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An elevated ankle-brachial index is not a valid proxy for peripheral medial arterial calcification

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ABSTRACT

Background and aims: The ankle brachial index (ABI) is often used as a proxy for medial arterial calcification (MAC) in studies investigating MAC as a cardiovascular risk factor, but evidence supporting this hypothesis is sparse. This study aims to investigate the use of an elevated ABI as proxy for MAC, as visualized with computed tomography (CT).

Methods: Cross-sectional data of 718 participants with, or at risk of cardiovascular disease was used. The ABI was calculated using cutoffs >1.4 and > 1.3. The presence of MAC was assessed in the crural and femoral arteries by CT imaging. Modified Poisson regression was used to assess the association between an elevated ABI and the presence of MAC, and test characteristics were calculated.

Results: MAC was found in 25.0% of participants. An ABI >1.4 was found in 8.7% of participants, of whom 45.2% had MAC. An elevated ABI was significantly associated with the presence of MAC (RR 1.74, CI: 1.26–2.40). However, poor positive specific agreement (23.3%, CI: 13.9–34.3), sensitivity (15.7%, CI: 10.4–21.1) and positive predictive value (45.2%, CI: 32.8–57.5) were found. Despite good specificity (93.6%, CI: 91.6–95.7) the area under the receiving operator curve remained poor (54.7%, CI: 51.8–57.6). Negative specific agreement (84.5%, CI: 81.4–87.0) and negative predictive value (77.0%, CI: 73.7–80.2) were acceptable.

Conclusions: An elevated ABI is insufficient to serve as a true diagnostic proxy for MAC. Studies that have drawn conclusions on the association between MAC and cardiovascular disease, solely based on the ABI, are likely to underestimate the found effects.

1. Introduction

The ankle-brachial index (ABI) is defined as the ratio of ankle systolic blood pressure (SBP) to brachial SBP. Derived values can be categorized into a decreased, normal range or elevated ABI, corresponding to cutoff values of ≤0.90, 0.90–1.40 and > 1.40 respectively [1,2]. A decreased ABI is an established marker of peripheral artery disease [3,4], and is used as a tool for the diagnosis of end stage atherosclerotic disease in a symptomatic population [1,2]. Furthermore, a decreased ABI has been associated with an increased risk for future cardiovascular disease (CVD) events and total mortality [5,6]. For an elevated ABI, similar associations with CVD events [6–8] and total mortality [5,9,10] are found. However, in contrast to the established relationship between a decreased ABI and the presence of atherosclerotic disease [3], less is known about the underlying pathophysiological mechanism responsible for the observed increased cardiovascular risk in a population with an elevated ABI.

A commonly proposed hypothesis states that an elevated ABI is the result of vascular stiffening, caused by calcification of the medial layer of the artery. This medial arterial calcification (MAC) or Mönckeberg's

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sclerosis, is a specific type of non-atherosclerotic vascular calcification that occurs through mineralization of the elastin fibers in the vascular smooth muscle cells and the internal elastic lamina, that will ultimately lead to reduced vascular compliance [11–13]. The theory stating that MAC is responsible for an elevated ABI is generally accepted and included in current guidelines [2,14–16]. As a result, the ABI is used as a direct proxy for MAC in studies investigating MAC as CVD risk factor [17–21]. However, evidence supporting this hypothesis is limited. Only two clinical studies directly investigated the relationship between an elevated ABI and the presence of MAC, showing an acceptable specificity and positive predictive value (PPV), but a poor sensitivity of 15.7%–30.9% [22,23]. Furthermore, these studies are limited by small sample sizes, specific study populations of people with type 1 and 2 diabetes and the use of X-ray to detect MAC, raising the question whether it is justified to use an elevated ABI as a proxy for MAC.

Therefore the primary aim of this study was to evaluate the test characteristics of an elevated ABI as a proxy for MAC in a population with, or at risk of cardiovascular disease as assessed by a histopathologically validated computed tomography (CT) score. Secondly, we aimed to analyze the association between an elevated ABI and the presence of MAC.

2. Materials and methods

2.1. Study population

The ARTEMIS study is a cross-sectional study that aimed to assess risk factors associated with vascular calcification in 718 participants with, or at high risk of vascular disease. This study is comprised of participants from two ongoing cohort studies; the Second Manifestations of ARTerial disease (SMART) study and the Diabetes Care System (DCS) cohort. The study was approved by the medical ethics review board of the University Medical Center Utrecht (METC 14/444), and all participants provided written informed consent. In both cohorts, only participants with bilateral lower limb amputations were excluded.

An extended description of the study population and detailed information on the research design and methods of the separate cohorts has been published previously [24–26]. In short, the SMART study is an on-going cohort study with participants aged 18–79 years with, or at high risk of CVD due to hypertension, diabetes or other cardiovascular risk factors. Participants who were newly referred to the University Medical Center Utrecht with either manifest vascular disease or important cardiovascular risk factors were invited to participate in the SMART cohort and were asked to undergo an additional unenhanced thin-slice CT scan of the legs. In total 520 participants gave informed consent and were included in a period from March 2015 until December 2017. The DCS cohort is an ongoing cohort of over 15,000 people with type 2 diabetes aged 50–75 years from the region of West Friesland (the Netherlands). Participants were referred to the DCS study center by their general practitioner after diagnosis of type 2 diabetes mellitus. The DCS study center provides annual monitoring of glycemic control and diabetes related risk factors and complications. Between June 2017 and February 2018 participants were invited for an additional ABI measurement and an unenhanced thin-slice CT scan of the legs and the thorax, 198 participants gave informed consent and were included.

2.2. Ankle brachial index

ABI measurements were conducted by an experienced researcher using a Vasoguard dopplerprobe (8 MHz). For each ankle, the highest SBP of the posterior tibial and dorsalis pedis (both measured twice) was used for the ABI calculations. An average SBP was calculated for each arm from at least two measurements of the brachial artery. The arm with the highest average was used for the ABI calculations. The leg-specific ABIs were thus calculated by dividing the highest average arm SBP by the highest of the ankle pressures of that leg. Incompressibility of the artery, defined as the inability to obtain an ankle SBP below 250 mmHg, was registered and if present the participants were categorized as having an ABI >1.4. ABI cutoff points were based on most recent guidelines in which a lower limit of ≤0.90 and an upper limit of >1.40 were used [1,2]. As a secondary analysis, a more liberal cutoff of >1.30 was used. In five participants the ABI was not obtained. These cases were excluded from the analysis.

2.3. Assessment of MAC

Participants underwent an unenhanced CT scan of the legs (femoral head to feet, slice thickness 1 mm, increment 0.7 mm). The presence and morphology of arterial calcification at the level of the femoral and crural arteries was scored by an experienced radiologist, blinded for participants characteristics, using a semi-quantitative scoring system based on a previously developed and histopathologically validated algorithm for scoring calcification at the level of the intracranial internal carotid artery in which different morphologic characteristics (circularity (absent, dot(s), <90°, 90–270°, 270–360°), thickness (absent, ≥1.5 mm, <1.5 mm), morphology (indistinguishable, irregular/patchy, continuous)) are combined. Based on the overall score, calcification patterns that show a high degree of circularity, thin and continuous calcifications are categorized as being predominant MAC, while low degree of circularity, thick and patchy calcifications are categorized as being predominant IAC. When no calcification was noticeable, the calcification was scored as absent and if a calcification was visible, but too small to assign any morphological characteristics to, it was classified as indistinguishable. Concordance between the CT score and the histopathologic dominant calcification type was reasonable and the score showed good reproducibility (kappa: 0.72 proportion of agreement: 0.82) [27]. Recently this algorithm was used to score calcification at the level of the crural and femoral arteries of 204 patients without known peripheral artery disease, showing a strong correlation between annular, thin and continuous calcification on the one hand and dot-like thick and patchy calcification on the other hand, indicating clusters of medial and intimal calcification [28]. All 718 participants included in our study underwent an unenhanced CT scan of the legs, a calcification score was derived at the level of the crural and femoral arteries in 718 and 713 participants respectively. In five participants the femoral calcification score was not obtained due to insufficient quality of the images, these cases were excluded from the analysis.

2.4. Covariates

In SMART, all participants underwent a comprehensive screening at baseline, including questionnaires on medical history and medication use. In DCS, this information was extracted from the medical records, which were obtained during the annual visits. Medical history of manifest CVD was categorized as coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm and peripheral artery disease which is diagnosed as Fontaine stage II-IV. In both cohorts, smoking was self-reported and classified as never, former and current smoker. Anthropometric measurements including weight and height were taken and blood pressure was obtained in seated position. Hypertension was defined as a SBP of ≥140 mmHg, a diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medication. Fasting blood samples were drawn for measurement of blood lipids. Hyperlipidemia was defined as a total cholesterol ≥5 mmol/L, LDL-cholesterol ≥3.2 mmol/L and/or use of lipid-lowering medication. Furthermore, glomerular filtration rate (eGFR) was estimated using the CKD-EPI formula [29]. SMART participants were diagnosed with diabetes mellitus when there was a referral diagnosis of diabetes mellitus, self-reported diabetes mellitus, the use of glucose-lowering agents or a baseline fasting plasma glucose ≥7 mmol/L and a definitive diagnosis of diabetes during the first year of follow-up. In the DCS cohort, type 2 diabetes mellitus was reported when a participant had at least one or more classic symptoms and fasting plasma

glucose ≥7.0 mmol/L or random plasma glucose ≥11.1 mmol/L or in the absence of symptoms, two elevated fasting plasma glucose concentration on two different time points when no symptoms are present.

2.5. Statistical analyses

Baseline characteristics were presented as means with standard deviations for continuous variables, or number of cases with percentages for categorical variables. Additionally, baseline characteristics were calculated according to the presence of predominantly MAC in both crural and femoral arteries.

Two-by-two tables were constructed on the presence or absence of a predominantly MAC pattern for both crural and femoral arteries against elevated ABI using both ABI values of >1.4 and > 1.3 as cutoffs. Evaluation of the test agreement characteristics was assessed by calculating the proportion of specific agreement (SA) according to de Vet et al. [30, 31]. SA can be calculated for a positive outcome as well as a negative outcome, and with regard to our results can be interpreted as the probability of finding an elevated ABI and a MAC pattern on CT scan in the same participant, and as the probability of finding a normal or decreased ABI and absence of a MAC pattern on CT scan in the same participant respectively. Test validity was assessed on all the constructed two-by-two tables by calculating sensitivity, specificity, PPV and negative predictive values (NPV), furthermore a receiver operating characteristic (ROC) analysis was performed. As an additional analyses, test characteristics were calculated in a subgroup of people with, and without hypertension.

Lastly, the association between an elevated ABI, using cutoffs of >1.4 and > 1.3, and the presence of a predominant MAC pattern was investigated using a modified Poisson regression with robust error variance, which was preferred over standard logistic regression since it avoids overestimation of the odds ratio in case of a highly prevalent outcome variable [32]. The analysis was adjusted for age, sex and clinic site. Smoking status, history of type 2 diabetes and history of manifest CVD were assessed as effect modifiers by including interaction terms in the model in which a *p*-value of <0.10 was considered significant.

All analyses were performed using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided *p*-values of <0.05 were considered statistically significant.

3. Results

3.1. Participant characteristics

A total of 718 participants were included in the study. Their mean age was 62.0 ± 10.6 years and 522 (76.9%) were male. Table 1 reports the distribution of demographic variables and risk factors in the total study population and among individuals with and without the presence of a predominantly MAC pattern on CT scan. Supplementary Table I reports the distribution of demographic variables and risk factors for each of the ABI categories (>1.4, 1.4–0.9, ≤0.9). Individuals with MAC were older, more frequently male, more likely to have diabetes mellitus and were less likely to be current smokers.

An overview of the prevalence of the different calcification patterns as scored on CT scan for each of the ABI categories (>1.4, 1.4–0.9, ≤0.9) is detailed in Table 2 for both the crural and femoral arteries. The prevalence of calcification pattern per ABI category using a cutoff of >1.3 is provided in Supplementary Table II. When using a cutoff of >1.4, an elevated ABI was found in 62 (8.7%) participants, a normal range ABI was found in 607 (85.1%) participants, and 46 (6.5%) participants had a decreased ABI (ABI ≤0.9). When using a cutoff of >1.3 an elevated ABI was found in 143 (20.1%) participants.

Among individuals with an ABI of >1.4, a predominant MAC pattern at the level of the crural artery was found in 45.2% (95% CI, 33.9–59.2). Among participants with a reference range or a decreased ABI, a MAC pattern was found in 22.7% (95% CI, 18.6–27.1) and 27.3% (95% CI, 13.6–43.2) respectively (Table 2). Using a cutoff of >1.3, a slightly

Table 1
Distribution of demographic variables and risk factors in the total study population and among individuals with and without MAC, assessed in both the crural and femoral artery.

	Total population	Crural		Femoral	
		No MAC[a]	MAC	No MAC[a]	MAC
N =	713	535	178	512	196
Age (years)	62.0 ± 10.6	60.5 ± 10.8	66.5 ± 8.5	60.6 ± 11.0	65.5 ± 8.8
Male sex	547 (76.7%)	389 (72.7%)	158 (88.8%)	381 (74.4%)	164 (83.7%)
BMI, kg/m^2	28.1 ± 4.4	27.9 ± 4.3	28.6 ± 4.7	28.0 ± 4.4	28.2 ± 4.6
Hypertension[c]	425 (59.6%)	313 (58.5%)	112 (62.9%)	289 (56.4%)	132 (67.3%)
- Systolic blood pressure	132.9 ± 17.1	132.3 ± 16.3	134.5 ± 19.2	132.2 ± 16.3	134.5 ± 18.8
- Diastolic blood pressure	78.4 ± 9.1	78.8 ± 9.1	77.2 ± 8.7	78.6 ± 9.2	77.8 ± 8.5
- Use of antihypertensive medication	402 (56.4%)	296 (55.3%)	106 (59.6%)	273 (53.3%)	126 (64.3%)
Hypercholesterolemia	247 (34.6%)	181 (33.8%)	66 (37.1%)	170 (33.2%)	73 (37.2%)
Diabetes (type 1 or 2)	276 (38.7%)	185 (34.6%)	91 (51.1%)	174 (34.0%)	97 (49.5%)
- Type 2 diabetes	273 (38.3%)	184 (34.4%)	89 (50.0%)	172 (33.6%)	96 (49.0%)
eGFR (ml/min/1.73m^2)	85.4 ± 25.0	85.0 ± 25.2	86.5 ± 24.2	84.5 ± 24.5	88.2 ± 26.0
Smoking					
- Never	216 (30.3%)	148 (27.7%)	68 (38.4%)	128 (25.0%)	85 (43.8%)
- Former	361 (50.6%)	267 (50.0%)	94 (53.1%)	266 (52.0%)	93 (47.9%)
- Current	134 (18.8%)	119 (22.3%)	15 (8.5%)	118 (23.0%)	16 (8.2%)
Manifest cardiovascular disease					
- Peripheral artery disease [b]	36 (5.0%)	31 (5.8%)	5 (2.8%)	32 (6.3%)	4 (2.0%)
- Cerebrovascular disease	106 (14.9%)	87 (16.3%)	19 (10.7%)	83 (16.2%)	23 (11.7%)
- Coronary artery disease	405 (56.8%)	293 (54.8%)	112 (62.9%)	287 (56.1%)	118 (60.2%)
- Abdominal aortic aneurysm	26 (3.6%)	20 (3.7%)	6 (3.4%)	20 (3.9%)	6 (3.1%)

Baseline characteristics are described as mean ± standard deviation or number of participants (%). BMI: body mass index, eGFR: estimated glomerular filtration rate (according to CKD_EPI formula).

[a] No MAC: participants without predominantly medial arterial calcification (e.g. predominantly intimal calcification, indistinguishable calcification, no calcification).

[b] Peripheral artery disease: Fontaine stage II-IV.

[c] Hypertension: systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medication.

Table 2
Predominant calcification pattern in the crural and femoral arteries according to ABI categories, using ABI >1.4

	Crural				Femoral			
	MAC	No calcification	IAC	Indistinguishable	MAC	No calcification	IAC	Indistinguishable
N =	178	215	217	103	196	161	270	81
ABI >1.4	28 (45.2%, 33.9–59.2)	21 (33.9%, 22.6–47.9)	6 (9.7%, 0.0–23.7)	7 (11.3%, 0.0–25.3)	31 (50.0%, 38.7–63.6	17 (27.4%, 16.1–41.0)	7 (11.3%, 0.0–24.9)	7 (11.3%, 0.0–24.9)
ABI 0.9–1.4	138 (22.7%, 18.6–27.1)	187 (30.8%, 26.7–35.2)	190 (31.3%, 27.2–35.7)	92 (15.2%, 11.0–19.6)	157 (26.1%, 21.9–30.5)	140 (23.3%, 19.1–27.6)	232 (38.5%, 34.4–42.9)	73 (12.1%, 8.0–16.5)
ABI ≤ 0.9	12 (27.3%, 13.6–43.2)	7 (15.9%, 2.3–31.8)	21 (47.7%, 34.1–63.6)	4 (9.1%, 0.0–25.0)	8 (18.2%, 6.8–31.9)	4 (9.1%, 0.0–22.8)	31 (70.5%, 59.1–84.2)	1 (2.3%, 0.0–16.0)

ABI described as number of participants and percentage grouped by ABI score. ABI: Ankle brachial index.

decreased prevalence of 38.5% (95% CI, 30.1–47.2) for MAC was found for the elevated ABI category (Supplementary Table II). Similar results were found for a predominant MAC pattern at the level of the femoral artery (Table 2).

3.2. Test characteristics

The test agreement for an ABI >1.4 as a proxy for a predominant MAC pattern at the level of the crural arteries showed a positive SA of 23.3% (95% CI, 13.9–34.3) and a negative SA of 84.5% (95%CI, 81.4–87.0). Using a cutoff of >1.3, a slightly higher positive SA was observed. Similar results were found for a MAC pattern at the level of the femoral arteries (Table 3). A sensitivity of 15.7% (95% CI, 10.4–21.1), specificity of 93.6% (95% CI, 91.6–95.7), PPV of 45.2% (95% CI, 32.8–57.5) and a NPV of 77.0% (95% CI, 73.7–80.2) were found for an ABI >1.4 as a proxy for MAC at the level of the crural arteries. ROC analysis showed an area under the curve of 54.7% (95% CI, 51.8–57.6). When using a cutoff of >1.3, a slight increase in sensitivity was observed, however accompanied by a decrease in specificity resulting in a comparable area under the area under the ROC curve of 57.2% (95% CI, 53.5–61.0). Similar results were found for the test characteristics of the ABI as a proxy of femoral MAC pattern (Table 3). When comparing the test characteristics of people with hypertension or the use of antihypertensive agents (Supplementary Table IV) to those without (Supplementary Table V), a minimal improvement of positive test characteristics was observed in the group of hypertensive participants, albeit overall test characteristics remain poor.

3.3. Association between an elevated ABI and the presence of a predominant medial calcification pattern

Compared to participants showing non-medial or absent arterial calcification, an elevated ABI was associated with a higher prevalence of predominant MAC in the crural, as well as in the femoral artery. This

Table 3
Test characteristics (95% CI) of an elevated ABI as a proxy for the presence of a predominant MAC pattern in the crural and femoral arteries.

		Crural MAC (95% CI)	Femoral MAC (95% CI)
ABI ≥ 1.4			
Test agreement	Positive specific agreement	23.3% (13.9–34.3)	24.0% (14.5–35.1)
	Negative specific agreement	84.5% (81.4–87.0)	83.1% (79.9–85.7)
Test validity	Sensitivity	15.7% (10.4–21.1)	15.8% (10.7–20.9)
	Specificity	93.6% (91.6–95.7)	93.9% (91.9–96.0)
	Positive predictive value	45.2% (32.8–57.5)	50.0% (37.6–62.4)
	Negative predictive value	77.0% (73.7–80.2)	74.5% (71.1–77.8)
	ROC area under the curve	54.7% (51.8–57.6)	54.9% (52.1–57.6)
ABI ≥ 1.3			
Test agreement	Positive specific agreement	34.3% (26.7–42.0)	32.4% (25.0–40.1)
	Negative specific agreement	80.9% (77.4–83.8)	78.7% (75.1–81.8)
Test validity	Sensitivity	30.9% (24.1–37.7)	28.1% (21.8–34.4)
	Specificity	83.6% (80.4–86.7)	82.8% (79.5–86.1)
	Positive predictive value	38.5% (30.5–46.4)	38.5% (30.5–46.4)
	Negative predictive value	78.4% (75.0–81.8)	75.0% (71.5–78.6)
	ROC area under the curve	57.2% (53.5–61.0)	55.4% (51.9–59.0)

association was found for both ABI cutoff points of >1.4 (crural RR 1.80 (95% CI, 1.32–2.45), femoral RR 1.74 (95% CI, 1.26–2.40)) and >1.3 (crural RR 1.42 (95% CI, 1.10–1.83), femoral RR 1.58 (95% CI, 1.23–2.04)) (Supplementary Table III). Effect modification by smoking status, diabetes mellitus or manifest CVD was not found.

4. Discussion

The primary aim of this study was to evaluate the test characteristics of an elevated ABI as a proxy for a MAC in a population with, or at high risk of CVD. A true proxy has to be able to accurately categorize abnormalities with as little false positives and false negatives as possible, in other words with a close to perfect sensitivity and specificity. Furthermore, these results have to be in agreement with pre-existing diagnostic tests, which should be reflected in an acceptable positive SA. Our results show a poor positive SA ranging from 23.3% to 34.3%, as well as low sensitivities ranging from 15.7% to 30.9%, resulting in a poor area under the ROC curve. However, acceptable negative test characteristics are found, with a negative SA ranging from 78.7% to 84.5%, specificities ranging from 82.8% to 93.9% and NPV's ranging from 74.5% to 78.4%. Analyses of test characteristics at the level of the crural and femoral artery yielded similar results.

When comparing our results to the only two prior studies that directly assessed this relationship, similar results were found. A study by Ix. et al. performed in a population of 185 people with type 1 diabetes reported a sensitivity and specificity of respectively 14% and 99%. The PPV found in our study differs from the reported PPV of 93% found by Ix et al. However, this finding was based on a small number of participants having a ABI of >1.3 (N = 15) and therefore should be interpreted with caution [22]. In a second study, Young et al. found a high ankle systolic pressure to be a marker for MAC in a population of 137 people with diabetes (type 1 N = 51, type 2 N = 86) and 50 age-, and sex-matched healthy control subjects, results showing a sensitivity of 43.2% and a specificity of 90% [23].

Nevertheless, a positive association between an elevated ABI and the presence of MAC in the crural and femoral arteries was observed. This indicates that, even though test characteristics show that an elevated ABI is not a valid proxy for MAC, MAC is able to give rise to elevation of the ABI. To our knowledge no prior studies investigated the association between an elevated ABI and the presence of MAC at the level of the peripheral arteries. A study by Iribarren et al. investigated the association between the ABI and breast arterial calcification (BAC) in a population of 3800 postmenopausal women who were free of symptomatic CVD at baseline. BAC is thought to be predominantly medial in nature [33,34]. They found that, even though the presence of BAC was associated with an ABI <0.90, no association between BAC presence or BAC gradation with an elevated ABI (>1.30) was found [35]. These results are at odds with our findings, which might be due to the difference in study population as well as due to the small number of participants with an elevated ABI (N = 26, 0.7% of total study population). Furthermore, even though BAC is believed to be a specific and useful marker for MAC [36], measurements taken by Iribarren et al. are not within the same vascular bed and can therefore not be compared with our results.

Although physiologically, MAC in the crural arteries would be expected to affect the ABI to a larger extent than the femoral arteries, our results showed similar test characteristics of an elevated ABI as a proxy for MAC in the crural and femoral arteries. These findings support the hypotheses that, even though MAC is more expressed in the distal arteries, calcifications are not bound to a single arterial bed, and a predominant calcification pattern can be found within one individual. This hypothesis is supported by a previously executed study in our cohort in which a good absolute agreement of 69% across crural and femoral arteries for predominant calcification pattern was found [26].

Overall, the significant association between an elevated ABI and a predominant MAC pattern, as measured on CT scan, implies that MAC can give rise to an elevated ABI. Nevertheless, the poor overall test characteristics indicate that the ABI is not strong enough to serve as a true diagnostic proxy and should not be advocated as such. Prior studies that have drawn conclusions on the association between MAC and CVD, solely based on ABI measurements as a proxy for MAC, should therefore be interpreted with caution since they are likely to underestimate the effect strength due to the high level of false negatives in the classification of MAC by means of the ABI.

It is likely that an elevated ABI is the result of a multifactorial process in which, besides MAC, a variety of other factors play a role. One proposed mechanism is exaggerated pulse pressure amplification. The pulse pressure, described as the difference between diastolic and systolic blood pressure, amplifies as the energy wave generated by the heart travels to the periphery with summation of forward and reflected waves as a normal physiological process. Exaggerated pulse pressure amplification occurs when a physiological pulse pressure is over amplified due to a variety of factors, resulting in an elevated ABI. Research shows that this phenomenon occurs in healthy individuals and is not associated with an increased cardiovascular risk [37]. A second factor postulated to interfere with the ABI is the amount of appendicular muscle mass, especially in obese as well as in muscular individuals [38,39]. Furthermore, non-calcific mechanisms affecting the structure of the vascular wall might give rise to increased vascular stiffness and an elevated ABI. Degradation of the elastin fibers due to aging or oxidative stress is believed to contribute to arterial stiffness. Damaged elastic fibers are generally not replaced, resulting in a decreased elastin to collagen ratio which shifts the arterial mechanical properties to the stiffer range [40,41]. Elastin degradation and calcification have been shown to interact, but are also believed to give rise to arterial stiffness independently from each other [42] and might therefore have similar effects on the ABI even though the underlying pathophysiological mechanisms differ from each other. Lastly, the effects of having concomitant types of peripheral artery disease on the ABI is not fully known. Pseudo normalization or even reversal of the ABI are observed in populations with vascular or systemic comorbidities [42,43].

The main limitation of our study is the use of a CT scan as a surrogate endpoint for MAC since histopathology, the standard of reference, is not feasible to obtain in large populations. Orr et al. showed that plain x-ray images of vascular calcifications can differentiate between IAC and MAC [44], however plain x-ray is limited by its two dimensionality and is therefore not easy to standardize and quantify. To overcome this, a radiology-histology validated CT score was developed by Kockelkoren et al. at the level of the carotid syphon. Concordance between the CT score and the histopathologic dominant calcification type was reasonable and the score showed good reproducibility (kappa: 0.72 proportion of agreement: 0.82) [27]. Recently, two large imaging studies applied this score on the crural and femoro-popliteal arteries, showing that an accurate distinction can be made between different calcification patterns in these vascular beds [26,28]. By using this score, different calcification patterns can be assessed in a population in a standardized way, therefore overcoming the limitations set by X-ray. Even though radiology is the best available option, it remains less sensitive compared to histopathology. Using radiology as a reference will likely result in an underestimation of the degree of calcification in which the more severe forms calcification will be accurately detected but lighter forms will be missed [12,45]. However, despite a decreased sensitivity, it is believed radiology remains sufficiently specific, in other words when MAC is found on CT, it is highly likely that the participant has true MAC. Since our conclusions are mainly based on sensitivity estimates, which rely solely on the presence and not on the absence of MAC, we argue this a valid conclusion even though a suboptimal technique is used to detect MAC. The strengths of this study include the relatively large sample size, and the use of a relevant population of people with or at risk of CVD.

In conclusion, an elevated ABI is associated with the presence of a predominant MAC pattern as diagnosed on CT scan. Even though acceptable negative test characteristics are found, the overall test characteristics are poor, and illustrate that an elevated ABI is not valid in

serving as a true diagnostic proxy for MAC. Consequently, prior studies that have drawn conclusions on the association between MAC and CVD, solely based on ABI measurements as a proxy for MAC, should be interpreted with caution since they are likely to underestimate the effect strength.

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Author contributions

Anna G. Hoek contributed to conception and design, acquisition, analysis, and interpretation, drafted the manuscript, critically revised it and gave final approval. Pim A. de Jong, Petra J. M. Elders and Joline W. J. Beulens contributed to conception and design, acquisition, analysis, and interpretation and critically revised the manuscript. Sabine R. Zwakenberg, Wilko Spiering, Jonas W. Bartstra, Teddo Doesburg, Amber A. van der Heijden and Yvonne T. van der Schouw contributed to conception and interpretation and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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