Intracranial Carotid Artery Atherosclerosis and the Risk of Stroke in Whites
The Rotterdam Study

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Importance Intracranial atherosclerosis represents a relatively unexplored, but potentially important, cause of stroke in a white population.

Objective To investigate the relationship between intracranial carotid artery calcification (ICAC) as a marker of intracranial atherosclerosis and the risk of stroke in whites.

Design, Setting, and Participants A population-based cohort study in the general community with 6 years of follow-up was conducted (the Rotterdam Study). Between 2003 and 2006, a random sample of 2323 stroke-free persons (mean age, 69.5 years) underwent computed tomography scanning to quantify ICAC volume. All participants were continuously monitored for the occurrence of stroke until January 1, 2012.

Exposure Atherosclerotic calcification in the intracranial internal carotid arteries.

Main Outcome and Measure Incident stroke.

Results During 14 055 person-years of follow-up, 91 participants had a stroke, of which 74 were ischemic. Larger ICAC volume was related to a higher risk of stroke, independent of cardiovascular risk factors, ultrasound carotid plaque score, and calcification in other vessels (fully adjusted hazard ratio per an increase of 1 SD in ICAC volume, 1.43 [95% CI, 1.04-1.96]). Intracranial carotid artery calcification contributed to 75% of all strokes; for aortic arch and extracranial carotid artery calcification this incidence was only 45% and 25%, respectively.

Conclusions and Relevance Our findings establish intracranial atherosclerosis as a major risk factor for stroke in the general white population and suggest that its contribution to the proportion of all strokes may be greater than that of large-artery atherosclerosis in more proximally located vessel beds.

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Stroke is the most frequent neurologic disease and the second most important cause of global mortality. The lifetime risk of stroke is estimated to be at least 1 in 6, and in the coming decades its burden is expected to increase even further.

Of all strokes, approximately 80% to 90% are of ischemic origin. Ischemic stroke is a multifactorial disease involving various overlapping and interacting pathways, such as vascular disease, inflammation, hemostasis, metabolism, and genetic factors. Among these, vascular disease is by far the most important and has been the target of many preventive and therapeutic interventions for stroke. When studying vascular disease, it is important to consider that its burden may vary substantially across different vessel beds. As such, several locations of vascular disease are considered relevant in stroke etiology. First, cardiac diseases, such as coronary heart disease and atrial fibrillation, increase the risk of stroke. Second, large-artery atherosclerosis is recognized as a major risk factor of stroke. Third, strokes may occur after occlusion of the small penetrating intracerebral arteries, in so-called cerebral small-vessel disease. These do not represent mutually exclusive categories, but in most patients vascular pathology is present at multiple sites.
Within this etiologic framework, large-artery atherosclerosis is considered to include all vessels from the aortic arch to the major cerebral arteries. Atherosclerosis of the intracranial vasculature is globally considered the most important risk factor for stroke. However, current numbers are solely driven by populations of Asian and African origin, which make up the largest proportion of strokes worldwide. In contrast, there are no data on the burden of stroke attributable to intracranial atherosclerosis in white populations. Yet surprisingly, most clinical trials targeting intracranial atherosclerosis include a majority of whites in their samples. There is now an emerging awareness that robust data from white populations on the role of intracranial atherosclerosis in ischemic stroke are urgently needed. These data can then serve as a basis for designing future intervention studies.

Recently, a study using intracranial carotid artery calcification (ICAC) as a proxy demonstrated a prevalence of intracranial atherosclerosis exceeding 80% in a general white population. In the present study, we set out to investigate in a white population the longitudinal association of ICAC with incident stroke during a 6-year follow-up period. We were specifically interested in estimating the total burden of stroke attributable to ICAC in white individuals.

Methods
Setting
This study was based on the Rotterdam Study, a prospective population-based trial investigating the determinants of chronic diseases in the elderly. This study was approved by the institutional review board of Erasmus Medical Center, Rotterdam, the Netherlands. All participants gave written informed consent and received no financial compensation.

The original cohort consisted of 7983 participants 55 years or older and was extended in 2000-2001 by 3011 persons. At study entry and every 3 to 4 years, all participants are reexamined in a dedicated research center. The Rotterdam Study represents a homogeneous middle-class population, largely of white descent (>96%).

For the present study, we used the visit between September 1, 2003, and February 1, 2006, as baseline, because we invited participants who visited the research center to undergo nonenhanced computed tomography (CT) scanning of the intracranial carotid arteries only during this period. We scanned 2524 participants (response rate, 78%). The follow-up for stroke took place continuously and was completed for this study on January 1, 2012.

Assessment of Intracranial Atherosclerosis
We used a 16-section (n = 789) or 64-section (n = 1739) multi-detector CT scanner (Somatom Sensation 16 or 64; Siemens) to perform nonenhanced CT scanning. Using a cardiac scan and a scan that reached from the aortic arch to the intracranial vasculature (1 cm above the sella turcica), we scanned the following vessel beds: coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries. Detailed information regarding the imaging settings of both scans is provided elsewhere.

As proxy for intracranial atherosclerosis, we measured ICAC bilaterally in the intracranial internal carotid artery from its horizontal petrous bone segment to its top (until the circle of Willis) (Figure 1). For quantification of ICAC, we used a semi-automated scoring method that is described in detail elsewhere. Briefly, we manually drew regions of interest...
around calcification in the course of the intracranial internal carotid arteries in consecutive CT sections. Next, we calculated calcification volumes by multiplying the number of pixels in excess of 130 Hounsfield units by the pixel size and the increment.

Calcification volumes in the coronary arteries, aortic arch, and extracranial internal carotid arteries were quantified using dedicated commercially available software (Syngo Calcium Scoring; Siemens). All calcification volumes are expressed in cubic millimeters. Correlations between calcification across the 4 vessel beds ranged from 0.5 to 0.6.\(^{2,22}\)

**Follow-up for Stroke**

The definition of stroke was based on the World Health Organization criteria including a syndrome of rapidly developing symptoms, with an apparent vascular cause, of focal or global cerebral dysfunction lasting 24 hours or longer or leading to death.\(^{23,24}\) We assessed prevalent stroke at baseline during an interview and verified these data with medical records.\(^ {23}\) After enrollment, we continuously monitored participants for incident stroke through linkage of the study database with files from general practitioners. Nursing home physicians' files and files from general practitioners of participants who moved out of the district were also checked.\(^{23}\) Additional information was obtained from hospital records. Potential strokes were reviewed by research physicians and verified by an experienced stroke neurologist. We categorized strokes as ischemic or hemorrhagic on the basis of neuroimaging reports. If neuroimaging was unavailable, the stroke was classified as unspecified.\(^{23}\) Subarachnoid hemorrhages due to ruptured aneurysms were not considered stroke events.\(^{23}\) Follow-up for incident stroke was conducted until January 1, 2012.

**Other Measurements in the Rotterdam Study**

We obtained information on cardiovascular risk factors by interview, physical examination, and blood sampling.\(^ {23}\) Obesity was defined as a body mass index of 30 or more (calculated as weight in kilograms divided by height in meters squared). Hypertension was defined as a systolic blood pressure of 140 mm Hg or more, a diastolic blood pressure of 90 mm Hg or more, use of blood-pressure–lowering medication, or any combination of these 3 factors.\(^ {25}\) Diabetes mellitus was defined as fasting serum glucose levels of 126 mg/dL or more (to convert to millimoles per liter, multiply by 0.555) and/or use of antidiabetic therapy.\(^ {26}\) Hypercholesterolemia was defined as a serum total cholesterol of 239 mg/dL or more (to convert to millimoles per liter, multiply by 0.259) and/or use of lipid-lowering medication.\(^ {27}\) We defined low high-density lipoprotein cholesterol (HDL-C) as HDL-C less than 39 mg/dL (to convert to millimoles per liter, multiply by 0.259).\(^ {27}\) Smoking was categorized as never smoked or ever (ie, past or current) smoked.

In addition to these cardiovascular risk factors, we assessed other imaging markers of atherosclerosis. These were atherosclerotic calcification volumes in the coronary arteries, aortic arch, and extracranial carotid arteries (as detailed above) and ultrasound carotid plaque score. Using ultrasound sound, we visualized the common carotid artery, carotid artery bifurcation, and internal carotid artery and examined both the left and right to assess a weighted plaque score ranging from 0 to 6.\(^ {28}\)

**Population for Analysis**

We restricted our population to persons of white descent, as assessed by self-report (2452 of the 2524 individuals who underwent CT). Because of artifacts, 27 images from the 2452 CT examinations were not gradable for ICAC, leaving 2425 participants with complete data on ICAC volume. Persons with prevalent stroke (n = 98) and those who did not participate in the stroke follow-up (n = 4) were excluded, leaving 2323 participants at risk for stroke in the population for analysis.

**Statistical Analysis**

As a result of the nonnormal distribution of ICAC volume, we performed a natural log (Ln) transformation and added 1.0 mm\(^3\) to the nontransformed values to deal with calcium volumes of zero (Ln [ICAC + 1.0 mm\(^3\)]). We calculated hazard ratios (HRs) for stroke per 1-SD increase in ICAC volume using Cox proportional hazards regression models. The proportional hazards assumption was met. In model 1, we adjusted for age, sex, and scanner type. In model 2, we additionally adjusted for the following cardiovascular risk factors: obesity, hypertension, diabetes mellitus, hypercholesterolemia, low HDL-C, and smoking. In model 3, we additionally adjusted for the ultrasound carotid plaque score and CT-assessed calcification volumes in the coronary arteries, aortic arch, and extracranial carotid artery.

Next, we dichotomized ICAC into presence vs absence of ICAC and related that to the risk of stroke. In contrast to established categories for absolute coronary calcification scores (ie, Agatston score),\(^ {29}\) there are no such categories for ICAC. Therefore, we categorized calcification into present vs absent, because this is most readily identified in a clinical situation. We used the same 3 Cox regression models as above; the only difference was that in model 3, calcification in other vessel beds was also dichotomized into present and absent. Stroke-free survival in the absence and presence of ICAC was estimated and compared using the Kaplan-Meier method and log-rank test.

Finally, we calculated the population-attributable risk (PAR) for stroke of calcification in each of the 4 vessel beds using the following formula\(^ {30}\):

\[
PAR = PD \left( \frac{RR - 1}{RR} \right) \times 100\% 
\]

In this formula, \(RR\) represents the relative risk, that is, HR, which we calculated for the presence of calcification in each vessel bed; \(PD\) is the proportion of cases exposed to the risk factor (the presence of calcification); and \(PAR\) provides a measure between 0% and 100%, which can be interpreted as the fraction of strokes that is due to calcification.\(^ {30}\) Statistical analyses were conducted with SPSS Statistics, version 20 (IBM Corp.).
Table 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, No.</td>
<td>2323</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>52.2</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>69.5 (6.7)</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>23.7</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.7 (4.0)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>73.9</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>146.7 (20.1)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80.2 (10.8)</td>
</tr>
<tr>
<td>Use of BP-lowering medication, %</td>
<td>39.3</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>10.7</td>
</tr>
<tr>
<td>Serum glucose, mg/dL</td>
<td>102.7 (21.6)</td>
</tr>
<tr>
<td>Use of antidiabetic medication, %</td>
<td>6.0</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>48.9</td>
</tr>
<tr>
<td>Serum total cholesterol, mg/dL</td>
<td>220.0 (38.6)</td>
</tr>
<tr>
<td>Use of lipid-lowering medication, %</td>
<td>23.2</td>
</tr>
<tr>
<td>Low HDL-C, %</td>
<td>10.6</td>
</tr>
<tr>
<td>Serum HDL-C, mg/dL</td>
<td>54.1 (15.4)</td>
</tr>
<tr>
<td>Past or current smoker, %</td>
<td>67.5</td>
</tr>
<tr>
<td>Presence of ICAC, %</td>
<td>81.4</td>
</tr>
<tr>
<td>ICAC volume, mm³</td>
<td>41.1 (6.2-135.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; ICAC, intracranial carotid artery calcification; IQR, interquartile range.

Results

Table 1 reports the baseline characteristics of the study population. The mean age was 69.5 years, and 52.2% of the participants were women. During 14,055 person-years of follow-up (mean, 6.1 years), 91 participants had a stroke, of which 74 were ischemic, 10 were hemorrhagic, and 7 were unspecified.

Table 2 reports the associations between ICAC and the risk of stroke. We found that larger ICAC volumes were associated with a higher risk of stroke. These results were similar for ischemic stroke. Additional adjustment for cardiovascular risk factors did not change any of these results (HRs per increase of 1 SD in ICAC volume, 1.52 [95% CI, 1.17-1.98] for stroke and 1.53 [1.14-2.04] for ischemic stroke). After additional adjustment for ultrasound carotid plaque score and calcification volumes in the other vessel beds, we found that larger ICAC volumes remained significantly associated with a higher risk of stroke (HR per increase of 1 SD in ICAC volume, 1.43 [95% CI, 1.04-1.96]). The effect size for the association with ischemic stroke was similar, although statistically nonsignificant (Table 2, model 3 for continuous ICAC).

We found that the presence of ICAC was associated with a higher risk of any stroke and ischemic stroke, even after adjustment for cardiovascular risk factors (HRs for presence vs absence of ICAC, 4.15 [95% CI, 1.51-11.42] for stroke and 3.43 [1.24-9.51] for ischemic stroke). Additional adjustment for ultrasound carotid plaque score and the presence of calcification in each of the 4 vessel beds also did not change these associations (Table 2, model 3 for dichotomous ICAC). Kaplan-Meier curves revealed that the stroke-free survival in persons with ICAC was significantly shorter than in persons without ICAC (Figure 2).

Table 3 indicates the proportion of strokes that were attributable to calcification in each of the 4 vessel beds. We found that ICAC played a role in up to 75% of all strokes; for aortic arch calcification and calcification in the extracranial carotid artery, association was 45% and 25%, respectively. We did not calculate the PAR for stroke for coronary artery calcification because the HR was less than 1.

Discussion

In this large population-based cohort study among middle-aged and elderly white persons, we found that the presence and severity of ICAC were associated with a higher risk of stroke. This was independent of conventional cardiovascular risk factors and atherosclerosis in other extracranial vessel beds. We also found that ICAC contributed to 75% of all strokes, whereas for aortic arch calcification and extracranial carotid artery calcification this association was only 45% and 25%, respectively.

With the present study, we demonstrated that intracranial atherosclerosis is a major risk factor for stroke in a white population. Thus far, evidence of a role in the etiology of stroke comes primarily from research in populations of Asian and African descent. In these populations, intracranial atherosclerosis is an established major risk factor for ischemic stroke, accounting for up to 50% of all strokes.
We acknowledge that the total burden of intracranial atherosclerosis comprises atherosclerotic disease in more arteries than only the intracranial carotid arteries that we measured.\(^{14,18}\) However, atherosclerotic plaques in other cerebral arteries are typically noncalcified.\(^{31,32}\) Visualization of noncalcified atherosclerotic disease demands administration of intravenous contrast material, which was not possible in our population-based setting. However, autopsy studies\(^{33,34}\) have shown that, specifically for the intracranial vasculature, there is a strong correlation between the severity and extent of atherosclerosis across cerebral arteries. Therefore, it is likely that if there is more ICAC, there are probably also more atherosclerotic changes in the distal cerebral vessels. In this light, ICAC would be a marker of total intracranial atherosclerosis. On the other hand, there may be a causal role of ICAC in stroke. Highly calcified vessels may in some instances have a stenotic lumen leading to hemodynamic disturbances.\(^{35-36}\) However, this association is complex because of remodeling (ie, compensatory enlargement) of arteries.\(^{35-37}\) Also, large calcification volumes reflect large plaques, which may be a source of emboli. To further unravel these mechanisms and the putative causal role of ICAC, future studies should focus on classifying strokes systemically according to vascular territories.

Using PAR, we estimated that intracranial atherosclerosis contributes to the occurrence of 75% of all strokes. The PAR for stroke of intracranial atherosclerosis was notably larger than that of atherosclerosis in the aortic arch or carotid bifurcation. Theoretically, a PAR of 75% indicates that the incidence of stroke may be reduced by 75% if intracranial atherosclerosis could be eradicated. However, a few considerations are needed for better interpretation of a PAR. First, this figure of 75% does not mean that only 25% of strokes remain to be explained by causes other than intracranial atherosclerosis.\(^{30}\) In fact, the sum of PARs for all possible risk factors of stroke exceeds 100%, reflecting interaction between risk factors. This also signifies that unknown causes may contribute considerably to the development of stroke. Nevertheless, the high PAR illustrates the large potential gain in public health that could be achieved by further developing therapeutic and preventive strategies aimed at reducing the amount of intracranial atherosclerosis. Earlier and more aggressive treatment of modifiable risk factors for intracranial atherosclerosis may prevent its formation and thereby contribute to the primary prevention of stroke. A beneficial effect of aggressive medical management on the occurrence of stroke has been demonstrated\(^{35}\) in patients with symptomatic intracranial atherosclerotic stenosis. Second, although we adjusted for conventional cardiovascular risk factors, as well as for calcification in other vessel beds, the HR that we used may be subject to residual confounding. If so, a more unbiased HR would have yielded an attenuation of the PAR. Still, the PAR of ICAC was highest among all studied vessel beds.

In the current literature, a major focus is on coronary artery calcification as an emerging determinant for various cardiovascular events. Some studies\(^{8}\) have shown coronary artery calcification to even improve the risk prediction of stroke, but this remains debatable.\(^{38,39}\) In our data set, we found no association between coronary artery calcification and stroke when taking into account calcification in all vessel beds. In a post hoc analysis, we found that coronary artery calcification was associated with stroke only in a crude age- and sex-adjusted model. This further corroborates that ICAC is a more important determinant of stroke than coronary artery calcification. Future studies should thus investigate the predictive value of ICAC for stroke.

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**Table 3. PAR for Stroke per Vessel Bed**

<table>
<thead>
<tr>
<th>Vessel Bed</th>
<th>Proportion of Stroke Cases Exposed to Calcification</th>
<th>Any Stroke, HR (95% CI)</th>
<th>PAR, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary arteries</td>
<td>0.87</td>
<td>0.80 (0.40-1.57)</td>
<td>NA(^b)</td>
</tr>
<tr>
<td>Aortic arch</td>
<td>0.98</td>
<td>1.84 (0.44-7.77)</td>
<td>45</td>
</tr>
<tr>
<td>Extracranial carotid arteries</td>
<td>0.86</td>
<td>1.41 (0.71-2.83)</td>
<td>25</td>
</tr>
<tr>
<td>Intracranial carotid arteries</td>
<td>0.96</td>
<td>4.64 (1.44-14.95)</td>
<td>75</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; NA, not applicable; PAR, population-attributable risk.

\(^a\) Adjusted for age, sex, scanner type, obesity, hypertension, diabetes mellitus, hypercholesterolemia; low high-density lipoprotein cholesterol; smoking; computed tomography-assessed presence of calcification volumes in the coronary arteries, aortic arch, and extracranial carotid artery; and ultrasound carotid plaque score.

\(^b\) The PAR for coronary artery calcification was not calculated because the HR was less than 1.

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**Figure 2. Kaplan-Meier Survival Plot for Stroke-Free Survival in Persons With and Without Intracranial Carotid Artery Calcification (ICAC)**

The difference between the 2 groups was statistically significant as determined by the log-rank test. For ICAC absent, 431 persons were at risk, with 4 cases identified. For ICAC present, 1892 persons were at risk, with 87 cases identified.
Strengths of our study include the population-based setting and the longitudinal design. Moreover, we used an accurate image-based method to quantify ICAC. We tried to minimize the number of persons who were lost to follow-up by using thorough stroke monitoring procedures. These allowed us to identify nearly all stroke events, including fatal strokes and strokes in participants living in nursing homes who were not referred to a hospital. There are also several potential limitations that should be taken into account. First, by using nonenhanced CT, we were able to measure calcification only and not the complete atherosclerotic plaque. Although strong evidence from autopsy studies shows that CT-based calcification is a sensitive and reliable marker of the total underlying atherosclerotic burden, this might have led to misclassification in certain instances. Second, it was not possible to describe any additional plaque characteristics, such as shape, stenosis, or ulceration, which may be of importance with regard to future events. Although a high correlation between CT-measured calcification and stenosis has been found in the carotid siphon, advances in plaque imaging with other imaging techniques, such as magnetic resonance imaging, may aid to overcome this issue.

Conclusions

The findings of our study suggest that intracranial atherosclerosis is a major risk factor for stroke in the general white population. Moreover, its contribution to the proportion of all strokes may be greater than that of large-artery atherosclerosis in other vessel beds.

REFERENCES