterial disease event was defined as definite in the presence of ischaemic symptoms and one or more of the following criteria: ultrasound evidence of obstruction; an exercise test positive for claudication; revascularization for PAD; amputation for ischaemia; ABI ≤ 0.8; imaging of an abdominal aortic aneurysm; or a vascular procedure for abdominal aortic aneurysm.

**Statistical analysis**

Baseline characteristics of participants were presented as mean ± standard deviation (SD), median [interquartile range (IQR)], or frequency (%). Student’s t-test, Wilcoxon’s rank test, and χ² test were used to compare the means and median (for continuous variables) and frequency (for categorical variables) between participants with and without clinical PAD. The continuous CACs, continuous TACs, and physical activity variables were transformed using natural logarithm (log) due to the skewed distribution of the original variables.

We used Cox proportional hazards (CPHs) models to analyse the association between incident clinical PAD with both continuous log (CACs + 1) and log (TACs + 1), and categorical CACs and TACs. Three models were developed for each analysis: Model 1: unadjusted; Model 2: adjusted for age, race, BMI, systolic blood pressure, diastolic blood pressure, use of anti-hypertension medication, total cholesterol, HDL-cholesterol, triglyceride, use of lipid-lowering medication, smoking status, diabetes, the highest level of education, eGFR, and physical activity; and Model 3: Model 2 adjusted for baseline ABI.

Multivariable logistic regression was deployed to assess the association between abnormal ABI in follow-up exam with both continuous log (CACs + 1) and log (TACs + 1), and categorical CACs and TACs. Three similar models were constructed with the covariates that were used for CPH analysis. All models were adjusted for follow-up time (time between baseline and follow-up ABI measurements). We finally investigated the interactions of CACs and TACs with sex and race. The analyses were conducted using R environment (version 4.0.0) for statistical computing.

**Results**

**Association between baseline coronary artery calcium and thoracic aortic calcium scores with incident clinical peripheral arterial disease**

After excluding participants with missing ABI (n = 79), ABI < 0.90 (n = 252), or ABI > 1.4 (n = 43) at baseline or missing follow-up (n = 31), a total of 6409 participants were included in the analysis. Table 1 shows the baseline characteristics of participants. Mean age (SD) was 61.7 (10.1) and 52.8% were female. At baseline, participants with incident clinical PAD were more likely to be older men with higher prevalence of cardiovascular risk factors and higher values for baseline CACs and TACs (Supplementary material online, Table S1).
Mean baseline ABI in participants with incident clinical PAD was lower than the rest of cohort (1.10 vs. 1.13, \( P \)-value <0.001). Over a median (IQR) of 16.7 (12.7–17.5) years of follow-up, 91 participants (30 females) developed clinical PAD. In Figure 1, Kaplan–Meier survival curves show lower probability of PAD-free survival in participants with higher categories of baseline CACs (Figure 1A, log-rank test \( P \)-value <0.001) and TACs (Figure 1B, log-rank test \( P \)-value <0.001). Table 2 shows the association between baseline CACs and incident clinical PAD. In the fully adjusted model, each unit increase in log (CACs + 1) was associated with 23% \((P < 0.001)\) increased risk of incident clinical PAD. Compared to those with a CACs = 0, participants with CACs > 300 AU had 3.77 \((P < 0.001)\) higher hazard of developing clinical PAD independent of cardiovascular risk factor and baseline ABI. The association between baseline TACs and incident clinical PAD is also shown in Table 2. Each unit increment in log (TACs + 1) was associated with 13% \((P=0.005)\) increased risk of incident clinical PAD in multivariable analysis. Compared with a TACs = 0, a TACs > 100 AU was associated with 2.07 \((P = 0.009)\) higher hazard of clinical PAD independent of traditional cardiovascular risk factors and baseline ABI.

The interaction between race and CACs was statistically significant \( (P \)-values for interactions: Caucasian = ref, Chinese American: 0.01, African American: 0.67, and Hispanic: 0.13). In the race-stratified analysis, CACs (continuous variable) predicted incident clinical PAD in Caucasian and African American participants (Supplementary material online, Table S2). In Hispanics, continuous CACs was associated with clinical PAD only in unadjusted model. In unadjusted model, CACs >300 AU was associated with higher hazard of clinical PAD compared with CACs = 0 in Caucasian, African American, and Hispanic participants. This association remained statistically significant in the fully adjusted model only in Caucasian participants. All four Chinese Americans who developed clinical PAD had CACs >300 AU. There was no statistically significant interaction between CACs/TACs and sex or TACs and race.

A sensitivity analysis was performed to investigate the association between CACs and TACs with incident clinical PAD excluding abdominal aortic aneurism \((n = 20)\). The magnitude and significance of associations remained largely unchanged (Supplementary material online, Table S3) except the association between CACs 1–100 AU category and incident clinical PAD which showed reduced statistical significance in adjusted models.

### Association between baseline coronary artery calcium and thoracic aortic calcium scores with abnormal ankle-brachial index in follow-up exam

After excluding participants with missing ABI \((n = 79)\), ABI ≤ 0.90 \((n = 252)\), or ABI > 1.4 \((n = 43)\) at baseline, we included 5725 participants who had at least one ABI measured at follow-up exams. The median (IQR) time between baseline and follow-up ABI was 9.2 (8.4–9.6) years. A total of 312 participants (Supplementary material online, Table S4) developed abnormal ABI \([<0.9(n = 224) \text{ or } >1.4(n = 88)]\). Higher CACs were associated with higher odds of incident abnormal ABI in multivariable analysis adjusted for the traditional cardiovascular risk factors and baseline ABI (Table 3). Each unit increase in log (CACs + 1) was associated with 1.15-fold higher odds of incident abnormal ABI \((P < 0.001)\). Participants with CACs > 300 AU had 2.41-fold higher odds of incident abnormal ABI than participants with CACs = 0.

Table 3 shows the association between baseline TACs and incident abnormal ABI. Every 1-unit increment in log (TACs + 1)
was associated with 1.07-fold higher odds of incident abnormal ABI ($P = 0.004$). Compared to TAC = 0, TACs > 100 was associated with 1.49-fold higher odds of abnormal ABI at follow-up exam ($P = 0.014$).

There was no statistically significant interaction between race or sex and CACs or TACs.

**Discussion**

In this study, we found that calcification in the thoracic aorta and coronary arteries were significantly associated with incident abnormal ABI ($<0.9$ or $>1.4$) and clinical PAD independent of traditional cardiovascular risk factors and baseline ABI. This is the first study to
explore the longitudinal association between baseline CACs and TACs with future clinical PAD and abnormal ABI in a multi-ethnic population free of CVD including abnormal ABI at enrolment.

Atherosclerosis is a systemic progressive arterial disease characterized by endothelial damage/dysfunction, deposition of lipid particles, accumulation of inflammatory cells, and intimal calcification. Calcification in the intimal layer may propagate into the medial layer in more advance stages of atherosclerosis. Coronary artery calcium score measured by CCT is an accurate tool to assess subclinical atherosclerosis in women. In this study, baseline CACs was associated with incident ABI < 0.9 and higher odds of CACs >20 AU in both men and women. 

Table 3  Association of coronary artery calcification and thoracic aortic calcification with abnormal ankle brachial index (≤0.9 or >1.4)

|          | Model 1a | Model 2 | Model 3 |
|----------|----------|---------|---------|
|          | Events/number at risk | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| CACs     |          |         |         |         |         |         |         |
| Continuous (per log unit) | 312/5725 | 1.25 (1.20–1.31) | <0.001 | 1.16 (1.10–1.22) | <0.001 | 1.15 (1.09–1.21) | <0.001 |
| Categories | 98/3086 | Reference |         | Reference |         | Reference |         |
| 0        | 93/1439 | 2.14 (1.60–2.86) | <0.001 | 1.65 (1.21–2.26) | 0.002 | 1.65 (1.20–2.25) | 0.002 |
| 1–100    | 46/596  | 2.63 (1.82–3.76) | <0.001 | 1.79 (1.20–2.65) | 0.004 | 1.78 (1.19–2.63) | 0.005 |
| 101–300  | 75/604  | 4.54 (3.29–6.23) | <0.001 | 2.51 (1.72–3.67) | <0.001 | 2.41 (1.64–3.53) | <0.001 |
| >300     |         |         |         |         |         |         |         |
| TACs     |          |         |         |         |         |         |         |
| Continuous (per log unit) | 312/5725 | 1.21 (1.16–1.25) | <0.001 | 1.08 (1.03–1.13) | 0.002 | 1.07 (1.02–1.13) | 0.004 |
| Categories | 172/4301 | Reference |         | Reference |         | Reference |         |
| 0        | 36/481  | 2.01 (1.36–2.88) | <0.001 | 1.27 (0.84–1.86) | 0.237 | 1.24 (0.82–1.82) | 0.295 |
| 1–100    | 104/943 | 3.16 (2.43–4.10) | <0.001 | 1.54 (1.12–2.12) | 0.008 | 1.49 (1.08–2.06) | 0.014 |

Model 1: adjusted for follow-up time; Model 2: adjusted for age, race, BMI, systolic blood pressure, diastolic blood pressure, use of anti-hypertension medication, total cholesterol, HDL-cholesterol, triglyceride, use of lipid-lowering medication, smoking status, diabetes, the highest level of education, eGFR, physical activity and adjusted for follow-up time; and Model 3: Model 2 adjusted for baseline ankle brachial index (ABI).

CACs, coronary artery calcium score; CI, confidence interval; OR, odds ratio; TACs, thoracic aortic calcium score.

Aortic arch calcification was associated with higher risk of CHD in both men and women and ischaemic stroke in women. Nevertheless, the authors did not find any significant association between aortic arch calcification and incident PAD in age-adjusted and multivariable-adjusted models. We found different findings using more rigorous TAC quantification with CT scan which is more sensitive compared to chest X-ray. Additionally, we relied not only on clinical PAD but also an objective change in ABI from baseline to follow-up exam.

To the best of our knowledge, this study is the first population-based study that investigated the association between CACs and TACs with an incident abnormal ABI and clinical PAD. However, this study has limitations. First, MESA used chest CT scan images obtained to follow-up exam. Second, we have found an interaction between race and CACs in the CPH analysis. Our data suggested that the effect of CACs on the incidence of clinical PAD is different among races. However, the sample sizes within races were unbalanced, and the incidence of low ABI was widely different among races, which made the variability within races significantly different. The difference in variability and sample sizes made the hazard ratios for individual races statistically non-comparable. These findings warrant further research with larger sample size to explore this interaction. Third, in 1396 participants (out of 5725) with missing ABI measurement in Exam 5, we used ABI measurement in Exam 3 as the follow-up ABI. To mitigate this limitation, we have used the follow-up time (time between baseline and follow-up ABI measurement) as a covariate in all
logistic regression models to adjust for this variability. Finally, MESA participants were free of clinically apparent CVD at enrollment, and this must be considered before extrapolating our results to other populations.

Conclusion

Coronary artery calcium score and thoracic aortic calcium score are independent predictors of incident abnormal ABI and clinical PAD in participants of a multi-ethnic population-based cohort. Further research with larger sample size is recommended to investigate these associations in different ethnicities.

Lead author biography

Hooman Bakhshi is a third-year cardiology fellow at INOVA Heart and Vascular Institute, Falls Church, VA, USA. He is interested in interventional/structural cardiology. His research is mainly focused on using novel biomarkers including proteomics to risk stratify population at risk for developing cardiovascular disease.

Supplementary material

Supplementary material is available at European Heart Journal Open online.

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Data availability statement

Data from the Multi-ethnic Study of Atherosclerosis (MESA study) is available through the National Institutes of Health and Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) open program at https://biolinc.nhlbi.nih.gov/studies/mesa. In addition to the public access repository, interested investigators may also access the data through the MESA Coordinating Center at the University of Washington. Use of the data via this mechanism is overseen by standard MESA policies and procedures, which assure that participant consents are honored and that the topic does not overlap with previously proposed or published work.

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