Aortic Valve Calcification and Risk of Stroke

The Rotterdam Study

Daniel Bos, MD, PhD; Atefeh Bozorgpourniazi, MD; Unal Mutlu, MD; Maryam Kavousi, MD, PhD; Meike W. Vernooij, MD, PhD; Adriaan Moelker, MD, PhD; Oscar H. Franco, MD, PhD; Peter J. Koudstaal, MD, PhD; M. Arfan Ikram, MD, PhD; Aad van der Lugt, MD, PhD

Background and Purpose—It remains uncertain whether aortic valve calcification (AVC) is a risk factor for stroke.

Methods—From the population-based Rotterdam Study, 2471 participants (mean age: 69.6 years; 51.8% women) underwent computed tomography to quantify AVC. We assessed prevalent stroke and continuously monitored the remaining participants for the incidence of stroke. Logistic and Cox regression models were used to investigate associations of AVC with prevalent stroke and risk of incident stroke.

Results—AVC was present in 33.1% of people. At baseline, 97 participants had ever suffered a stroke. During 18665 person-years of follow-up (mean: 7.9 years), 135 people experienced a first-ever stroke. The presence of AVC was not associated with prevalent stroke (fully adjusted odds ratio: 0.97 [95% confidence interval, 0.61–1.53]) or with an increased risk of stroke (fully adjusted hazard ratio: 0.99 [95% confidence interval, 0.69–1.44]).

Conclusions—Although AVC is a common finding in middle-aged and elderly community-dwelling people, our results suggest that AVC is not associated with an increased risk of stroke. (Stroke. 2016;47:2859-2861. DOI: 10.1161/STROKEAHA.116.015200.)

Key Words: aortic valve • calcification • computed tomography • follow-up studies • stroke

Aortic valve pathology, including aortic valve calcification (AVC), has been established as an important risk factor for major cardiac events, exerting its influence independent of traditional cardiovascular risk factors or coronary artery calcification.1–4 Interestingly, knowledge on the relation of AVC with subsequent risk of stroke remains uncertain,5,6 because of limited and conflicting data. Yet, as potential source of cardioembolism and its relatively high prevalence in the general population of ≥60 years,5,8 further evaluation of AVC in relation with future stroke is warranted.

Therefore, we investigated the relationship between presence and extent of AVC and the risk of stroke during almost 8 years of follow-up in a large sample of community-dwelling elderly.

Methods

Details on Methods are available in the online-only Data Supplement.

Setting

The Rotterdam Study is a prospective population-based study,7 in which between 2003 and 2006, multidetector computed tomography was performed in 2524 participants to assess vascular calcification, including AVC.10

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Dutch Ministry of Health, Welfare and Sports, implementing the Wet Bevolkings Onderzoek: ERGO (Population Screening Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Analysis of Aortic Valve Calcification

AVC was quantified using dedicated software (Syngo. ViaCalciumScoring; Siemens, Forchheim, Germany) and expressed in cubic millimeters. We quantified all calcified lesions (Hounsfield unit >130)11 that were located on the aortic valve cusps, including the base of the cusps, and annulus.2,12

Assessment of Stroke

Participants were continuously monitored for incident stroke using medical records. All potential strokes were reviewed by research physicians and verified by an experienced stroke neurologist.13 Follow-up for incident stroke was complete until January 1, 2014.

Cardiovascular Risk Factors

Information on cardiovascular risk factors was obtained by interview, physical examination, and blood sampling.7

American Heart Association, Inc.

Received August 23, 2016; final revision received August 23, 2016; accepted September 7, 2016.
From the Department of Radiology and Nuclear Medicine (D.B., A.B., M.W.V., A.M., M.A.I., A.v.d.L.), Department of Epidemiology (D.B., U.M., M.K., M.W.V., O.H.F., M.A.I.), and Department of Neurology (P.J.K., M.A.I.), Erasmus MC University Medical Center, Rotterdam, the Netherlands; and Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA (D.B.).

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org lookup/suppl/doi:10.1161/STROKEAHA.116.015200/DC1.

Correspondence to Daniel Bos, MD, PhD, Department of Radiology, Erasmus MC University Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail d.bos@erasmusmc.nl

© 2016 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.116.015200

2859
We investigated the association of AVC with prevalent stroke using logistic regression models and with incident stroke using Cox regression models. Adjustments were made for age, sex, scanner type, cardiovascular risk factors, prevalent coronary heart disease, prevalent atrial fibrillation, and the amount of cervical carotid artery calcification. Next, we reanalyzed all associations in people with AVC (33.1% of participants). Finally, we meta-analyzed our results with reported effect estimates from previous population-based studies on AVC and the risk of stroke.1,2,4

### Results
The population characteristics are shown in Table 1 (and separately for those without and with incident stroke in Table I in the online-only Data Supplement). AVC was present in 33.1% of the population (median volume: 57.0 mm³, interquartile range: 125.5 mm³). In total, 97 of the 2471 had suffered a stroke before the study baseline. During 18,665 person-years of follow-up (mean: 7.9 years), 135 people experienced a first-ever stroke (incidence rate: 7.2/1000 person-years): 109 ischemic origin, 14 hemorrhagic, and 12 unspecified.

We found no association between presence of AVC and prevalent stroke (fully adjusted odds ratio 0.97 [95% confidence interval {CI}, 0.61–1.53]), nor with risk of incident stroke (fully adjusted hazard ratio [HR], 0.99 [95% CI, 0.69–1.44]; Table 2). Restricting our analyses to persons with AVC

### Table 1. Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (N=2471)</th>
<th>No AVC (N=1652)</th>
<th>AVC (N=819)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69.6 (6.8)</td>
<td>68.1 (6.0)</td>
<td>72.6 (7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>51.8%</td>
<td>56.5%</td>
<td>42.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.7 (3.9)</td>
<td>27.6 (3.9)</td>
<td>27.8 (4.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>147 (20)</td>
<td>145 (19)</td>
<td>150 (22)</td>
<td>0.218</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>80 (11)</td>
<td>80 (10)</td>
<td>80 (12)</td>
<td>0.495</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.7 (1.0)</td>
<td>5.7 (1.0)</td>
<td>5.6 (1.0)</td>
<td>0.732</td>
</tr>
<tr>
<td>Serum high-density lipoprotein cholesterol, mmol/L</td>
<td>1.4 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.4 (0.4)</td>
<td>0.026</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12.5%</td>
<td>12.5%</td>
<td>13.8%</td>
<td>0.430</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>15.3%</td>
<td>15.4%</td>
<td>16.0%</td>
<td>0.012</td>
</tr>
<tr>
<td>Use of blood pressure–lowering agents</td>
<td>40.3%</td>
<td>37.5%</td>
<td>47.3%</td>
<td>0.006</td>
</tr>
<tr>
<td>Use of lipid-lowering medication</td>
<td>24.4%</td>
<td>21.2%</td>
<td>31.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalent coronary heart disease</td>
<td>8.7%</td>
<td>5.9%</td>
<td>14.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalent atrial fibrillation</td>
<td>3.7%</td>
<td>3.3%</td>
<td>4.5%</td>
<td>0.111</td>
</tr>
<tr>
<td>Cervical carotid artery calcification, mm³</td>
<td>23.7 (0.0–118.5)</td>
<td>11.5 (0.0–70.3)</td>
<td>72.6 (11.7–240.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means (SD) for continuous variables or percentages for dichotomous variables. Values represent original data without imputed values. AVC indicates aortic valve calcification.

### Table 2. Aortic Valve Calcification Volume and Stroke

<table>
<thead>
<tr>
<th></th>
<th>History of Stroke</th>
<th>Risk of Stroke</th>
<th>Risk of Ischemic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Presence vs absence of AVC</td>
<td>Model 1</td>
<td>1.46 (0.94–2.26)</td>
<td>1.06 (0.73–1.52)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>0.97 (0.61–1.53)</td>
<td>0.99 (0.69–1.44)</td>
</tr>
<tr>
<td>Restricted to sample with AVC</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Model 1</td>
<td>1.15 (0.94–1.41)</td>
<td>1.07 (0.88–1.30)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>1.05 (0.84–1.30)</td>
<td>1.05 (0.86–1.29)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, and scanner type. Model 2: as model 1, and additionally for body mass index, smoking, diabetes mellitus, systolic blood pressure, diastolic blood pressure, use of blood pressure–lowering medication, total cholesterol, high density lipoprotein cholesterol, use of lipid-lowering medication, prevalent coronary heart disease, prevalent atrial fibrillation, and cervical carotid artery calcification volume.

AVC indicates aortic valve calcification; CI, confidence interval; HR, hazard ratio; n, number of cases; N, number of persons at risk; and OR, odds ratio.

*Analysis with AVC volume as continuous measure in the persons with AVC.

†Ln (calcification volume + 1 mm³)–transformed volumes.
also did not show associations of AVC with prevalent stroke (fully adjusted OR per 1-SD increase in AVC, 1.05 [95% CI, 0.84–1.30]) or the risk of incident stroke (HR, 1.05 [95% CI, 0.86–1.29]; Table 2).

Meta-analysis of our results with those from previous population-based studies demonstrated a pooled random-effects HR for the presence of AVC on the risk of stroke of 1.10 (95% CI, 0.90; 1.36; Figure I in the online-only Data Supplement).

Discussion
In this prospective population-based study, we found no association of AVC with prevalent stroke or risk of incident stroke. Strengths of our study include the long and virtually complete follow-up (97%) for stroke and the quantitative computed tomography–based assessment of AVC. Yet, some potential limitation should also be addressed. First, some misclassification of aortic atherosclerotic calcification as AVC might have occurred. Yet, given the strong association of aortic atherosclerosis with stroke,14 this cannot explain our current findings. Second, we were not able to further classify the ischemic and hemorrhagic strokes into specific subtypes, given insufficient clinical information.

AVC is a relatively common pathology and relates to a higher risk of major coronary events and cardiovascular mortality.1–4 Remarkably, data on AVC and risk of incident stroke have been less unambiguous.5–6 Previous population-based studies demonstrated substantial variations in risk estimates,1–2,4 with HRs ranging from 1.09 to 1.38. Especially, significantly increase the risk of stroke. Thromboembolic effects of AVC may be too limited to significantly increase the risk of stroke.

Conclusions
In summary, although AVC is a common finding in middle-aged and elderly community-dwelling people, our findings suggest no association of AVC with an increased risk of stroke.

Sources of Funding
The Rotterdam Study is supported by the Erasmus MC, the Erasmus University Rotterdam, the Netherlands Organisation for Scientific Research, the Netherlands Organisation for Health Research and Development (ZonMW), 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, and the Municipality of Rotterdam.

Disclosures
None.

References
Aortic Valve Calcification and Risk of Stroke: The Rotterdam Study
Daniel Bos, Atefeh Bozorgpourniazi, Unal Mutlu, Maryam Kavousi, Meike W. Vernooij, Adriaan Moelker, Oscar H. Franco, Peter J. Koudstaal, M. Arfan Ikram and Aad van der Lugt

*Stroke*. 2016;47:2859-2861; originally published online October 13, 2016;
doi: 10.1161/STROKEAHA.116.015200

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/11/2859

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/10/13/STROKEAHA.116.015200.DC1
ONLINE SUPPLEMENT

Aortic valve calcification and risk of stroke: the Rotterdam Study
Supplementary Methods

Setting

This study was embedded in the Rotterdam Study,¹ a prospective population-based study in middle-aged and elderly persons. Between 2003 and 2006, all participants visiting the research center were invited to undergo multidetector computed tomography (MDCT) for the visualization of vascular calcifications, including AVC. In total, 2,524 participants were scanned.²

The Rotterdam Study has been approved by the medical ethics committee according to the Population Screening Act: Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants provided written informed consent.

CT acquisition

Non-contrast CT-scanning was performed with a 16-slice (n = 785) or 64-slice (n = 1,739) multidetector computed tomography (MDCT) scanner (Somatom Sensation 16/64, Siemens, Forchheim, Germany). Using an ECG-gated cardiac imaging protocol, we visualized the aortic root encompassing the aortic valves. Detailed information on imaging parameters of this scan is given elsewhere.²

Analysis of aortic valve calcification

Quantification of AVC was performed using dedicated commercially available software (Syngo.ViaCalciumScoring, Siemens, Germany), and expressed in cubic millimeters. We quantified all calcified lesions (Hounsfield unit >130),³ that were located on the aortic valve cusps, including the base of the cusps, and annulus.⁴,⁵ Inter- and intraobserver reliabilities for this method with two observers (DB, AB) on a random set of 50 scans was good to excellent (intraclass correlation coefficients were 0.94 and 0.99, respectively).

Assessment of stroke

Stroke was defined according to WHO criteria as a syndrome of rapidly developing symptoms of focal or global disturbance of cerebral function lasting 24 hours or longer or leading to death, with apparent cause of vascular origin. We assessed prevalent stroke at baseline during interview and verified these data with...
medical records. In addition, we continuously monitored participants for incident stroke through linkage between the study database and data from general practitioners. We also checked nursing home physicians’ files, data from general practitioners of participants who moved out of the district. Additional information was obtained from hospital records. All potential strokes were reviewed by research physicians and verified by an experienced stroke neurologist. We classified strokes as ischemic or haemorrhagic on the basis of neuroimaging-reports. If neuroimaging was unavailable, the stroke was classified as unspecified. Follow-up for incident stroke was complete until January 1, 2014.

Cardiovascular risk factors

Information on cardiovascular risk factors was obtained by interview, physical examination and blood sampling. Body mass index (BMI) was calculated as weight (kg)/ height² (m). Systolic and diastolic blood pressures were measured twice at the right arm and the mean of these measurements was used in the analyses. We used blood samples to determine serum total cholesterol and high-density lipoprotein (HDL) cholesterol, and glucose. Diabetes mellitus was defined as fasting serum glucose levels ≥ 7.0 mmol/L (or non-fasting serum glucose levels ≥11.1 mmol/L if fasting samples were unavailable) and/or the use of anti-diabetic therapy. Smoking status was categorized into “current”, “former”, or “never”. We assessed the use of blood pressure-lowering medication and lipid-lowering medication by interview. Prevalent coronary heart disease at time of the CT was defined as previous myocardial infarction or revascularization procedure. We also assessed prevalent atrial fibrillation at time of the CT. Finally, we assessed the amount of cervical carotid artery calcification (bifurcation) as marker of carotid artery atherosclerosis, using the extra-cardiac MDCT scan that was made at the same time as the cardiac MDCT-scan on which AVC was assessed.

Population for analysis

A total of 53 CT-scans from the 2,524 were excluded from because we were not able to measure AVC. Reasons were aortic valve replacements, image artifacts due to presence of pacemakers or coronary stent implantations, or bad image acquisition. From the remaining 2,471 participants, 97 had suffered a
stroke prior to CT-scanning, and 5 participants did not participate in the stroke follow-up, leaving 2,369 participants at risk for first-ever stroke for the longitudinal analyses.

Statistical analysis

Population characteristics were compared for persons without and with AVC, and for those without and with incident stroke using age- and sex-adjusted logistic regression. Given the right skewness of AVC-volume, a natural-log transformation was performed after 1.0 mm$^3$ was added to the original volumes in order to deal with participants with a zero calcium score [LN(AVC+1.0mm$^3$)]. We investigated the association of AVC and stroke using two strategies.

First, we investigated the relation of presence of AVC with prevalent stroke using logistic regression models, and the relationship of AVC with risk of incident stroke with Cox regression models. These models included adjustments for age, sex and scanner type (model 1), and additionally for BMI, systolic and diastolic blood pressure, use of blood pressure-lowering medication, total cholesterol, HDL cholesterol, diabetes mellitus, use of lipid-lowering medication, smoking, prevalent coronary heart disease, prevalent atrial fibrillation, and the amount of cervical carotid artery calcification (model 2).

Second, we selected only those persons with AVC (33.1% of participants) and investigated among these persons, the relation of AVC volume with prevalent stroke and risk of incident stroke, using similar regression models.

Missing values in the covariates were handled by multiple imputation (n=5). Missing values were present for body mass index (0.8%), blood pressure (0.4%), total cholesterol (1.6%), HDL cholesterol (1.6%), diabetes mellitus (6.0%), lipid-lowering and blood pressure-lowering medication (1.5%), smoking (2.9%), prevalent coronary heart disease (0.3%), prevalent atrial fibrillation (5.6%), and cervical carotid artery calcification (0.1%).

Finally, we conducted a meta-analysis using inverse variance weighting and random-effects pooling of our results with previously published studies. To ensure we did not miss studies we searched PubMed using the key-words aortic valve calcification, aortic valve sclerosis, and stroke, and accurately evaluated all population-based studies included in two recent meta-analyses on aortic valve pathology and risk of cardiovascular events.\textsuperscript{7,8} Note: The Cardiovascular Health Study published two articles on the relation...
between aortic valve calcification and the risk of cardiovascular disease (including stroke).\textsuperscript{9,10} Given a longer follow-up period and larger number of stroke events we included the report from 2006 in this analysis.\textsuperscript{9}.

All analyses were performed with IBM SPSS Statistics version 23 (International Business Machines Corporation, Armonk, New York), and Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to conduct the meta-analysis.
Supplementary Table I. Population characteristics separately for persons without and with incident stroke

<table>
<thead>
<tr>
<th></th>
<th>No incident stroke</th>
<th>Incident stroke</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2,234</td>
<td>N=135</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>69.3 (6.7)</td>
<td>72.2 (7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>52.5%</td>
<td>46.7%</td>
<td>0.182</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.7 (4.0)</td>
<td>27.5 (3.6)</td>
<td>0.932</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>146 (20)</td>
<td>153 (21)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>80 (11)</td>
<td>81 (13)</td>
<td>0.080</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.7 (1.0)</td>
<td>5.5 (1.0)</td>
<td>0.102</td>
</tr>
<tr>
<td>Serum high-density lipoprotein cholesterol, mmol/L</td>
<td>1.5 (0.4)</td>
<td>1.3 (0.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11.8%</td>
<td>18.5%</td>
<td>0.024</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>14.7%</td>
<td>23.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of blood-pressure lowering agents</td>
<td>38.5%</td>
<td>51.1%</td>
<td>0.037</td>
</tr>
<tr>
<td>Use of lipid-lowering medication</td>
<td>23.4%</td>
<td>24.4%</td>
<td>0.848</td>
</tr>
<tr>
<td>Prevalent coronary heart disease</td>
<td>7.7%</td>
<td>16.3%</td>
<td>0.013</td>
</tr>
<tr>
<td>Prevalent atrial fibrillation</td>
<td>3.3%</td>
<td>6.7%</td>
<td>0.232</td>
</tr>
<tr>
<td>Cervical carotid artery calcification, mm³</td>
<td>20.4 (0.0-103.7)</td>
<td>46.3 (3.2-180.8)</td>
<td>0.136</td>
</tr>
</tbody>
</table>

Values are means (standard deviation) for continuous variables or percentages for dichotomous variables.

Values represent original data without imputed values.
Supplementary Figure I. Meta-analysis of published population-based studies on the association of aortic valve calcification and risk of stroke.

CI: confidence interval

The effect sizes (boxes) with 95% confidence intervals are plotted. The size of the box is proportional to the weight of the study. The diamond is the result of the random-effect meta-analysis.

Heterogeneity: $\tau^2 = 0$; $\chi^2 = 1.11$; degrees of freedom = 3 ($P = 0.77$); $I^2 = 0\%$. 
Supplementary References


9. Barasch E, Gottdiener JS, Marino Larsen EK, Chaves PH, Newman AB. Cardiovascular morbidity and mortality in community-dwelling elderly individuals with calcification of the fibrous skeleton of the base of the heart and aortosclerosis (the cardiovascular health study). *Am J Cardiol*. 2006;97:1281-1286