Calcification in Major Vessel Beds Relates to Vascular Brain Disease

Daniel Bos, M. Arfan Ikram, Suzette E. Elias-Smale, Gabriel P. Krestin, Albert Hofman, Jacqueline C.M. Witteman, Aad van der Lugt, Meike W. Vernooij

Objective—Calcification in atherosclerotic plaques is a novel marker of atherosclerosis and is related to cardiovascular disease. However, its relationship with cerebrovascular disease has not been investigated extensively. We investigated the relationship between calcification in various vessel beds outside the brain and imaging markers of vascular brain disease.

Methods and Results—A total of 885 community-dwelling people (mean age, 66.7 years) underwent computed tomography of the coronary arteries, aortic arch, and extracranial and intracranial carotid arteries to assess arterial calcification. Brain magnetic resonance imaging scans were performed to assess cerebral infarcts, microbleeds, and white matter lesions (WMLs). Calcification in each vessel bed was associated with presence of cerebral infarcts and with larger WML volume. The most prominent associations were found between intracranial carotid calcification and WML volume and between extracranial carotid calcification and infarcts. Adjustment for cardiovascular risk factors or ultrasound carotid plaque scores did not change these results. No associations were found between calcification and cerebral microbleeds.

Conclusion—Arterial calcification in major vessel beds is associated with vascular brain disease on magnetic resonance imaging. Most notably, larger intracranial carotid calcification load relates to larger WML volumes, and larger extracranial carotid calcification load relates to the presence of cerebral infarcts, independently of ultrasound carotid plaque score. This suggests that calcification of atherosclerotic plaque yields other information in addition to merely the presence of plaques, providing novel insights into the etiology of vascular brain disease. (Arterioscler Thromb Vasc Biol. 2011;31:2331-2337.)

Key Words: atherosclerosis • calcification • epidemiology • imaging • vascular brain disease

Atherosclerosis is a systemic vascular process that is considered a major cause of cardiovascular and cerebrovascular disease.1 The more advanced stages consist of calcified plaques,1 which can be assessed noninvasively with the use of computed tomography (CT).2-3 Vessel calcification on CT is a predictor of coronary heart disease4 and a potential marker for clinical stroke.5 White matter lesions (WMLs), cerebral infarcts, and cerebral microbleeds are considered important magnetic resonance imaging (MRI) markers of vascular brain disease.6 Various studies investigating associations between atherosclerosis and MRI-defined markers of vascular brain disease found that coronary, carotid, and aortic atherosclerosis is associated with WMLs,7–11 cerebral infarcts,10–12 or cerebral microbleeds.11 However, in most of these studies, either plain radiographs8 or ultrasound-based carotid intimal-media-thickness and plaque scores7,9,12 were used to measure atherosclerosis. Although assessment of arterial calcification on CT was investigated several times in relation to clinical outcomes,13 only 2 studies used CT-assessed arterial calcification in relation to subclinical MRI markers of vascular brain disease,10–11 and they did so only in the coronary arteries. Finally, quantification of intracranial carotid calcification has hardly been performed.14

An important advantage of CT is the fact that multiple vessel beds that may have relevant effects on the brain can be examined at once. Previously, moderate correlations were found between CT calcification in the coronary arteries, aortic arch, and extracranial carotid arteries,15 suggesting that calcification in different vessel beds may have a different role in disease prediction.

Furthermore, correlations between plaque assessed by ultrasound methods and calcified plaque assessed with CT have been found to be only modest,16 supporting the hypothesis that calcified plaque may carry independent information as well.

In a large population-based study in Rotterdam, we quantified CT calcification in 4 major vessel beds, including the
intracranial carotid artery, in almost 900 participants. The purpose of this study was to explore associations between calcification in these vessel beds and MRI markers of vascular brain disease.

Methods

Study Population

This study is based on the Rotterdam Study, a prospective, population-based cohort study on determinants of diseases in the elderly. The study started in 1990, when all inhabitants of a suburb of Rotterdam with an age of 55 years or greater were invited to participate. In 2000, the original cohort of 7983 people was extended by 3011 participants with the same inclusion criteria. From 2003 onward, all participants completing a center visit were invited to undergo CT of the heart, aorta, and carotid arteries. A total of 2521 participants (response rate, 79%) were scanned. Because of the presence of a pacemaker, 6 people underwent only an aorta and carotid artery scan. Because of coronary stent implantation or image artifacts, 77 scans were not gradable, leaving a total of 2438 complete CT examinations.

From August 2005 to May 2006, 1073 participants with complete CT examinations were randomly selected for participation in the Rotterdam Scan Study, a prospective brain MRI study. At the time of invitation for MRI, all participants were aged 60 years or older. People with MRI contraindications (eg, claustrophobia) were excluded, leaving 965 MRI-eligible people. Of these, 987 participated (response rate, 93%). Because of physical inability, MRI was not performed in 12 individuals, leaving a total of 885 participants with a complete CT and MRI examination, with a mean interscan interval of 8 months (±5 months). This study was approved by the Medical Ethics Committee and the Radiation Protection Unit at Erasmus Medical Center in the Netherlands. All participants gave informed consent.

CT Acquisition and Processing

Noncontrast CT was performed using a 16-slice (n=75) or 64-slice (n=810) multidetector CT scanner (SOMATOM Sensation 16 or 64, Siemens). Using a cardiac scan and an extracardiac scan that reached from the aortic arch to the intracranial circulation (1 cm above the sella turcica), 4 vessel beds were examined: the coronary arteries, the aortic arch, and the extracranial and intracranial carotid arteries. Imaging parameters of both scans are described elsewhere. The estimated radiation dose was up to 2.1 millisievert (mSv) for the carotid artery scan. Because of coronary stent implantation or image artifacts, 77 scans were not gradable, leaving a total of 2438 complete CT examinations.

From August 2005 to May 2006, 1073 participants with complete CT examinations were randomly selected for participation in the Rotterdam Scan Study, a prospective brain MRI study. At the time of invitation for MRI, all participants were aged 60 years or older. People with MRI contraindications (eg, claustrophobia) were excluded, leaving 965 MRI-eligible people. Of these, 987 participated (response rate, 93%). Because of physical inability, MRI was not performed in 12 individuals, leaving a total of 885 participants with a complete CT and MRI examination, with a mean interscan interval of 8 months (±5 months). This study was approved by the Medical Ethics Committee and the Radiation Protection Unit at Erasmus Medical Center in the Netherlands. All participants gave informed consent.

MRI Acquisition and Processing

Brain MRI scans were obtained with a 1.5T scanner (GE Healthcare, Milwaukee, WI). The MRI protocol included a T1-weighted sequence, a proton density–weighted sequence, a fluid-attenuated inversion-recovery sequence, and a T2*-weighted gradient echo sequence. Slice thickness was 1.6 mm for all sequences except for the fluid-attenuated inversion-recovery sequence (2.5 mm). No contrast material was administered.

A previously described validated automated tissue-classification technique was used to classify WML volumes in milliliters. WMLs were automatically segmented on the fluid-attenuated inversion-recovery sequence using an atlas-based k-nearest-neighbor classifier. Lacunar and cortical infarcts were rated on the fluid-attenuated inversion-recovery, proton density–weighted, and T1-weighted sequences, and microbleeds were rated on the T2*-weighted gradient echo sequence, blinded for the results of the CT-calcification score. Microbleeds were categorized into 1 of 3 locations: lobar, deep, or infratentorial.

Covariates

Cardiovascular risk factors were assessed by interview, physical examination, and laboratory tests, as described previously. Ultrasound carotid plaque scores were calculated as follows. The common carotid artery, carotid bifurcation, and internal carotid artery were visualized over a length as great as possible and examined both left and right for the presence of plaques. Briefly, a weighted plaque score ranging from 0 to 6 was computed by adding the number of sites at which a plaque was detected, divided by the total number of sites for which an ultrasonographic image was available and multiplied by 6 (the maximum number of sites).

Statistical Analysis

Correlations between calcification in the vessel beds were calculated using Spearman’s correlation coefficient. Gender-specific quartiles

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Population Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>885</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>450 (50.8)</td>
</tr>
<tr>
<td><strong>Age, y†</strong></td>
<td>66.7±5.5</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>27.5±3.7</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td>143.8±18.5</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
<td>81.0±10.2</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>89 (10.2)</td>
</tr>
<tr>
<td><strong>Serum total cholesterol, mmol/L</strong></td>
<td>5.70±0.95</td>
</tr>
<tr>
<td><strong>Serum HDL cholesterol, mmol/L</strong></td>
<td>1.43±0.39</td>
</tr>
<tr>
<td><strong>Smoking (ever)</strong></td>
<td>600 (68.9)</td>
</tr>
<tr>
<td><strong>Use of blood pressure-lowering medication</strong></td>
<td>324 (36.6)</td>
</tr>
<tr>
<td><strong>Use of lipid-lowering medication</strong></td>
<td>199 (22.5)</td>
</tr>
<tr>
<td><strong>Ultrasound-based carotid plaque score</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>186 (21.0)</td>
</tr>
<tr>
<td>1</td>
<td>166 (18.8)</td>
</tr>
<tr>
<td>2</td>
<td>168 (19.0)</td>
</tr>
<tr>
<td>≥3</td>
<td>345 (39.0)</td>
</tr>
<tr>
<td><strong>WMIs, mL, median (interquartile range)</strong></td>
<td>3.57 (2.14 to 7.01)</td>
</tr>
<tr>
<td><strong>Cerebral infarct</strong></td>
<td>84 (9.5)</td>
</tr>
<tr>
<td><strong>Cerebral microbleed</strong></td>
<td>176 (19.9)</td>
</tr>
</tbody>
</table>

*Values are means±standard deviation for continuous variables and numbers (percentages) for dichotomous variables.
†Mean age at computed tomography examination.
were calculated because calcification load differed significantly between men and women and had a nonnormal distribution and to obtain results that were comparable to those of previous studies. In the analyses with calcification as continuous measure (per SD increase), we used natural log–transformed values and added 1.0 mm³ to the nontransformed values to deal with participants with a calcium score of zero. Because of the positive skewness of the WML volume distribution, this measure was natural log transformed.

Associations between arterial calcification and the presence of cerebral infarcts and microbleeds were assessed with logistic regression. Analyses with WML volume as the outcome were corrected for individual head size. Microbleeds were categorized as strictly lobar (restricted to lobar locations) or deep or infratentorial (deep or infratentorial location, with or without lobar microbleeds present). All analyses were performed per vessel bed. To test whether the associations found per vessel bed were independent of calcification elsewhere, a model was created in which all vessel beds were entered together. All analyses were adjusted for age, gender, and cardiovascular risk factors. Finally, all analyses were adjusted for carotid plaque scores. SPSS 17.0 was used for statistical analyses.

**Results**

Table 1 describes the characteristics of the study population. Mean age at the time of the CT scan was 66.7 (±5.5) years, and 450 subjects (50.8%) were women.

Only 9 participants did not have calcification in any vessel bed. The calcification load differed substantially between men and women. Table 2 shows the cut-off values for the gender-specific quartiles. Correlations between calcification in various vessel beds were moderate and higher in men than in women (Supplemental Table I, available online at http://atvb.ahajournals.org).

With increasing calcification volume quartile in all vessel beds, people had larger WML volumes (Table 3). The most prominent association was between intracranial carotid calcification and WML volume, especially for the fourth quartile.

### Table 2. Gender-Specific Quartiles of Calcification Distribution

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Coronary Arteries</th>
<th>Aortic Arch</th>
<th>Extracranial Carotid Arteries</th>
<th>Intracranial Carotid Arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>8.8</td>
<td>21.4</td>
<td>0.1</td>
<td>5.9</td>
</tr>
<tr>
<td>50</td>
<td>80.4</td>
<td>168.1</td>
<td>21.4</td>
<td>40.3</td>
</tr>
<tr>
<td>75</td>
<td>322.1</td>
<td>666.1</td>
<td>102.0</td>
<td>126.9</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>17.1</td>
<td>0</td>
<td>3.2</td>
</tr>
<tr>
<td>50</td>
<td>6.0</td>
<td>134.5</td>
<td>4.1</td>
<td>21.8</td>
</tr>
<tr>
<td>75</td>
<td>63.3</td>
<td>480.1</td>
<td>40.3</td>
<td>78.5</td>
</tr>
</tbody>
</table>

Values are calcification volumes in mm³.

Values represent difference in white matter lesion volume (ln-transformed) with 95% confidence intervals for each quartile of vessel calcification compared with the lowest quartile and per SD increase in ln(calcification + 1.0), standardized. Model 1: Adjusted for age, gender, and intracranial volume (ICV). Model 2: Adjusted for age, gender, ICV, and cardiovascular risk factors. Model 3: Adjusted for age, gender, ICV, ultrasound carotid plaque scores.
compared with the first. Additional adjustment for cardiovascular risk factors or ultrasound carotid plaque scores did not materially change these associations.

Arterial calcification in all vessel beds was also associated with the presence of cerebral infarcts (Table 4). After adjustment for cardiovascular risk factors and ultrasound carotid plaque scores, the association between coronary artery calcification and the presence of cerebral infarcts was no longer significant. Among the other vessel beds, the associations for extra- and intracranial carotid calcification remained the most prominent. Subtyping the infarcts into cortical and lacunar infarcts rendered the number of cortical infarcts per quartile too low to yield meaningful results. However, when analyzed per SD increase in calcification volume, aortic arch calcification was significantly associated with the presence of cortical infarcts, and both extra- and intracranial carotid calcification to the presence of lacunar infarcts (Supplemental Tables II and III).

No associations were found between calcifications and the presence of any microbleeds (Table 5). Subtyping the microbleeds according to location did not yield any associations either.

After entering all vessel bed calcifications into 1 model, the separate associations remained no longer significant except for the above-described associations between intracranial carotid calcification and WML volume and extracranial carotid calcification and the presence of brain infarcts (Supplemental Table IV). Gender-stratified analyses did not reveal different patterns between men and women (data not shown).

### Discussion

In a large sample from the general population, we found that higher CT-calcification load was associated with larger WML volume and extracranial carotid calcification and the presence of brain infarcts. Gender-stratified analyses did not reveal different patterns between men and women (data not shown).

A possible limitation concerns the fact that the calcified lesion on CT is only a part of the complete atherosclerotic plaque. The “soft” part of the plaque, which is presumed to be most vulnerable and generally does not contain calcium,1 was therefore not measured. Furthermore, it has been suggested that calcification in carotid or aortic plaques, in patients with atherosclerosis, might actually be a plaque-stabilizing agent and may reduce the risk of stroke.13,22–23 An important difference with our study is that we used calcification as an

### Table 4. Calcification in Different Vessel Beds and Presence of Cerebral Infarcts

<table>
<thead>
<tr>
<th>Location of Calcification</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st (reference)</td>
<td></td>
<td>1st (reference)</td>
<td></td>
<td>1st (reference)</td>
<td></td>
</tr>
<tr>
<td>Coronary calcification</td>
<td>1.35 (0.61, 3.00)</td>
<td></td>
<td>1.17 (0.52, 2.64)</td>
<td></td>
<td>1.04 (0.45, 2.40)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>1.45 (0.68, 3.12)</td>
<td></td>
<td>1.29 (0.59, 2.81)</td>
<td></td>
<td>1.36 (0.63, 2.93)</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>2.33 (1.13, 4.79)</td>
<td></td>
<td>1.93 (0.91, 4.09)</td>
<td></td>
<td>2.04 (0.96, 4.33)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td>1.38 (1.05, 1.82)</td>
<td></td>
<td>1.28 (0.95, 1.71)</td>
<td></td>
<td>1.34 (0.99, 1.79)</td>
<td></td>
</tr>
<tr>
<td>Aortic arch calcification</td>
<td>1.32 (0.57, 3.08)</td>
<td></td>
<td>1.39 (0.59, 3.28)</td>
<td></td>
<td>1.26 (0.54, 2.95)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>1.27 (0.55, 2.95)</td>
<td></td>
<td>1.18 (0.49, 2.80)</td>
<td></td>
<td>1.04 (0.43, 2.49)</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>3.14 (1.45, 6.82)</td>
<td></td>
<td>2.99 (1.32, 6.77)</td>
<td></td>
<td>2.72 (1.19, 6.23)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td>1.49 (1.10, 2.01)</td>
<td></td>
<td>1.41 (1.02, 1.94)</td>
<td></td>
<td>1.38 (1.00, 1.91)</td>
<td></td>
</tr>
<tr>
<td>Extracranial carotid calcification</td>
<td>2.01 (0.86, 4.72)</td>
<td></td>
<td>1.99 (0.83, 4.73)</td>
<td></td>
<td>1.93 (0.80, 4.65)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>2.11 (0.94, 4.67)</td>
<td></td>
<td>2.11 (0.94, 4.75)</td>
<td></td>
<td>2.02 (0.85, 4.83)</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>3.58 (1.68, 7.61)</td>
<td></td>
<td>3.44 (1.57, 7.52)</td>
<td></td>
<td>3.47 (1.42, 8.52)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td>1.58 (1.22, 2.06)</td>
<td></td>
<td>1.54 (1.18, 2.02)</td>
<td></td>
<td>1.61 (1.15, 2.25)</td>
<td></td>
</tr>
<tr>
<td>Intracranial carotid calcification</td>
<td>1.38 (0.58, 3.29)</td>
<td></td>
<td>1.44 (0.59, 3.48)</td>
<td></td>
<td>1.24 (0.51, 3.02)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>2.17 (0.96, 4.89)</td>
<td></td>
<td>2.16 (0.94, 4.98)</td>
<td></td>
<td>2.02 (0.88, 4.64)</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>2.95 (1.32, 6.60)</td>
<td></td>
<td>2.79 (1.21, 6.43)</td>
<td></td>
<td>2.46 (1.06, 5.73)</td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td>1.67 (1.25, 2.23)</td>
<td></td>
<td>1.63 (1.20, 2.21)</td>
<td></td>
<td>1.60 (1.18, 2.18)</td>
<td></td>
</tr>
</tbody>
</table>

Values represent odds ratios with 95% confidence intervals for each quartile of vessel calcification compared with the lowest quartile and per SD increase in ln(calcification + 1.0), standardized. Model 1: Adjusted for age and gender. Model 2: Adjusted for age, gender, and cardiovascular risk factors. Model 3: Adjusted for age, gender, and ultrasound carotid plaque scores.
indicator of atherosclerotic burden in a healthy population to study cross-sectionally how this relates to presence of vascular brain disease (instead of future events).

We found that higher CT-calcification load was related to larger WML volume. This is consistent with the findings of others who studied this only for the coronary arteries. However, we found that the associations appeared stronger when the investigated vessel bed was closer to the brain, with the most prominent association between intracranial carotid calcification and WML volume. Chung et al also reported that qualitatively graded CT calcification of the intracranial carotid artery was associated with white matter intensities. In contrast, others found no association between extracranial or intracranial carotid calcification and WMLs. Both studies assessed WMLs using a qualitative grading system instead of quantified volumes. This may have led to loss of information and misclassification, resulting in an underestimation of the true associations.

Vidal et al described a significant association between coronary calcification load and the presence of MRI-defined cerebral infarcts. We found the same results; however, after adjustment for cardiovascular risk factors and ultrasound plaque scores, these associations were no longer significant.

In our data, it was mainly calcification in the extracranial carotid artery that was associated with the presence of cerebral infarcts. This is in line with a study in stroke patients that showed an association between carotid calcification and acute lacunar infarcts on diffusion imaging, but not with 2 others who found no association. The small number of cortical infarcts did not allow us to analyze infarcts divided into cortical and lacunar infarcts per quartile of CT calcification. However, when analyzed continuously, aortic arch calcification was significantly associated with cortical infarcts, whereas both extra- and intracranial carotid calcification was associated with the presence of lacunar infarcts. It may be hypothesized that this contrast reflects the presumed underlying pathophysiology, ie, that WMLs and lacunar brain infarcts are primarily an expression of cerebral small vessel disease and that cortical brain infarcts are in large part related to embolic or stenotic disease in larger vessels.

Only 1 study reported associations between vessel calcification (coronary arteries) and cerebral microbleeds. We found no significant associations between calcification in any vessel bed and the presence of microbleeds. Categorizing microbleeds according to location did not alter these findings.

We found that calcification in the different vessel beds was correlated and that the associations with vascular brain disease were strongest when the calcification load was in the intracranial carotid artery.

### Table 5. Calcification in Different Vessel Beds and Presence of Cerebral Microbleeds

<table>
<thead>
<tr>
<th>Location of Calcification</th>
<th>Correlation with CMBs</th>
<th>Model 1</th>
<th>P Value</th>
<th>Model 2</th>
<th>P Value</th>
<th>Model 3</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary calcification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (reference)</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>1.25 (0.78, 2.04)</td>
<td></td>
<td>1.22 (0.75, 1.99)</td>
<td>1.17 (0.72, 1.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>0.84 (0.51, 1.38)</td>
<td></td>
<td>0.83 (0.50, 1.38)</td>
<td>0.80 (0.48, 1.33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>1.36 (0.85, 2.17)</td>
<td></td>
<td>1.36 (0.83, 2.23)</td>
<td>1.26 (0.77, 2.07)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td>1.01 (0.88, 1.27)</td>
<td>0.57</td>
<td>1.06 (0.87, 1.29)</td>
<td>0.59</td>
<td>1.03 (0.84, 1.25)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Aortic arch calcification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (reference)</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>0.95 (0.57, 1.60)</td>
<td></td>
<td>0.98 (0.58, 1.65)</td>
<td>0.97 (0.57, 1.63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>1.41 (0.87, 2.31)</td>
<td></td>
<td>1.46 (0.88, 2.43)</td>
<td>1.40 (0.84, 2.33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>1.41 (0.84, 2.36)</td>
<td></td>
<td>1.40 (0.81, 2.42)</td>
<td>1.42 (0.82, 2.47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td>1.12 (0.92, 1.35)</td>
<td>0.26</td>
<td>1.10 (0.90, 1.35)</td>
<td>0.34</td>
<td>1.10 (0.90, 1.35)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Extracranial carotid calcification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (reference)</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>1.10 (0.65, 1.86)</td>
<td></td>
<td>1.09 (0.64, 1.85)</td>
<td>1.07 (0.63, 1.84)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>1.05 (0.67, 1.67)</td>
<td></td>
<td>1.05 (0.66, 1.68)</td>
<td>1.00 (0.60, 1.65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>1.17 (0.74, 1.84)</td>
<td></td>
<td>1.12 (0.69, 1.81)</td>
<td>1.07 (0.61, 1.85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td>1.09 (0.91, 1.30)</td>
<td>0.34</td>
<td>1.07 (0.89, 1.29)</td>
<td>0.47</td>
<td>1.07 (0.86, 1.33)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Intracranial carotid calcification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (reference)</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>1.04 (0.63, 1.70)</td>
<td></td>
<td>1.10 (0.67, 1.81)</td>
<td>1.00 (0.61, 1.64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>0.91 (0.55, 1.51)</td>
<td></td>
<td>1.01 (0.60, 1.70)</td>
<td>0.86 (0.51, 1.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>1.45 (0.88, 2.37)</td>
<td></td>
<td>1.54 (0.92, 2.59)</td>
<td>1.40 (0.83, 2.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td>1.12 (0.94, 1.35)</td>
<td>0.22</td>
<td>1.15 (0.95, 1.39)</td>
<td>0.16</td>
<td>1.11 (0.91, 1.34)</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

Values represent odds ratios with 95% confidence intervals for each quartile of vessel calcification compared with the lowest quartile and per SD increase in ln(calcification + 1.0), standardized. Model 1: Adjusted for age and gender. Model 2: Adjusted for age, gender, and cardiovascular risk factors. Model 3: Adjusted for age, gender, and ultrasound carotid plaque scores.
disease on MRI were partly interrelated. This reflects that atherosclerosis is a generalized process and that calcification in 1 vessel bed partly reflects the vascular status elsewhere in the body. However, several associations remained when we adjusted for atherosclerosis in other vessel beds. This was mainly true for calcification in the carotid arteries, again supporting the notion that atherosclerosis in vessels closer to the brain has a larger impact on vascular brain pathology.30

When adjusted for ultrasound plaque scores, the associations between CT-assessed calcifications and vascular brain disease did not change materially. From an etiologic point of view, this indicates that the knowledge of whether or not a plaque is calcified provides additional information over plaque load alone. Another benefit of CT is that more vessel beds can be evaluated at the same time.

An important drawback that should be kept in mind, though, is that the applicability on a large scale of CT-calcification measurement is hampered by radiation exposure, especially in neurologically healthy people, and requires further research. However, we can speculate about the possibilities for clinical applicability, although such speculation is outside the scope of the present study. Nowadays, CT is being used more frequently for both diagnostic and screening purposes, for example, for assessment of coronary pathology.31 Such a CT scan provides information on both coronary and aortic calcification. Our results show that calcification in these vessel beds not only is informative regarding cardiac disease but also relates to vascular brain disease. Thus, calcium scoring in clinical practice would, for example, be informative and applicable in people who receive a CT examination for other reasons. Another important note is that newer generation CT scanners, especially dual source and dual energy scanners, will lead to much lower radiation doses in the near future.

In conclusion, this study shows that arterial calcifications in different vessel beds contribute to WML volume and the presence of cerebral infarcts. Compared with ultrasound plaque imaging, quantification of CT calcification provides additional information in regard to the pathophysiology of vascular brain disease.

Sources of Funding
The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research; the Netherlands Organization for Health Research and Development; the Research Institute for Diseases in the Elderly; the Netherlands Genomics Initiative; the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. Prof van der Lugt and Dr Vermeer were supported by Alzheimer’s Association Grant NIRC-08-91391/NIRC-09-13168. Dr Ikram was supported by Grant 2009B102 from the Netherlands Heart Foundation.

Disclosures
None.

References


Calcification in Major Vessel Beds Relates to Vascular Brain Disease
Daniel Bos, M. Arfan Ikram, Suzette E. Elias-Smale, Gabriel P. Krestin, Albert Hofman, Jacqueline C.M. Witteman, Aad van der Lugt and Meike W. Vernooij

Arterioscler Thromb Vasc Biol. 2011;31:2331-2337; originally published online August 25, 2011;
doi: 10.1161/ATVBAHA.111.232728
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/31/10/2331

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/