Clinical, Radiological, and Flow-Related Risk Factors for Growth of Untreated, Unruptured Intracranial Aneurysms

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Background and Purpose—Unruptured intracranial aneurysms are frequently followed to monitor aneurysm growth. We studied the yield of follow-up imaging and analyzed risk factors for aneurysm growth.

Methods—We included patients with untreated, unruptured intracranial aneurysms and ≥6 months of follow-up imaging from 2 large prospectively collected databases. We assessed the proportion of patients with aneurysm growth and performed univariable and multivariable Cox regression analyses to calculate hazard ratios with corresponding 95% confidence intervals (CI) for clinical and radiological risk factors for aneurysm growth. We repeated these analyses for the subset of small (<7 mm) aneurysms.

Results—Fifty-seven (12%) of 468 aneurysms in 363 patients grew during a median follow-up of 2.1 years (total follow-up, 1372 patient-years). In multivariable analysis, hazard ratios for aneurysm growth were as follows: 1.1 (95% CI, 1.0–1.2) per each additional mm of initial aneurysm size; 2.7 (95% CI, 1.2–6.4) for dome > neck ratio; 2.1 (95% CI, 0.9–4.9) for location in the posterior circulation; and 2.0 (95% CI, 0.8–4.8) for multilobarity. In the subset of aneurysms <7 mm, 37 of 403 (9%) enlarged. In multivariable analysis, hazard ratios for aneurysm growth were 1.1 (95% CI, 0.8–1.5) per each additional mm of initial aneurysm size, 2.2 (95% CI, 1.0–4.8) for smoking, 2.9 (95% CI, 1.0–8.5) for multilobarity, 2.4 (95% CI, 1.0–5.8) for dome/neck ratio, and 2.0 (95% CI, 0.6–7.0) for location in the posterior circulation.

Conclusions—Initial aneurysm size, dome/neck ratio, and multilobarity are risk factors for aneurysm growth. Cessation of smoking is pivotal because smoking is a modifiable risk factor for growth of small aneurysms. (Stroke. 2015;46:42-48. DOI: 10.1161/STROKEAHA.114.005963.)

Key Words: follow-up studies ◼ intracranial aneurysm ◼ subarachnoid hemorrhage

A proximately 3% of the population has an asymptomatic unruptured intracranial aneurysm.1 With the increasing availability of noninvasive imaging techniques, aneurysms are often detected before rupture. Rupture of an intracranial aneurysm causes subarachnoid hemorrhage (SAH), which has a high case fatality and morbidity,2 and is associated with a high socio-economic burden.3 Elective occlusion of the unruptured aneurysm to prevent rupture is possible, but the risks of preventive treatment often do not outweigh the risks of rupture for small aneurysms.4,5 Therefore, small unruptured aneurysms are often followed with repeated imaging, with the intention to treat the aneurysm when it grows. The effectiveness of this strategy, the optimal interval for repeated imaging, and risk factors for aneurysm growth other than aneurysm size are unknown. Identification of clinical or radiological markers for aneurysm growth could tailor follow-up strategies and shed more light on pathogenesis of aneurysm growth and rupture. The most consistent risk factor for aneurysm growth in the literature is initial aneurysm size.6–8 In a previous prospective, small, short-term follow-up study, previous SAH and familial SAH were also risk factors for aneurysm growth.9 Suggested risk factors for aneurysm growth include smoking,10 multiplicity of aneurysms,11 aneurysm shape,12 flow direction into the aneurysm,13 and bifurcation angles.14 Prospective long-term follow-up data on these factors are lacking. Moreover, most studies were too small to perform reliable multivariable analyses.

We combined 2 large data sets with prospectively collected, consecutive series of patients with an unruptured, untreated intracranial aneurysm and follow-up imaging. This international data set has a uniquely large number of patients, which enables us to study the independence of potential clinical and radiological risk factors for aneurysm growth in untreated, unruptured intracranial aneurysms that are managed with follow-up imaging rather than occlusion.
Materials and Methods

Patient Inclusion Criteria
Data from all patients from the Toronto Western Hospital (Canada) and the University Medical Center Utrecht (the Netherlands) with an unruptured aneurysm were prospectively collected. From these databases, all patients aged ≥18 years with ≥1 saccular untreated intracranial aneurysm and ≥6 months of radiological follow-up by computerized tomographic angiography or magnetic resonance angiography were retrieved.

Risk Factors
Data on sex, age, smoking, hypertension (previous diagnosis made by a general practitioner or other physician), antihypertensive medication, previous SAH, and family history of SAH at the time of detection of the unruptured aneurysm were retrieved from clinical records. The imaging data were assessed for aneurysm location, maximum aneurysm height, maximum aneurysm dome width, aneurysm neck width, flow direction into the aneurysm, and bifurcation angles. Shape of the aneurysm was scored visually (round, elliptical, multilobed) and calculated as dome-neck ratio (aneurysm dome width divided by aneurysm neck width in mm) and as aspect ratio (aneurysm height divided by aneurysm neck width in mm). An example of some of these measurements is shown in Figure 1.

Outcome Measurement
Initial aneurysm size was measured on the first and last imaging available in 2 directions: maximum height and maximum dome width. Aneurysm growth was defined as (1) growth ≥1 mm in ≥1 direction for identical or different imaging modalities; (2) growth ≥0.5 mm in 2 directions for identical imaging modalities (computerized tomographic angiography or magnetic resonance angiography); or (3) undisputable change in shape of the aneurysm, such as change from unilobar to multilobar shape. An example of aneurysm growth is shown in Figure 2.

Figure 1. Example of aneurysm measurements in an aneurysm of the right internal carotid artery (ICA) bifurcation. A, Asymptomatic unruptured aneurysms on right ICA bifurcation. B, Aneurysm in the window setting in which we performed all measurements (window width and window level equal the Hounsfield density measurement in the aneurysm), with the surrounding arteries: ICA; M1 segment middle cerebral artery (M1); and A1 segment anterior cerebral artery (A1). C, Measurement of the bifurcation angles with $\Phi_X$ as the maximum angle and $\Phi_Y$ as the minimum angle. D, Measurement of the aneurysm height (H), aneurysm neck (N), and aneurysm dome (D).

Figure 2. Example of a grown unruptured aneurysm of the left middle cerebral artery, showing the initial magnetic resonance (MR) angiography in 2007 (top) and a follow-up MR angiography in 2010 (bottom). A and C, Original windowing. B and D, Windowing used for measurements (window width and window level equal the Hounsfield density measurement in the aneurysm), with measurement of aneurysm dome and height.
Table 1. Baseline Characteristics of Patients and Aneurysms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Utrecht, n (%)</th>
<th>Toronto, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>174</td>
<td>189</td>
<td>363</td>
</tr>
<tr>
<td>Median follow-up (range), y</td>
<td>3.5 (0.5–9.3)</td>
<td>1.8 (0.5–7.1)</td>
<td>2.1 (0.5–9.3)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>57 (33)</td>
<td>56 (29)</td>
<td>113 (31)</td>
</tr>
<tr>
<td>50–60</td>
<td>68 (40)</td>
<td>68 (36)</td>
<td>136 (38)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>49 (28)</td>
<td>65 (34)</td>
<td>114 (31)</td>
</tr>
<tr>
<td>Smoking*</td>
<td>72 (53)</td>
<td>59 (31)</td>
<td>131 (40)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>60 (44)</td>
<td>78 (42)</td>
<td>138 (43)</td>
</tr>
<tr>
<td>Family history of SAH*</td>
<td>30 (25)</td>
<td>42 (29)</td>
<td>72 (27)</td>
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<tr>
<td>Previous SAH*</td>
<td>69 (42)</td>
<td>29 (16)</td>
<td>98 (28)</td>
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<tr>
<td>Multiple aneurysms</td>
<td>94 (54)</td>
<td>69 (37)</td>
<td>163 (45)</td>
</tr>
<tr>
<td>Patients with a grown aneurysm</td>
<td>23 (13)</td>
<td>32 (17)</td>
<td>55 (15)</td>
</tr>
<tr>
<td>Aneurysm characteristics</td>
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<tr>
<td>No. of aneurysms</td>
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<td>246</td>
<td>468</td>
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<td>Aneurysm location</td>
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<tr>
<td>Internal carotid artery</td>
<td>67 (30)</td>
<td>116 (47)</td>
<td>183 (39)</td>
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<tr>
<td>Middle cerebral artery</td>
<td>89 (40)</td>
<td>67 (27)</td>
<td>156 (33)</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>40 (18)</td>
<td>32 (13)</td>
<td>72 (15)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>26 (12)</td>
<td>31 (13)</td>
<td>57 (12)</td>
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<tr>
<td>Initial aneurysm size, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>18 (8)</td>
<td>15 (6)</td>
<td>33 (7)</td>
</tr>
<tr>
<td>2.0–3.9</td>
<td>125 (56)</td>
<td>111 (45)</td>
<td>236 (50)</td>
</tr>
<tr>
<td>4.0–6.9</td>
<td>63 (28)</td>
<td>71 (29)</td>
<td>134 (29)</td>
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<tr>
<td>7.0–14.9</td>
<td>16 (7)</td>
<td>36 (15)</td>
<td>52 (11)</td>
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<tr>
<td>≥15.0</td>
<td>0 (0)</td>
<td>13 (5)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Aneurysm rupture during follow-up</td>
<td>2 (1)</td>
<td>1 (0.4)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Aneurysm growth during follow-up</td>
<td>25 (11)</td>
<td>32 (13)</td>
<td>57 (12)</td>
</tr>
</tbody>
</table>

SAH indicates subarachnoid hemorrhage.
*Variable not known for all patients.

Radiological Assessment

All images were assessed by 1 of 2 observers (A.S.E.B. or A.T.T.G.). Training for this assessment was done under supervision of an experienced neuroradiologist (B.K.V.), and included extensive analyses of a training data set with scans from both participating academic centers to ascertain identical measurement methods. Assessment was done without knowledge on (presumed) clinical risk factors for aneurysm growth. First and last imaging of each patient was assessed in a single session by the same researcher to avoid interobserver variability and to minimize intraobserver variability. All aneurysms with possible growth were re-evaluated in a consensus meeting with A.S.E.B., A.T.T.G., and B.K.V. to confirm aneurysm growth. If consensus on growth was reached, aneurysm size was assessed in all imaging studies performed between the first and the last imaging study. The first follow-up imaging that showed growth and the time that had elapsed between this imaging and the initial imaging was used for further analyses. For aneurysms that ruptured, the last follow-up imaging before rupture was used as end-point imaging. All radiological measurements were performed in a single center in a single radiological data evaluation program (Philips Intellispace Portal software; Philips Healthcare).

Statistical Analysis

We performed univariable Cox regression analyses and calculated hazard ratios with corresponding 95% confidence intervals (CI) and P values. We performed a multivariable Cox regression analysis including all risk factors related to aneurysm growth in the univariable Cox regression analysis with a P value of <0.2. All analyses were performed on a per aneurysm basis. Because initial aneurysm size is a known strong risk factor for aneurysm growth and rupture, an identical secondary analysis was performed including only small aneurysms defined as initial aneurysm size <7 mm. Data are presented in Kaplan–Meier survival curves for all aneurysms and for aneurysms with initial aneurysm size <7 mm and ≥7 mm separately. We reported the number of aneurysms with and without growth per 2 years of follow-up.

The following risk factors were entered in the univariable Cox regression analysis: sex, age, smoking, and hypertension at the time of diagnosis, previous SAH (SAH predating or at the time of diagnosis), presence of multiple aneurysms (ruptured or unruptured), family history of SAH (≥2 first-degree relatives with an (un)ruptured intracranial aneurysm), initial aneurysm size (maximum aneurysm height or dome width), aneurysm location (posterior versus anterior circulation), multilobarity (multilobar versus unilobar shape), dome/neck ratio (aneurysm dome width larger than aneurysm neck width versus aneurysm dome width smaller than aneurysm neck width), aspect ratio ≥2 median range (aspect ratio larger than the median versus aspect ratio smaller than the median), flow direction into the aneurysm (highest versus lowest tertile), and bifurcation angles (highest versus lowest tertile).

In addition, the following variables were analyzed in categories to increase discrimination: age (<50, 50–60, and >60 years at initial diagnosis), initial aneurysm size (<2, 2–4, 4–7, 7–15, and >15 mm), and aneurysm location in the anterior circulation (middle cerebral artery versus carotid artery, and anterior communicating/cerebral artery versus carotid artery).

This study was approved by the institutional review board of the University Medical Center Utrecht.

Results

The baseline characteristics of the included 363 patients with 468 unruptured aneurysms are described in Table 1. Two hundred seventy-eight patients had 1 aneurysm, 67 patients had 2, 16 patients had 3, and 2 patients had 4 aneurysms. In total 57 aneurysms (12%) grew during the total follow-up time of 1372 patient years, with a median follow-up time of 2.1 years (mean follow-up time, 2.8 years per aneurysm). None of the aneurysms had indisputable change in shape without simultaneous growth in size. Four patients had an SAH during follow-up; 3 from a known and followed aneurysm (3/468 aneurysms, 0.6%), 1 from a de novo aneurysm. One of the 3 known aneurysms showed growth (largest diameter from 7.3–8.5 mm) on the last follow-up imaging.
16 months before the rupture. The other 2 known aneurysms that ruptured did not show growth at follow-up imaging at 9 (aneurysm size, 2.9 mm) and 15 months (aneurysm size 4.0 mm) before rupture.

In multivariable analysis on risk factors for aneurysm growth, hazard ratios were 1.1 (95% CI, 1.0–1.2) per each additional mm of initial aneurysm size, 2.7 (95% CI, 1.2–6.4) for dome/neck ratio, 2.0 (95% CI, 0.8–4.8) for multilobarity, and 2.1 (95% CI, 0.9–4.9) for location in the posterior circulation (Table 2). In the subset of aneurysms <7 mm, 37 of 403 aneurysms (9%) were enlarged.

### Table 2. Results of Univariable and Multivariable Cox Regression Analyses of Clinical and Radiological Risk Factors in Hazard Ratios With 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Stable Aneurysms (n=411), %</th>
<th>Grown Aneurysms (n=57), %</th>
<th>Univariable Analyses</th>
<th>Multivariable Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>55</td>
<td>55</td>
<td>1.0 (1.0–1.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>&lt;50</td>
<td>123 (30)</td>
<td>19 (33)</td>
<td>1.2 (0.6–2.1)</td>
<td>0.60</td>
</tr>
<tr>
<td>50–60</td>
<td>158 (38)</td>
<td>20 (35)</td>
<td>Ref</td>
<td>...</td>
</tr>
<tr>
<td>&gt;60</td>
<td>130 (32)</td>
<td>18 (32)</td>
<td>1.3 (0.7–2.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Women</td>
<td>329 (80)</td>
<td>43 (75)</td>
<td>0.7 (0.4–1.2)</td>
<td>0.19</td>
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<tr>
<td>Smoking</td>
<td>153 (42)</td>
<td>26 (50)</td>
<td>1.3 (0.7–2.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>155 (43)</td>
<td>27 (52)</td>
<td>1.3 (0.7–2.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Family history of SAH</td>
<td>95 (32)</td>
<td>7 (18)</td>
<td>0.5 (0.2–1.1)</td>
<td>0.09</td>
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<tr>
<td>Previous SAH</td>
<td>123 (31)</td>
<td>7 (13)</td>
<td>0.3 (0.1–0.6)</td>
<td>0.00</td>
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<tr>
<td>Multiple aneurysms</td>
<td>240 (58)</td>
<td>28 (49)</td>
<td>0.6 (0.3–0.9)</td>
<td>0.03</td>
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<td>Initial aneurysm size, mm</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.3</td>
<td>7.7</td>
<td>1.1 (1.1–1.2)</td>
<td>0.00</td>
</tr>
<tr>
<td>&lt;2</td>
<td>31 (8)</td>
<td>2 (4)</td>
<td>0.9 (0.2–3.9)</td>
<td>0.89</td>
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<tr>
<td>2–3.9</td>
<td>220 (54)</td>
<td>16 (28)</td>
<td>Ref</td>
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<tr>
<td>4.0–6.9</td>
<td>115 (28)</td>
<td>19 (33)</td>
<td>2.7 (1.4–5.3)</td>
<td>0.00</td>
</tr>
<tr>
<td>7.0–14.9</td>
<td>39 (9)</td>
<td>13 (23)</td>
<td>6.9 (3.3–14.5)</td>
<td>0.00</td>
</tr>
<tr>
<td>≥15.0</td>
<td>6 (1)</td>
<td>7 (12)</td>
<td>23.4 (9.4–58.3)</td>
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<td>Aneurysm anterior circulation</td>
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<tr>
<td>Internal carotid artery</td>
<td>161 (39)</td>
<td>22 (39)</td>
<td>Ref</td>
<td>...</td>
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<tr>
<td>Middle cerebral artery</td>
<td>141 (34)</td>
<td>15 (26)</td>
<td>0.7 (0.4–1.4)</td>
<td>0.29</td>
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<td>Anterior cerebral artery</td>
<td>63 (15)</td>
<td>9 (16)</td>
<td>0.8 (0.4–1.7)</td>
<td>0.57</td>
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<td>Aneurysm posterior circulation</td>
<td>46 (11)</td>
<td>11 (19)</td>
<td>2.1 (1.1–4.1)</td>
<td>0.03</td>
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<tr>
<td>Multilobar aneurysm</td>
<td>43 (11)</td>
<td>13 (23)</td>
<td>3.9 (2.1–7.5)</td>
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<td>Size ratio</td>
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<tr>
<td>Dome &gt; neck</td>
<td>152 (40)</td>
<td>33 (64)</td>
<td>2.9 (1.7–5.1)</td>
<td>0.00</td>
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<tr>
<td>Aspect ratio ≥ median (1.0)</td>
<td>176 (46)</td>
<td>33 (64)</td>
<td>2.3 (1.3–4.1)</td>
<td>0.00</td>
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<td>Flow into aneurysm, °</td>
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<tr>
<td>First tertile (54–112)</td>
<td>136 (33)</td>
<td>21 (37)</td>
<td>Ref</td>
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<tr>
<td>Second tertile (112–143)</td>
<td>140 (34)</td>
<td>13 (23)</td>
<td>0.7 (0.3–1.4)</td>
<td>0.30</td>
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<tr>
<td>Third tertile (143–180)</td>
<td>135 (33)</td>
<td>23 (40)</td>
<td>1.2 (0.7–2.3)</td>
<td>0.47</td>
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<td>Bifurcation (largest angle), °</td>
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<td>First tertile (133–178)</td>
<td>83 (36)</td>
<td>7 (22)</td>
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<tr>
<td>Second tertile (112–133)</td>
<td>72 (31)</td>
<td>10 (31)</td>
<td>1.5 (0.6–3.9)</td>
<td>0.41</td>
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<td>Bifurcation (smallest angle), °</td>
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<td>15 (47)</td>
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<td>Second tertile (71–90)</td>
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<td>6 (19)</td>
<td>0.5 (0.2–1.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Third tertile (26–71)</td>
<td>79 (35)</td>
<td>11 (34)</td>
<td>0.5 (0.8–1.6)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and SAH, subarachnoid hemorrhage.
Aneurysms 0.3 (95% CI, 0.1–0.9) (Table 3). Kaplan–Meier survival curves show aneurysm growth for all aneurysms (Figure 3A) and for aneurysms with initial size <7 mm and aneurysm size ≥7 mm separately (Figure 3B). Rate of aneurysm growth per year of follow-up is shown in Table I in the online-only Data Supplement. Aneurysmal growth was seen in 15 of 188 aneurysms (0.08; 95% CI, 0.05–0.13) with follow-up ≥3 years and 5 of 77 aneurysms (0.06; 95% CI, 0.02–0.05) with follow-up ≥5 years.

### Discussion

In this large data set, >1 of 10 aneurysms grew during a mean follow-up time of ≤3 years. Initial aneurysm size and dome/neck ratio were risk factors for aneurysm growth for all aneurysms combined; and dome/neck ratio, multilobarity, and smoking were risk factors for growth in small aneurysms. Aneurysm location in the posterior circulation was a risk factor in the univariable analyses but was not shown to be an independent risk factor in the multivariable analyses. We found no

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**Table 3. Results of Univariable and Multivariable Cox Regression Analyses of Clinical and Radiological Risk Factors in Hazard Ratios With 95% Confidence Intervals, in 403 Aneurysms With Initial Aneurysm Size <7 mm**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Stable Aneurysms (n=366), %</th>
<th>Grown Aneurysms (n=37), %</th>
<th>Univariable Analyses</th>
<th>Multivariable Analyses</th>
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<tr>
<td></td>
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<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
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<tr>
<td>Age, y</td>
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</tr>
<tr>
<td>&lt;50</td>
<td>116 (32)</td>
<td>16 (43)</td>
<td>1.3 (0.6–2.6)</td>
<td>0.49</td>
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<tr>
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<td>15 (41)</td>
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</tr>
<tr>
<td>&gt;60</td>
<td>109 (30)</td>
<td>6 (16)</td>
<td>0.7 (0.3–1.8)</td>
<td>0.43</td>
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<tr>
<td>Women</td>
<td>297 (81)</td>
<td>28 (76)</td>
<td>0.6 (0.3–1.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Smoking</td>
<td>143 (44)</td>
<td>19 (58)</td>
<td>1.6 (0.8–3.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>140 (44)</td>
<td>14 (42)</td>
<td>0.8 (0.4–1.6)</td>
<td>0.60</td>
</tr>
<tr>
<td>Familial history of SAH</td>
<td>93 (34)</td>
<td>7 (25)</td>
<td>0.7 (0.3–1.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Previous SAH</td>
<td>118 (34)</td>
<td>7 (21)</td>
<td>0.4 (0.2–0.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiple aneurysms</td>
<td>226 (62)</td>
<td>16 (43)</td>
<td>0.4 (0.2–0.7)</td>
<td>0.00</td>
</tr>
<tr>
<td>Initial aneurysm size, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.4</td>
<td>4.1</td>
<td>1.4 (1.2–1.8)</td>
<td>0.00</td>
</tr>
<tr>
<td>&lt;2</td>
<td>31 (9)</td>
<td>2 (5)</td>
<td>0.9 (0.2–3.9)</td>
<td>0.87</td>
</tr>
<tr>
<td>2–3.9</td>
<td>220 (60)</td>
<td>16 (43)</td>
<td>Ref</td>
<td>...</td>
</tr>
<tr>
<td>4.0–6.9</td>
<td>115 (31)</td>
<td>19 (51)</td>
<td>2.7 (1.4–5.3)</td>
<td>0.00</td>
</tr>
<tr>
<td>Aneurysm anterior circulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>143 (43)</td>
<td>12 (38)</td>
<td>Ref</td>
<td>...</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>133 (40)</td>
<td>11 (34)</td>
<td>0.9 (0.4–2.0)</td>
<td>0.79</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>58 (17)</td>
<td>9 (28)</td>
<td>1.4 (0.6–3.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Aneurysm posterior circulation</td>
<td>32 (9)</td>
<td>5 (14)</td>
<td>1.9 (0.7–4.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Multilobar aneurysm</td>
<td>27 (7)</td>
<td>5 (14)</td>
<td>3.0 (1.2–7.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Size ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dome &gt; neck</td>
<td>117 (34)</td>
<td>19 (53)</td>
<td>2.3 (1.2–4.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aspect ratio ≥ median (0.9)</td>
<td>171 (50)</td>
<td>19 (53)</td>
<td>1.7 (0.9–3.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>Flow into aneurysm, °</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile (54–112)</td>
<td>136 (33)</td>
<td>21 (37)</td>
<td>Ref</td>
<td>...</td>
</tr>
<tr>
<td>Second tertile (112–137)</td>
<td>140 (34)</td>
<td>13 (23)</td>
<td>0.9 (0.4–2.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>Third tertile (137–180)</td>
<td>135 (33)</td>
<td>23 (40)</td>
<td>1.4 (0.7–3.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>Bifurcation (largest angle), °</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile (136–178)</td>
<td>83 (36)</td>
<td>7 (22)</td>
<td>Ref</td>
<td>...</td>
</tr>
<tr>
<td>Second tertile (114–136)</td>
<td>72 (31)</td>
<td>10 (31)</td>
<td>1.8 (0.6–5.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Third tertile (67–114)</td>
<td>78 (34)</td>
<td>15 (47)</td>
<td>1.7 (0.6–5.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Bifurcation (smallest angle), °</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First tertile (90–139)</td>
<td>75 (33)</td>
<td>15 (47)</td>
<td>Ref</td>
<td>...</td>
</tr>
<tr>
<td>Second tertile (71–90)</td>
<td>75 (33)</td>
<td>6 (19)</td>
<td>0.5 (0.2–1.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Third tertile (26–71)</td>
<td>79 (35)</td>
<td>11 (34)</td>
<td>0.8 (0.3–2.1)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and SAH, subarachnoid hemorrhage.
Aneurysm location in the posterior circulation is an established risk factor for aneurysm rupture, and is therefore a probable risk factor for aneurysm growth. In this study, aneurysm location in the posterior circulation was not an independent risk factor for aneurysm growth, although the effective size with a doubled risk was rather large. The lack of statistical significance is probably caused by small numbers because posterior circulation aneurysms are relatively rare.6,8,9,16

We found multiplicity of aneurysms to be related to a decreased risk of aneurysm growth for small aneurysms, which may be explained by the choice to perform analyses on a per-aneurysm rather than on a per-patient basis. In a post hoc patient-based analysis with the largest aneurysm per patient included in patients with multiple aneurysms, multiplicity of aneurysms was no longer related to aneurysm growth.

Strengths of our study are the meticulous measurements of the aneurysms and adjacent vessels and the unique size of our international data set, which enabled performing multivariable analyses for many factors and even multivariable analyses for the subset of small aneurysms only. A post hoc analysis including exclusively the 46 aneurysms with growth ≥1 mm showed similar results in univariable and multivariable analyses, with hazard ratio 1.1 (95% CI, 1.0–1.2) per mm growth for initial aneurysm size and 4.1 (95% CI, 1.5–11.2) for dome/neck ratio in the multivariable analysis.

Limitations of our study include the selection bias of patients and aneurysms because we included only aneurysms that were left untreated for ≥6 months and followed with repeated imaging. Aneurysms that were deemed fit for immediate treatment by the treating neurologist, neurosurgeon, or radiologist, and aneurysms in patients who were deemed unfit for repeated imaging because of their medical condition or age, are therefore not included in this study. We found previous SAH and family history of SAH not to be risk factors for aneurysm growth, in contrast to previous studies.6,8,9,11,16 This may be attributable to selection bias because persons with a positive family history or previous SAH may be inclined to treat unruptured aneurysms at a smaller aneurysm size. We did not correct our analysis for multiple comparisons. We did not have data on blood pressure management and smoking status during follow-up, so no conclusions can be drawn about the effects of management of hypertension and smoking on risk of aneurysm growth.

We consider growth of aneurysms to be a marker for increased risk of rupture in follow-up studies because size is the most important risk factor for rupture. Therefore, an aneurysm that increased in size has a higher risk of rupture than before growth. Aneurysm growth is probably an irregular and discontinuous process, with long periods of aneurysm wall instability interjected with short periods of aneurysm wall instability, temporarily allowing aneurysm growth or aneurysm rupture.17,18 Growth at follow-up should therefore not be interpreted as instability of the aneurysm wall at the time of imaging. From the 3 patients with SAH from a known aneurysm during follow-up in this study, only 1 showed aneurysm growth on the follow-up imaging preceding the rupture.

The similarity in risk factors for aneurysm growth and aneurysm rupture supports the hypothesis that aneurysm growth is related to patient-related risk factors, such as age, hypertension, familial history of SAH, previous SAH, and flow direction into the aneurysm or bifurcation angles. There have been several previous studies on aneurysm growth; however, our study is the largest study performed to date, data have been collected prospectively rather than retrospectively, and this is the first study to do a time-dependent multivariable regression analysis. Also, previous studies focused on patient-related risk factors, such as age, hypertension, and smoking, and usually included only aneurysm size and aneurysm location as aneurysm-related risk factors. This is the first study to include multiple aneurysm-related risk factors for aneurysm growth in the analysis, such as dome/neck ratio, multilobarity, and bifurcation and inflow angles.

When we compare the proportion aneurysm enlargement per year of follow-up, the 4% per year of follow-up we found is in agreement with previous studies, which found rates of 2% to 5% per year of follow-up.6,8,11,16 Initial aneurysm size was a risk factor for aneurysm growth in our study, which is in agreement with previous studies.6,9,11,15 For small aneurysms (<7 mm), size was not related to aneurysm growth in the multivariable analysis. A recent study on aneurysm growth in 258 aneurysms; 18% in 2-year follow-up) which may be explained by different criteria for growth because those authors used the ABC/2 method with slightly smaller margins for growth than we did.13 Initial aneurysm size and smoking status were independent covariables and were able to predict the majority of instances of aneurysm growth. No relation between aneurysm location and aneurysm growth was shown, which is in agreement with our study.15
growth and aneurysm rupture are both signs of aneurysm wall instability. Aneurysm size, dome/neck ratio, and multilobarity should be validated in an external data set as predictors for aneurysm growth and rupture, so that they may be incorporated in treatment decisions for newly diagnosed unruptured intracranial aneurysms. Because smoking at the time of diagnosis is a modifiable risk factor for aneurysm growth, patients with an unruptured intracranial aneurysm should be urged to stop smoking. The optimal interval of follow-up imaging is still uncertain, as is the duration of follow-up. Recent literature suggests a decrease in the risk of rupture after 5 years, which may indicate that unstable aneurysms disappear from the research population, lowering risk of rupture for the remaining aneurysms.

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**Disclosures**

None.

**References**


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## SUPPLEMENTAL MATERIAL.

Table I:
Growth per number of aneurysms with follow-up screening, presented per year of follow-up

<table>
<thead>
<tr>
<th>Duration of follow-up</th>
<th>All aneurysms growth/total (%)</th>
<th>Initial aneurysm size &lt;7 mm growth/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>11/468 (2%)</td>
<td>4/403 (1%)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>18/393 (5%)</td>
<td>11/347 (3%)</td>
</tr>
<tr>
<td>2-3 years</td>
<td>13/267 (5%)</td>
<td>8/249 (3%)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>7 /188 (4%)</td>
<td>7/178 (4%)</td>
</tr>
<tr>
<td>4-5 years</td>
<td>3/127 (2%)</td>
<td>2/119 (2%)</td>
</tr>
<tr>
<td>5-6 years</td>
<td>3/77 (4%)</td>
<td>3/72 (3%)</td>
</tr>
<tr>
<td>6-7 years</td>
<td>1/41 (2%)</td>
<td>1/39 (3%)</td>
</tr>
<tr>
<td>7-8 years</td>
<td>1/24 (4%)</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td>&gt;8 years</td>
<td>0/11 (0%)</td>
<td>0/11 (0%)</td>
</tr>
</tbody>
</table>
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未治療の未破裂頭蓋内動脈瘤の増大と臨床的危険因子、放射線学的危険因子、および脳血流量関連の危険因子の関連

Clinical, Radiological, and Flow-Related Risk Factors for Growth of Untreated, Unruptured Intracranial Aneurysms

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1 Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands; and Division of Neuroradiology, Department of Medical Imaging, Toronto Western Hospital, Toronto, Ontario, Canada.

背景および目的：未破裂頭蓋内動脈瘤は、動脈瘤の増大を監視するために経過観察が行われることが多い。本研究では追跡調査時の画像検査の結果について検討し、動脈瘤増大の危険因子を分析した。

方法：2つの大規模前向きデータベースから未治療の未破裂動脈瘤があり6ヶ月以上にわたる経過観察で画像検査を行っている患者を抽出し、本研究の対象とした。動脈瘤が増大した患者の割合を調べ、単変量および多変量コッタス回帰分析を行って動脈瘤増大に関する臨床的危険因子と放射線学的危険因子のハザード比およびそれに対応する95%信頼区間（CI）を算出した。サブセットの小さな動脈瘤（< 7 mm）に関しても上記の解析を行った。

結果：追跡期間中央値2.1年間（全追跡；1,372患者・年）で患者363例の動脈瘤468個中57個（12%）が増大した。多変量解析による動脈瘤増大のハザード比は、動脈瘤が最初のサイズから1 mm増大する毎に1.1（95%CI：1.0～1.2）、ドーム/ネック比は2.7（95%CI：1.2～6.4）、後方循環における位置は2.1（95%CI：0.9～4.9）、多変量は2.0（95%CI：0.8～4.8）であった。動脈瘤のサイズが< 7 mmのサブセットでは、403個中37個（9%）に動脈瘤増大が認められた。多変量解析による動脈瘤増大のハザード比は、動脈瘤が最初のサイズから1 mm増大する毎に1.1（95%CI：0.8～1.5）、喫煙は2.2（95%CI：1.0～4.8）、多変量は2.9（95%CI：1.0～8.5）、ドーム/ネック比は2.4（95%CI：1.0～5.8）、後方循環における位置は2.0（95%CI：0.6～7.0）であった。

結論：動脈瘤増大の危険因子は、動脈瘤の最初のサイズ、ドーム/ネック比、および多変量である。喫煙は小さなサイズの動脈瘤の増大において修正可能な危険因子であるため、禁煙は極めて重要である。


図2 左中大脳動脈の増大した未破裂動脈瘤の症例。2007年に撮影した最初の核磁気共鳴血管造影（MRA）（上）と追跡調査期間中の2010年に撮影したMRA（下）。

AおよびB：元画像、BおよびD：動脈瘤のドームと窩の測定に使用した画像（画像の幅とレベルは動脈瘤のHounsfieldの密度測定と同じ）。

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