Background and Purpose—Growth of an intracranial aneurysm occurs in around 10% of patients at 2-year follow-up imaging and may be associated with aneurysm rupture. We investigated whether PHASES, a score providing absolute risks of aneurysm rupture based on 6 easily retrievable risk factors, also predicts aneurysm growth.

Methods—In a multicenter cohort of patients with unruptured intracranial aneurysms and follow-up imaging with computed tomography angiography or magnetic resonance angiography, we performed univariable and multivariable Cox regression analyses for the predictors of the PHASES score at baseline, with aneurysm growth as outcome. We calculated hazard ratios and corresponding 95% confidence intervals (CI), with the PHASES score as continuous variable and after division into quartiles.

Results—We included 557 patients with 734 unruptured aneurysms. Eighty-nine (12%) aneurysms in 87 patients showed growth during a median follow-up of 2.7 patient-years (range 0.5–10.8). Per point increase in PHASES score, hazard ratio for aneurysm growth was 1.32 (95% CI, 1.22–1.43). With the lowest quartile of the PHASES score (0–1) as reference, hazard ratios were for the second (PHASES 2–3) 1.07 (95% CI, 0.49–2.32), the third (PHASES 4) 2.29 (95% CI, 1.05–4.95), and the fourth quartile (PHASES 5–14) 2.85 (95% CI, 1.43–5.67).

Conclusions—Higher PHASES scores were associated with an increased risk of aneurysm growth. Because higher PHASES scores also predict aneurysm rupture, our findings suggest that aneurysm growth can be used as surrogate outcome measure of aneurysm rupture in follow-up studies on risk prediction or interventions aimed to reduce the risk of rupture. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.008198.)

Key Words: follow-up ■ growth ■ imaging ■ PHASES ■ unruptured aneurysm

The prevalence of unruptured intracranial aneurysms in the adult population is ~3%.1 With increasing availability of modern imaging techniques, such as magnetic resonance angiography and computed tomography angiography, an increasing number of aneurysms is being detected.2 The current endovascular or surgical treatment options to prevent aneurysmal rupture with its devastating consequences are invasive and carry considerable risks of complications.3,4 For most small aneurysms in the anterior circulation, the predicted risk of rupture is much smaller than the risk of treatment complications, and therefore, many of these small aneurysms are left untreated. However, a small proportion of these aneurysms do rupture, and because these aneurysms by far outnumber other aneurysms, most instances of aneurysmal subarachnoid hemorrhage (SAH) come from small aneurysms in the anterior circulation.5,6 Therefore, we need better risk prediction. Because the average 5-year risk of rupture for these small aneurysms is so small, tens if not hundreds of thousands patient-years are needed to have enough outcome events to improve existing prediction tools.7,8 Thus, surrogate markers of rupture are needed to facilitate improvement of risk prediction models. Such markers could also be used as surrogate outcome measurement in phase II trials evaluating new, noninvasive treatment strategies aiming to reduce the risk of rupture. Aneurysm growth may be such a marker and has already been the subject of research in several previous studies.9–17 However, despite strong associations between aneurysm size or aneurysm growth and rupture, uncertainty exists if aneurysm growth is indeed a good surrogate marker for aneurysm rupture in current risk assessment models.

The PHASES score is a model that provides absolute risks of rupture for aneurysms based on 6 easily retrievable factors
(population, hypertension, age, size of aneurysm, earlier SAH from another aneurysm, site of aneurysm). We assessed whether this score also predicts aneurysm growth.

Methods

Study Population and Data Extraction

Approval for this study was obtained from the local Institutional Review Board of the participating centers. Data from consecutive patients with an unruptured intracranial aneurysm were prospectively collected at 3 tertiary care referral hospitals: Toronto Western Hospital, Canada; University Medical Center Utrecht, The Netherlands; and Leiden University Medical Center, The Netherlands. From these databases, we included all patients aged ≥18 years with ≥1 unruptured intracranial saccular aneurysms and ≥6 months of radiological follow-up with magnetic resonance angiography or computed tomography angiography. The indication and time-interval for follow-up imaging was determined by the local treating physician. Data on sex, age, geographical region, history of hypertension, and history of SAH at the time of aneurysm detection were retrieved from the electronic patient files. A history of hypertension was defined as a diagnosis of hypertension previously made by another physician or use of antihypertensive drugs. From all follow-up imaging, we retrieved the date of imaging and imaging modality (magnetic resonance angiography or computed tomography angiography).

Imaging

The baseline and the last imaging were assessed at the end of the follow-up study by one of 3 observers (DB, ASEB, ATTG) who were blinded for clinical data and patient-specific risk factors for aneurysm growth but not for the dates of the imaging studies. Aneurysm rupture was not an outcome event. If aneurysm rupture occurred during follow-up, the last imaging study before aneurysm rupture was used to assess whether growth had occurred. Assessment of imaging was done per patient within a single session by the same observer to avoid interobserver variability. Imaging data were reviewed for aneurysm location and divided into 3 categories according to the PHASES score: (1) internal carotid artery; (2) middle cerebral artery; and (3) anterior and posterior communicating artery or posterior circulation (the vertebrobasilar arteries and branches). Aneurysm height and width were measured on 3-dimension rotational images on a 0.1 mm scale. Aneurysm height was defined as the maximum distance from the aneurysm neck to the aneurysm dome, and aneurysm width was defined as the maximum width measured perpendicular to the maximum aneurysm height (Figure 1). Aneurysm growth was defined as (1) growth ≥1.0 mm in at least 1 direction for identical or different imaging modalities; (2) growth ≥0.5 mm in 2 directions for identical imaging modalities; (3) indisputable change in aneurysm shape (ie, change from regular shape to irregular shape). An example of aneurysm growth is shown in Figure 2. All aneurysms with possible aneurysm growth were reviewed in a consensus meeting with a neuroradiologist (B.K.V. or M.A.A.v.W.) who was not aware of the study objectives. If consensus on aneurysm growth based on the baseline and last imaging study was reached, all imaging studies in between were evaluated for aneurysm growth. The time elapsed between the baseline imaging and the first follow-up imaging that showed aneurysm growth was used for further analysis. In aneurysms without growth, the time elapsed between the first and the last imaging was used. We used Philips Intellispace Portal software from Philips Healthcare Netherlands to evaluate all imaging studies.

Statistical Analysis

The PHAGES score for each aneurysm was calculated at baseline by summing up the number of points associated with each predictor: age (0, <70 years; 1, ≥70 years), hypertension (0, no; 1, yes), history of SAH (0, no; 1, yes), aneurysm size (0, <7.0 mm; 3, 7.0–9.9 mm; 6, 10.0–19.9 mm; 10, ≥20.0 mm), aneurysm site (0, internal carotid artery; 2, middle cerebral artery; 4, anterior cerebral arteries, posterior communicating artery, and posterior circulation), and geographical region (0, North American, European [other than Finnish]; 3, Japanese; 5, Finnish). Because all patients included in this study were North American or European (other than Finnish), all patients scored zero points for geographical region. First, we performed an aneurysm-based univariable and multivariable Cox regression analysis for the predictors of the PHAGES score with aneurysm growth as outcome and calculated hazard ratios with corresponding 95% confidence intervals (CI). Second, we performed Cox regression analysis with the PHAGES score as a continuous variable. Third, we repeated this analysis after division of the PHAGES score within 4 quartiles. We calculated the concordance (c) statistic to express the extent of discrimination of the Cox regression models. The c-statistic for prognostic models is typically between 0.60 and 0.85. In addition, we did a patient-based sensitivity analysis, in which the only largest aneurysm and its location were used to calculate the PHAGES score in patients with multiple intracranial aneurysms. We plotted Kaplan–Meier growth-free survival curves to visualize the association between quartiles of the PHAGES score and aneurysm growth. Missing data for hypertension (4% missing values) and history of SAH (2% missing values) were assigned by multiple imputation with linear regression method (multivariable analysis) available in SPSS version 20. A sensitivity analysis was done in which all patients with a missing value were excluded.

Figure 1. Example of aneurysm measurements. A, MRI shows an unruptured intracranial aneurysm located on the right middle cerebral artery (MCA) bifurcation on a time of flight sequence in Philips Intellispace Portal. B, Window settings are adjusted according to our measurement protocol (window width and window level equal to the Hounsfield unit density measured within the aneurysm). The imaging studies were linked, so that both imaging studies could be rotated in the same axis in 3 dimensions to establish the cross-sectional projection in which the maximum aneurysm height (H) and width (W) were visualized. Aneurysm height was measured from the center of the aneurysm neck (N) to the aneurysm dome, and aneurysm width was measured perpendicular to the aneurysm height.

Figure 2. Imaging of aneurysm growth. A, Example of an aneurysm in which aneurysm height (H) and width (W) were visualized. Aneurysm height was defined as the maximum distance from the aneurysm neck to the aneurysm dome, and aneurysm width was defined as the maximum width measured perpendicular to the maximum aneurysm height. B, An example of an aneurysm with possible aneurysm growth. Aneurysm growth criteria include (1) growth ≥1.0 mm in at least 1 direction for identical or different imaging modalities; (2) growth ≥0.5 mm in 2 directions for identical imaging modalities; (3) indisputable change in aneurysm shape (ie, change from regular shape to irregular shape). An example of aneurysm growth is shown in Figure 2.
Results

Baseline characteristics of the 557 included patients with 734 saccular unruptured intracranial aneurysms are shown in Tables 1 and 2. The mean age at aneurysm detection was 55 years (SD 11 years) and 417 patients (75%) were women. In total, 415 patients had 1 unruptured aneurysm, 110 patients had 2 unruptured aneurysms, 29 patients had 3 unruptured aneurysms, and 3 patients had 4 unruptured aneurysms. Six patients (1%) had an SAH from a known aneurysm during follow-up, with a median PHASES score at baseline of 6 (range 4–9). Eighty-nine aneurysms (12%) in 86 patients (16%) showed aneurysm growth during a median follow-up of 2.7 patient-years (range 0.5–10.8 years).

The results of the univariable and multivariable Cox logistic regression analysis of the predictors of the PHASES score are shown in Table 3. Aneurysm size was significantly associated with aneurysm growth in the multivariable analysis, with increasing hazard ratios observed in larger aneurysms (Table 3). The median PHASES score per aneurysm was 4 (range 0–14). Aneurysm-based Cox regression analysis with the PHASES score as continuous variable showed a hazard ratio of 1.32 (95% CI, 1.22–1.43) for aneurysm growth per point increase in PHASES score, with a c-statistic of 0.68 (95% CI, 0.61–0.74). An increasing hazard ratio for aneurysm growth was detected when the PHASES score was divided into quartiles, with a PHASES score of 0 to 1 as reference (Table 4; Figure 3), with a c-statistic of 0.64 (95% CI, 0.58–0.70). The patient-based sensitivity analysis showed similar results, with a hazard ratio of 1.29 (95% CI, 1.19–1.39) for aneurysm growth per point increase in PHASES score, and increasing hazard ratios after division into quartiles (PHASES 0–1 as reference; PHASES 2–3: hazard ratios 1.02 [95% CI, 0.46–2.23]; PHASES 4: hazard ratios 1.86 [95% CI, 0.84–4.15]; PHASES 5–14: hazard ratios 2.73 [95% CI, 1.82–4.09]).

Figure 2. Example of aneurysm growth. Computed tomography angiography (CTA) in 2004 (top row) shows an unruptured intracranial aneurysm of 1.9 mm (height) by 2.2 mm (width) located on the anterior cerebral artery (ACA) A1–A2 bifurcation. Follow-up CTA in 2010 (bottom row) shows aneurysm growth (height 3.2 mm, width 4.1 mm). A and C, Default window setting. Window settings are adjusted for aneurysm measurements in B and D.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Utrecht n=305</th>
<th>Toronto n=189</th>
<th>Leiden n=63</th>
<th>Total n=557</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up in years (range)</td>
<td>3.8 (0.5–10.8)</td>
<td>1.8 (0.5–7.1)</td>
<td>2.6 (0.5–6.8)</td>
<td>2.7 (0.5–10.8)</td>
</tr>
<tr>
<td>Female</td>
<td>233 (76%)</td>
<td>147 (78%)</td>
<td>37 (59%)</td>
<td>417 (75%)</td>
</tr>
<tr>
<td>Median age years (range)</td>
<td>54 (24–83)</td>
<td>56 (18–78)</td>
<td>57 (41–84)</td>
<td>55 (18–84)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>113 (40%)</td>
<td>78 (41%)</td>
<td>29 (46%)</td>
<td>220 (41%)*</td>
</tr>
<tr>
<td>Previous SAH</td>
<td>140 (46%)</td>
<td>29 (16%)</td>
<td>17 (27%)</td>
<td>186 (34% †)</td>
</tr>
<tr>
<td>Patients with aneurysm growth</td>
<td>50 (16%)</td>
<td>32 (17%)</td>
<td>4 (6%)</td>
<td>86 (16%)</td>
</tr>
</tbody>
</table>

SAH indicates subarachnoid hemorrhage.
*Missing value for 20 cases.
†Missing value for 9 cases.
Sensitivity analysis with exclusion of cases with missing values yielded similar results.

**Discussion**

This study shows that the PHASES risk score, which provides 5-year absolute risks of aneurysmal rupture, can also be used to identify aneurysms with a high relative risk of aneurysm growth. Increasing PHASES scores were associated with increasing hazard ratios for growth.

The aneurysm growth rate of 12% during a median follow-up of 2.7 years in our study is in line with other studies on aneurysm growth, which found aneurysm growth rates of 4% to 45% with a mean follow-up of 1.5 to 18.9 years. In contrast with our study, these previous studies lacked time-dependent regression analysis in which follow-up duration was taken into account. As in previous studies, initial aneurysm size was the strongest predictor for aneurysm growth, with larger initial aneurysm size associated with an increased risk of aneurysm growth. With regard to aneurysm location, previous studies showed a trend toward a higher risk of growth for aneurysms located in the posterior circulation. We pooled aneurysms in the posterior circulation and anterior communicating arteries according to the PHASES score and observed the same trend.

In addition to the risk factors included in the PHASES score, several other risk factors for aneurysm growth have been described, such as female sex, cigarette smoking, a family history of SAH, irregular aneurysm shape, and the presence of multiple aneurysms. Implementation of additional (aneurysm-related) risk factors for aneurysm rupture, such as aspect ratio (aneurysm neck-to-dome length/neck-width), size ratio (maximum aneurysm diameter/average vessel diameter), and irregular aneurysm shape, might improve current rupture risk assessment. However, assessment whether implementation of additional risk factors improves risk prediction has several difficulties, such as the need of large numbers of patients-years as a result of an annual rupture rate of 1%. By using aneurysm growth with a rate of 12% during a median follow-up of 3 years as surrogate

### Table 3: Aneurysm-Based Univariable and Multivariable Cox Regression Analysis of Predictors of Aneurysm Growth

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable Analysis HR (95% CI)</th>
<th>Multivariable Analysis HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.40 (0.92–2.12)</td>
<td>1.40 (0.92–2.15)</td>
</tr>
<tr>
<td>Age ≥70 y</td>
<td>2.68 (1.33–5.41)</td>
<td>0.99 (0.45–2.18)</td>
</tr>
<tr>
<td>Size of aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.0 mm</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>7.0–9.9 mm</td>
<td>5.43 (2.77–10.64)</td>
<td>4.14 (2.04–8.37)</td>
</tr>
<tr>
<td>10.0–19.9 mm</td>
<td>9.37 (4.79–18.32)</td>
<td>8.06 (3.89–16.72)</td>
</tr>
<tr>
<td>≥20.0 mm</td>
<td>12.45 (4.46–34.74)</td>
<td>12.92 (4.11–40.62)</td>
</tr>
<tr>
<td>Earlier SAH from another aneurysm</td>
<td>0.45 (0.28–0.72)</td>
<td>0.62 (0.37–1.03)</td>
</tr>
</tbody>
</table>

### Table 4: Number of Aneurysms With Aneurysm Growth According to PHASES Score in Quartiles

<table>
<thead>
<tr>
<th>PHASES Quartile (Score)</th>
<th>Aneurysms With Growth/Total No. of Aneurysm</th>
<th>Percentage of Aneurysms With Growth (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (0–1)</td>
<td>10/149</td>
<td>7 (3–12)</td>
<td>Reference</td>
</tr>
<tr>
<td>II (2–3)</td>
<td>18/217</td>
<td>8 (5–13)</td>
<td>1.07 (0.49–2.32)</td>
</tr>
<tr>
<td>III (4)</td>
<td>18/125</td>
<td>14 (8–21)</td>
<td>2.29 (1.05–4.95)</td>
</tr>
<tr>
<td>IV (5–14)</td>
<td>43/243</td>
<td>18 (13–23)</td>
<td>2.85 (1.43–5.67)</td>
</tr>
</tbody>
</table>

ACI indicates anterior cerebral arteries (including anterior communicating artery); CI, confidence interval; HR, hazard ratio; ICA, internal carotid artery; MCA, middle cerebral artery; PCom, posterior communicating artery; posterior, posterior circulation arteries; and SAH, subarachnoid hemorrhage.

### Table 2: Aneurysm Characteristics

<table>
<thead>
<tr>
<th>Aneurysm Characteristics</th>
<th>Utrecht (n=403)</th>
<th>Toronto (n=246)</th>
<th>Leiden (n=85)</th>
<th>Total (n=734)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>89 (22%)</td>
<td>86 (35%)</td>
<td>14 (17%)</td>
<td>189 (26%)</td>
</tr>
<tr>
<td>MCA</td>
<td>167 (41%)</td>
<td>67 (27%)</td>
<td>32 (38%)</td>
<td>266 (36%)</td>
</tr>
<tr>
<td>ACA/PCom/posterior</td>
<td>147 (37%)</td>
<td>93 (38%)</td>
<td>39 (46%)</td>
<td>279 (38%)</td>
</tr>
<tr>
<td>Initial aneurysm size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.0 mm</td>
<td>377 (94%)</td>
<td>197 (80%)</td>
<td>85 (100%)</td>
<td>659 (90%)</td>
</tr>
<tr>
<td>7.0–9.9 mm</td>
<td>19 (5%)</td>
<td>25 (10%)</td>
<td>0 (0%)</td>
<td>44 (6%)</td>
</tr>
<tr>
<td>10.0–19.9 mm</td>
<td>6 (2%)</td>
<td>15 (6%)</td>
<td>0 (0%)</td>
<td>21 (3%)</td>
</tr>
<tr>
<td>≥20.0 mm</td>
<td>1 (&lt;1%)</td>
<td>9 (4%)</td>
<td>0 (0%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Aneurysms growth during FU</td>
<td>53 (13%)</td>
<td>32 (13%)</td>
<td>4 (5%)</td>
<td>89 (12%)</td>
</tr>
</tbody>
</table>

ACI indicates anterior cerebral arteries (including anterior cerebral artery, anterior communicating artery, and pericallosal artery); ICA, internal carotid artery (excluding posterior communicating artery); MCA, middle cerebral artery; PCom, posterior communicating artery; and posterior, posterior circulation (including vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery).
marker, the efficiency of further studies on risk prediction can be greatly facilitated.

A limitation of this study is that aneurysm growth was determined with imaging studies with variable time intervals, with the date of the first imaging study with aneurysm growth as end point. Because it is likely that aneurysms have long periods without aneurysm growth and short periods with aneurysm growth, the date of the first imaging study with aneurysm growth will be an approximation of the actual time of growth.37,38 Another limitation is that follow-up imaging of unruptured aneurysms was performed in a selected group of patients, namely in patients in whom the benefit of preventive aneurysm treatment was thought not to outweigh the risks of complications. This selection could have resulted in an underestimation of the risk of growth for the entire group of patients with unruptured intracranial aneurysms. A last limitation is that, despite the multicenter and bicontinental study population, we could not include patients from Japan and Finland in the current study, which are populations with a higher risk of rupture according to the PHASES score.7 The strength of our study is the use of a strict protocol for the measurement of aneurysm growth, which was discussed in a consensus meeting with an experienced neuroradiologist. Furthermore, our study describes the largest cohort of patients with data on natural history of aneurysm growth to date, with patients included from 3 centers and 2 continents.

Our results show that higher PHASES scores are associated with an increased risk of aneurysm growth. Because higher PHASES scores also predict aneurysm rupture, these findings suggest that aneurysm growth is a valid surrogate outcome measure for aneurysm rupture in follow-up studies on risk prediction or interventions aimed to reduce the risk of rupture.

Acknowledgments
We thank Elbert H. Witvoet, MD, for his help with data collection.

Disclosures
None.


PHASES Score for Prediction of Intracranial Aneurysm Growth

Stroke. published online March 10, 2015;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 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/early/2015/03/10/STROKEAHA.114.008198

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/03/10/STROKEAHA.114.008198.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke 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 Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
Abstract

Recovery to Preinterventional Functioning, Return-to-Work, and Life Satisfaction After Treatment of Unruptured Aneurysms

Daan Backes, MD; Gabriel J.E. Rinkel, MD, FRCPE; Irene C. van der Schaaf, MD, PhD, et al.

1 Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, and 2 Department of Radiology, University Medical Center Utrecht, Utrecht, the Netherlands.

Stroke 2015; 46: 1607-1612. DOI: 10.1161/STROKEAHA.115.008795.