Arterial calcification at different sites and prediction of atherosclerotic cardiovascular disease among women and men

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ABSTRACT
Background and aims: The sex-specific contributions of arterial calcification to atherosclerotic cardiovascular disease (ASCVD) risk prediction and stratification in the light of recent modifications by cardiovascular prevention guidelines remain unclear. We assessed the sex-specific value of calcification in different arteries, beyond the Pooled Cohort Equations (PCE) risk factors, for 10-year ASCVD risk prediction.

Methods: From 2003 to 2006, participants from the population-based Rotterdam Study (n = 2167) underwent CT to quantify coronary artery calcification (CAC), aortic arch calcification (AAC), extracranial (ECAC) and intracranial carotid artery calcification (ICAC). Follow-up for ASCVD was complete on January 1, 2015. We refitted the PCE (base model), and categorized participants into low (<5%), borderline (5%-7.5%), intermediate (7.5%-20%), and high (≥20%) ASCVD risk. We extended the models with calcifications and calculated c-statistics and net reclassification improvements for events (NRI e) and non-events (NRI ne).

Results: CAC predicted ASCVD in women [hazard-ratio (95%-CI) per 1-SD: 1.40 (1.14-1.73)] and men [1.62 (1.27-1.93)]. After addition of CAC to the base model, the c-statistic improved from 0.71 to 0.72 in women; from 0.65 to 0.68 in men. Addition of CAC led to NRI e of 14.3% in women, 4.8% in men and NRI ne of 1.5% in women, 15.1% in men. Only in women, ICAC predicted ASCVD [hazard-ratio (95%-CI) per 1-SD: 1.62 (1.26-2.08)], and improved the model (c-statistic from 0.71 to 0.73, NRI e: 9.8% and NRI ne: 5.9%).

Conclusions: Assessment of CAC improves ASCVD risk prediction and stratification. In women, the added value of ICAC for ASCVD risk prediction is comparable to that of CAC.

1. Introduction

Major society guidelines on primary prevention of cardiovascular disease recommend estimation of individuals’ 10-year global cardiovascular risk to guide decision-making for preventive interventions. Based on the premise that coronary artery calcium (CAC) improves cardiovascular risk prediction and stratification [1-3], cardiovascular prevention guidelines recommend CAC as an additional tool to guide decisions regarding preventive interventions [4,5].

In the last decade, the American College of Cardiology/American Heart Association (ACC/AHA) prevention guidelines have been updated. The 2013 guidelines expanded the focus from prediction of coronary heart disease only to the broader atherosclerotic cardiovascular disease (ASCVD) with the inclusion of stroke as a key cardiovascular endpoint [4]. In the 2019 guidelines, the intermediate ASCVD risk category has been redefined to encompass those with a 10-year risk of 7.5%-20% [6]. While CAC assessment is regarded as reasonable supplemental tool to facilitate treatment decision, the added predictive ability of CAC beyond the traditional risk factors along these recent modifications in the guidelines remains unclear.

Moreover, evidence points towards a varying burden of calcification across various arteries [7,8], translating into differences in coronary heart disease and stroke risk depending on the proximity of the artery to the heart or brain [9,10]. The expanded focus of recent guidelines with
the inclusion of stroke raises questions about the value of calcification assessment in other vascular territories for ASCVD risk prediction and stratification, beyond sole assessment of CAC. As cardiovascular disease risk differs between women and men [11–13] assessment of arterial calcifications in 10-year ASCVD risk prediction should be performed in a sex-specific manner.

Within the population-based Rotterdam Study, we assessed the sex-specific contribution of coronary, aortic, and carotid calcification over traditional cardiovascular risk factors for ASCVD risk prediction. Since the 2019 guideline recommends CAC assessment mainly in the intermediate risk group, we further examined the added predictive values for the intermediate risk group.

2. Materials and methods

2.1. Study population

This study is embedded within the Rotterdam Study, a population-based cohort initiated in 1990 including adults living in the Ommoord district in Rotterdam [14]. The original study population is composed of 7893 participants aged ≥55 years. In 2000, the cohort was extended with 3011 participants who reached the age of 55 years or had moved into the study district. Each participant undergoes extensive follow-up examinations at a dedicated research center every 3–4 years. Between 2003 and 2006 a random sample of 3229 participants visiting the research center were invited to undergo a multidetector computed tomography (CT) scan to visualize calcification in the following arteries: coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries. In total, 2524 participants were scanned (response rate, 78%).

The Rotterdam Study was conducted according to the tenets of the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

2.2. Assessment of arterial calcification

We used 16-slice or 64-slice multidetector CT scanners (Somatom Sensation 16 or 64; Siemens, Forchheim, Germany) to obtain non-contrast CT images. To quantify calcification in different arteries, we performed a cardiac scan and an extra-cardiac scan that ranged from the aortic root to the circle of Willis. Coronary artery calcification (CAC), aortic arch calcification (AAC), and extracranial carotid artery calcification (ECAC) were quantified using dedicated software (Syngo Calcium Scoring; Siemens, Forchheim, Germany). Intracranial carotid artery calcification (ICAC) was quantified using a semiautomatic scoring method that allows to manually segment calcification in each consecutive CT-slice after which the calcification volume (mm$^3$) is computed using the pixel size and the slice increment [15,16]. Detailed description on the evaluation methods is provided elsewhere [7,16].

2.3. Assessment of ASCVD

The outcome measure, incident ASCVD, comprised fatal and nonfatal myocardial infarction (MI), other coronary heart disease mortality, and stroke. Information on the events was obtained through continuously monitoring of digital linkage with general practitioner files and discharge reports from medical specialists. Subsequently, research physicians adjudicated all events as described previously [17,18]. The coronary heart disease mortality definitions were based on the International Classification of Diseases, 10th revision (ICD-10) codings. All clinical information of each new fatal coronary heart disease case were reviewed by research physicians who ascertained the underlying cause of death. Detailed information on this procedure and the definitions have been reported previously [19]. Stroke was defined based on the World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting ≥24 h or leading to death, with no apparent cause other than of vascular origin. All potential strokes were reviewed by research physicians, and verified by an experienced stroke neurologist [17,18]. Follow-up for ASCVD was completed until January 1, 2015. Participants were censored at date of first ASCVD event, death due to other causes, loss to follow-up, or January 1, 2015, whichever came first.

2.4. Assessment of cardiovascular risk factors

Data collection on cardiovascular risk factors included a standardized home interview, clinical examination, and blood sampling. Blood samples were obtained to determine cholesterol- and glucose levels. Blood pressure was measured with a random-zero sphygmomanometer, and the average of two readings was used. By means of interview, we obtained information on smoking habits, and medication use. Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/L and/or the use of blood glucose-lowering medication. Information on history of cardiovascular disease, defined as myocardial infarction, stroke, and coronary revascularization procedures was obtained at baseline and during follow-up visits as described previously [17,18].

2.5. Population for analyses

Out of 2524 scans, 111 were not fully gradable for arterial calcification because of the presence of a coronary stent, pacemaker, or image artifacts, leaving a total of 2413 complete examinations with information on calcification in four arteries. From these 2413 complete examinations, 239 participants with history of cardiovascular disease and 7 participants without informed consent for ASCVD follow-up were excluded, leaving a total of 2167 participants for the analyses.

2.6. Statistical analysis

Descriptive characteristics of the study population at the time of the CT scan are shown in means ± standard deviations or medians with interquartile ranges (IQR) for continuous variables and in absolute numbers and percentages for categorical variables. To account for missing data of covariables (maximum 5.8% of missings), we used multiple imputation by chained equations (n = 5 imputations) along with age, sex, calcification volumes, cardiovascular risk factors, and ASCVD events.

Using multivariable Cox regression, we developed a prediction model for women and men separately comprising variables included in the PCE, i.e., age, total- and HDL-cholesterol, systolic blood pressure, blood pressure lowering medication, current smoking, and diabetes mellitus, with first ASCVD event as outcome. The PCE function overestimates the risk of ASCVD among older adults [20], which in turn could lead to suboptimal reflection of the added value of calcification. Therefore, we developed a model that included the same variables as the PCE, and based the coefficients on data of our own population instead of using the original PCE coefficients. Considering the nonlinearity of age and the better model fit based on the likelihood ratio test (p < 0.05), we included a restricted cubic spline with four knots for age [21]. According to this refitted model, referred to as the ‘base model’, we calculated the 10-year risk of ASCVD for each individual and categorized participants according to the 2019 ACC/AHA guideline into low-risk (<5%), borderline risk (5%–7.5%), intermediate risk (7.5%–20%), and high risk
We computed sex-specific quartiles of calcification volumes per location and defined the highest quartile as severe calcification. Next, we determined the sex-specific distribution of severe CAC, AAC, ECAC, and ICAC across the ASCVD risk categories. Likewise, we assessed the distribution of the presence and volume of calcification across the risk categories.

We examined the association between calcification and ASCVD risk by extending the sex-specific base model with single additions of calcification in each artery (Ln [calcification volume + 1 mm³]). We then assessed the incremental predictive performance of calcification. The global performance of the “base model” and “base model + calcification” was determined based on the likelihood chi-square. The discriminative ability of each model was determined using the bootstrap corrected c-statistic with 200 repetitions, to account for potential bias inative ability of each model was determined using the bootstrap corrected c-statistic with 200 repetitions, to account for potential bias in

Table 2
Baseline characteristics of the study population

|                    | Women (N = 1184) | Men (N = 983) |
|--------------------|------------------|--------------|
| Age (years)        | 69.2 (6.7)       | 69.1 (6.4)   |
| Body mass index (kg/m²) | 27.8 (4.5)     | 27.3 (3.5)   |
| Systolic blood pressure (mmHg) | 146.9 (20.3)  | 146.5 (19.5) |
| Diastolic blood pressure (mmHg) | 79.4 (10.6)  | 82.0 (10.7)  |
| Total cholesterol (mmol/L) | 6.0 (0.9)      | 5.5 (0.9)    |
| HDL-cholesterol (mmol/L) | 1.6 (0.4)      | 1.3 (0.3)    |
| Glucose (mmol/L)   | 5.6 (1.2)        | 5.8 (1.2)    |
| Current smoking (%) | 162 (13.7%)      | 188 (19.1%)  |
| Diabetes mellitus (%) | 143 (12.1%)   | 126 (12.9%)  |
| Blood pressure lowering (%) | 436 (36.8%)  | 345 (35.1%)  |
| Medication (%)     | 250 (21.1%)      | 158 (16.1%)  |
| Lipid lowering medication (%) | 85.6 (12.5-361.2) | 240.1 (39.0-787.0) |
| Volume of calcification (mm³) | 13.3 (0.0-100.5) | 30.3 (0.4-128.0) |
| Aortic arch calcification | 203.6 (36.1-710.0) | 38.9 (6.4-144.6) |
| Extracranial carotid artery calcification | 10.3 (0.0-66.9) | 38.9 (6.4-144.6) |
| Intracranial carotid artery calcification | 32.5 (4.6-107.6) | 38.9 (6.4-144.6) |
| Presence of calcification (%) | 10.3 (0.0) | 38.9 (6.4-144.6) |
| Coronary artery calcification | 869 (73.4%) | 874 (76.7%) |
| Aortic arch calcification | 1084 (93.6%) | 909 (92.5%) |
| Extracranial carotid artery calcification | 783 (66.1%) | 754 (76.7%) |
| Intracranial carotid artery calcification | 948 (80.1%) | 793 (80.7%) |

Presented is the mean (standard deviation) or median (interquartile ranges) for continuous variables and absolute number (percentage) for categorical variables. Values are based on imputed data. HDL: high-density lipoprotein, N: number of participants.

To further assess the burden of calcification beyond CAC, within the group without CAC (i.e. CAC score of zero) we calculated the proportion of individuals with presence of any and severe AAC, ECAC, or ICAC.

Additionally, to provide insight into the risk of coronary heart disease and stroke separately, we performed the analyses for CHD and stroke separately; i.e. using first coronary heart disease event (myocardial infarction, or other coronary heart disease mortality) or first stroke event as outcomes. We used Cox proportional hazard regression in our analyses to be congruent with the original PCE derivation. Since we analyzed an older population at risk for non-ASCVD death, we also used a Fine and Gray model to assess the association of calcification with coronary heart disease and stroke accounting for the competing risk of death due to other causes [23]. Finally, to be in line with the intended purpose and target population of the PCE model in clinical practice, we performed sensitivity analyses in which the risk estimation and associations of calcification with ASCVD were restricted to participants not

Table 2
Distribution of the study population across 10-year ASCVD risk categories

| 10-year ASCVD risk% | Incidence rate (95%-CI) |
|---------------------|------------------------|
| **Women, N = 1184** |                        |
| Low-risk (<5%)      | 469 (39.6)             |
| Borderline risk (5%-7.5%) | 194 (16.4)           |
| Intermediate risk (7.5%-20%) | 378 (31.9)          |
| High risk (≥20%)    | 143 (12.1)             |
| **Men, N = 983**    |                        |
| Low-risk (<5%)      | 11 (1.1)               |
| Borderline risk (5%-7.5%) | 90 (9.2)              |
| Intermediate risk (7.5%-20%) | 608 (61.8)         |
| High risk (≥20%)    | 274 (27.9)             |

a Absolute numbers (percentages) of individuals in each risk category.

b Incidence rate per 1000 person years. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval. The risk categories are defined based on the most recent American Heart Association/American College of Cardiology guidelines [5].
Hazard ratios are per 1-SD increase in ln-transformed calcification volumes, adjusted for age (restricted cubic spline), total- and high-density lipoprotein (HDL)-cholesterol, systolic blood pressure, blood pressure lowering medication, current smoking, and diabetes mellitus. CI, confidence interval; HR, hazard ratio; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcification; AAC, aortic arch calcification; ECAC, extracranial carotid artery calcification; ICAC, intracranial carotid artery calcification.

receiving lipid-lowering medication. The proportional hazards assumption was tested on the basis of Schoenfeld residuals, and was met for all analyses (p > 0.05). Analyses were performed using Stata version 15 (StataCorp).

3. Results

3.1. Study population

Baseline characteristics of the study population are shown in Table 1. The mean age at the time of CT scan was 69.2 (SD, 6.5) years and 54.6% were women. During a median follow-up of 9.3 years, 112 women and 146 men had incident ASCVD of which 49 women (44% of ASCVD events) and 89 men (61% of ASCVD events) developed coronary heart disease as first event while 63 women (56% of ASCVD events) and 57 men (39% of ASCVD events) developed stroke as the first event. The ASCVD incidence rate was 10.8, 95%-CI = 9.0–13.0 per 1000 person years among women, and 17.9, 95%-CI = 15.3–21.1 per 1000 person years among men.

Among women (N = 1184), 40% were classified as low-risk, 16% as borderline risk, 32% as intermediate risk, and 12% as high risk. Among men (N = 983), 1% were classified as low-risk, 9% as borderline risk, 62% as intermediate risk, and 28% as high risk (Table 2). The observed ASCVD incidence rate across various risk categories in men and women is also presented in Table 2. With increasing risk of ASCVD, we found a higher prevalence of severe calcification (Fig. 1) and larger calcification volumes (Supplemental Table 1). For the intermediate risk group, the presence of severe calcification in various arteries ranged from 32% to 37% in women and 21% to 24% in men (Fig. 1).

3.2. Incremental value of CAC in ASCVD risk prediction

We found a clear association of CAC with ASCVD (adjusted hazard ratio per 1-SD increase in ln-transformed CAC volume in women: 1.40, 95% CI = 1.14–1.73; and in men: 1.57, 95% CI = 1.27–1.93) (Table 3).

In both women and men, single addition of CAC improved the global performance of the base model in terms of likelihood chi-square values. In women, after addition of CAC the c-statistic improved from 0.71 (95% CI = 0.66–0.75) to 0.72 (95% CI = 0.68–0.77); in men from 0.65 (95% CI = 0.60–0.69) to 0.68 (95% CI = 0.64–0.72). In women, addition of CAC improved reclassification among those with event (NRI\text{e}= 14.3%) and without event (NRI\text{ne}= 1.5%). In men, we observed an NRI\text{e}= 4.8% and an NRI\text{ne}= 15.1%.

When we focused on only the intermediate group, 12.9% of the events (bias-corrected NRI\text{e}) and 0.3% of the non-events (bias-corrected NRI\text{ne}) were correctly reclassified in women after addition of CAC (Fig. 2A). Corresponding results for men were a bias-corrected NRI\text{e}= 3.4% and bias-corrected NRI\text{ne}= 8.6% (Fig. 2B).

3.3. Incremental value of other calcification in other arteries for ASCVD risk prediction

With the exception of ECAC in women and AAC in men, calcifications in all other arteries were associated with ASCVD risk. In particular, ICAC among women was strongly associated with ASCVD (adjusted HR per 1-SD: 1.62, 95% CI = 1.26–2.08) (Table 3). Single addition of ICAC in women improved the c-statistic from 0.71 (95% CI = 0.66–0.75) to 0.73 (95% CI = 0.69–0.77), and resulted in NRI\text{e}= 9.8% and NRI\text{ne}= 5.9%. In women, the single addition of AAC to the base model resulted in an adjusted HR of 1.47, 95% CI = 1.11–1.94, improved the c-statistic to 0.72 (95% CI = 0.68–0.76) and led to an NRI\text{e}= 10.7% and an NRI\text{ne}= 0.6% (Fig. 2A). Because ICAC in women led to a better discriminative ability than CAC, we further investigated the value of ICAC beyond CAC. The c-statistic (95%-CI) improved from 0.72 (0.60–0.77) to 0.74 (0.70–0.78) after additionally adding ICAC to the “base model + CAC”, the NRI\text{e}= 1.8%, and NRI\text{ne}= 1.0% (Supplemental Fig. 1). In men, ECAC and ICAC were associated with a higher ASCVD risk (adjusted HR per 1-SD for ECAC: 1.25, 95% CI = 1.04–1.50, and ICAC: 1.26, 95% CI = 1.05–1.51). The c-statistic improved from 0.65 (95% CI = 0.60–0.69) to 0.66 (95% CI = 0.62–0.71) by addition of ECAC and to 0.66 (95% CI = 0.62–0.70) by addition of ICAC. In men, adding ECAC led to an NRI\text{e}= 2.1% and an NRI\text{ne}= 3.4%; addition of ICAC to an NRI\text{e}= of −1.4% and an NRI\text{ne}= of 8.7% (Fig. 2B). Considering the simultaneous addition of all four calcifications, the c-statistic improved from 0.71 (95% CI = 0.66–0.75) to 0.74 (95% CI = 0.70–0.78) among women and from 0.65 (95% CI = 0.60–0.69) to 0.68 (95% CI = 0.64–0.72) among men. Among women, simultaneous addition of all calcification measures to the base model resulted in an NRI\text{e}= 12.5% and NRI\text{ne}= 1.0%. Among men, simultaneous addition resulted in an NRI\text{e}= 4.8% and NRI\text{ne}= 17.3% (Supplemental Fig. 2).

When we focused on only the intermediate group, 12.5% of the events (bias-corrected NRI\text{e}) and −0.3% of the non-events (bias-corrected NRI\text{ne}) were correctly reclassified in women after single addition of ICAC. After addition of ICAC to the “base model + CAC”, we found a net decline in reclassification of both the events and non-events (bias-corrected NRI\text{e}= -5.1%, bias-corrected NRI\text{ne}= -1.8%) (Fig. 2A).
3.4. Burden of calcification beyond CAC

Among women with a CAC Agatston score of 0, the presence of AAC, ECAC, and ICAC was 85%, 52%, and 69%, respectively. The presence of severe AAC, ECAC, and ICAC in women without CAC was 12%, 10%, and 10%, respectively. In men without CAC, the presence of AAC, ECAC, and ICAC was 79%, 49%, and 66%, while for the presence of severe calcification, this was 5%, 5%, and 2%, respectively (Supplemental Table II).

3.5. Incremental value of calcification in coronary heart disease and stroke risk prediction

Among both women and men, CAC was most strongly associated with coronary heart disease (adjusted HR per 1-SD increase in CAC volume in women: 2.30, 95% CI = 1.60–3.31; in men: 1.92 95% CI = 1.45–2.55). Addition of CAC to the base model led to an increase in c-statistic from 0.71 (95% CI = 0.64–0.78) to 0.79 (95% CI = 0.73–0.84) for coronary heart disease risk prediction in women and from to 0.62 (95% CI = 0.57–0.68) to 0.69 (95% CI = 0.64–0.74) in men. The c-statistic of the base model with stroke as outcome was 0.70 (95% CI = 0.63–0.74) in women and 0.68 (95% CI = 0.61–0.74) in men. These c-statistics did not change after addition of CAC in line with the non-significant associations. We found that ICAC was associated with a higher risk of both coronary heart disease (adjusted HR 2.07, 95% CI = 1.35–3.17) and stroke (adjusted HR: 1.40, 95% CI = 1.03–1.90) in women but not in men (Supplemental Table III). Addition of ICAC to the base model led to an increase in c-statistic from 0.71 to 0.77 (95% CI = 0.71–0.82) for coronary heart disease and from 0.69 to 0.70 (95% CI = 0.65–0.75) for stroke risk prediction in women. A complete overview of results regarding performance of the calcification measures for coronary heart disease and stroke risk prediction is provided in Supplemental Table III.

Effect estimates for the associations of calcification with coronary heart disease and stroke did not materially change after taking competing risk of death into account using a Fine and Gray model (Supplemental Table IV). Restricting the risk estimation and associations of calcification with ASCVD to persons not receiving lipid-lowering medication revealed yielded similar results (Supplemental Tables V and VI).

4. Discussion

In this population-based cohort, we found that CAC improved 10-year ASCVD risk prediction and stratification among both women and
men. Interestingly, among women, the added value of ICAC for ASCVD risk prediction and stratification was comparable to that of CAC.

To our knowledge, only one study evaluated the sex-specific value of CAC for 10-year ASCVD risk prediction [24] showing, in line with our study, a clear association of CAC with ASCVD risk among both women and men. Although CAC has been shown to be an important risk predictor in a variety of populations [3,25–29] the main focus has been on coronary heart disease. In the current study, we found that CAC was a strong predictor for coronary heart disease but not for stroke. Previous literature pertaining to the value of CAC for stroke in particular has been inconclusive. The Multi-Ethnic Study of Atherosclerosis (MESA) did not find an association of CAC, among 6698 participants aged 45–84 years, with incident stroke [30] whereas others reported CAC being an independent predictor for stroke [31,32].

We showed the ability of CAC to reclassify 10-year ASCVD risk based on established risk thresholds by the 2019 ACC/AHA cardiovascular prevention guideline [6]. The current guideline recommends CAC assessment mainly in the intermediate ASCVD risk group. Along with previous studies on coronary heart disease [1,3], we observed that assessment of CAC in the intermediate group could help to correctly reclassify individuals. In particular among women, the reclassification was more clinically relevant and coming mainly from correct reclassification of events. Nevertheless, the utility of CAC in clinical practice should be further evaluated, for example by estimating numbers needed to scan to prevent an additional ASCVD event or to reduce interventions in individuals unlikely to benefit from it.

Although CAC is often used as proxy for the systemic atherosclerotic burden, important location-specific variations may not be captured by sole assessment of CAC. Therefore, we also assessed the potential of calcification across multiple arteries to improve 10-year ASCVD risk prediction and stratification among women and men. We found that calcifications in all arteries were associated with coronary heart disease and total ASCVD risk but in varying magnitudes. Differing associations between calcification and cardiovascular disease risk depending on the vascular territory have been reported [33,34]. This is likely driven by differences in risk profiles for calcification in other arteries than only the coronary arteries. Of note, we showed sex differences in contribution of coronary heart disease and stroke to the composite ASCVD outcome; with coronary heart disease comprising 61% of ASCVD events in men and stroke comprising 56% of ASCVD events in women. While CAC remained the strongest ASCVD risk predictor in men, we found that in women ICAC in particular was a strong predictor of ASCVD. Interestingly, although in particular intracranial atherosclerosis plays an important role in the etiology of stroke [35,36], we found that ICAC was more strongly associated with coronary heart disease than with stroke, in women. This indicates that in women, besides its location-specific consequences, ICAC could also be an important marker of systemic atherosclerosis.

The high prevalence of (severe) calcification among persons without CAC in our study emphasizes the varying burden of calcification across
different vascular territories. In persons without CAC, we particularly observed a striking contrast in the presence of severe ICAC between women and men, with a noticeably higher presence of ICAC among women. Numerous studies demonstrated the value of a CAC score of zero which is associated with extremely low incident coronary heart disease event rates [24,37,38]. Considering the strong predictive value of ICAC for ASCVD prediction among women, we may argue that this protective value of CAC zero does not necessarily rule out the presence of arteriosclerosis elsewhere and subsequent risk of cardiovascular disease, in particular among women. Our results warrant further investigation into the clinical value of presence of severe calcification in other arteries among persons without CAC.

Overall, besides showing the added predictive value of CAC in both women and men, we found that the added value of ICAC to predict and correctly reclassify 10-year ASCVD risk was comparable to that of CAC in women. Moreover, after adding ICAC to the model that included CAC, ICAC showed a modest incremental value beyond CAC and traditional risk factors. Whether this modest incremental value is clinically relevant and would lead to improvements in patient outcomes remains to be investigated. This should also be weighed against associated costs and radiation exposure. It should be noted that, when evaluating calcification at various arteries, focusing on a composite cardiovascular outcome may limit estimation of personalized risks [39]. As such, in this regard coronary heart disease and stroke risk should ideally be assessed separately.

Strengths of our study include its population-based setting, availability of information on calcification measures at different sites that allowed head-to-head comparisons within the same population, access to detailed information on cardiovascular risk factors at baseline and meticulously adjudicated events during follow-up. Some limitations need to be addressed. Rotterdam Study participants are mainly of European ancestry and were relatively old at baseline. This might limit generalizability of our findings to other ethnicities and younger age groups. Although the CAC Agatston score is widely used in clinical practice, we used volumetric measures in our analyses to allow for head-to-head comparison of the contributions of calcification in different arteries to ASCVD risk assessment. In conclusion, assessment of CAC improves ASCVD risk prediction and stratification among women and men. Among women, the added value of ICAC for ASCVD risk prediction and stratification is comparable to that of CAC.

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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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.10.009.

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