Clinical relevance of short-term follow-up of unruptured intracranial aneurysms

Rob Molenberg, BSc,¹ Marlien W. Aalbers, MD, PhD,¹ Jan D. M. Metzemaekers, MD, PhD,¹ Aryan Mazuri, MD,³ Gert-Jan Luijckx, MD, PhD,² Rob J. M. Groen, MD, PhD,¹ Maarten Uyttenboogaart, MD, PhD,^{2,3} and J. Marc C. van Dijk, MD, PhD¹

Departments of ¹Neurosurgery, ²Neurology, and ³Radiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

OBJECTIVE Unruptured intracranial aneurysms are common incidental findings on brain imaging. Short-term follow-up for conservatively treated aneurysms is routinely performed in most cerebrovascular centers, although its clinical relevance remains unclear. In this study, the authors assessed the extent of growth as well as the rupture risk during short-term follow-up of conservatively treated unruptured intracranial aneurysms. In addition, the influence of patient-specific and aneurysm-specific factors on growth and rupture risk was investigated.

METHODS The authors queried their prospective institutional neurovascular registry to identify patients with unruptured intracranial aneurysms and short-term follow-up imaging, defined as follow-up MRA and/or CTA within 3 months to 2 years after initial diagnosis. Medical records and questionnaires were used to acquire baseline information. The authors measured aneurysm size at baseline and at follow-up to detect growth. Rupture was defined as a CT scan-proven and/or CSF-proven subarachnoid hemorrhage (SAH).

RESULTS A total of 206 consecutive patients with 267 conservatively managed unruptured aneurysms underwent short-term follow-up at the authors' center. Seven aneurysms (2.6%) enlarged during a median follow-up duration of 1 year (range 0.3–2.0 years). One aneurysm (0.4%) ruptured 10 months after initial discovery. Statistically significant risk factors for growth or rupture were autosomal-dominant polycystic kidney disease (RR 8.3, 95% CI 2.0–34.7), aspect ratio > 1.6 or size ratio > 3 (RR 10.8, 95% CI 2.2–52.2), and initial size ≥ 7 mm (RR 10.7, 95% CI 2.7–42.8).

CONCLUSIONS Significant growth of unruptured intracranial aneurysms may occur in a small proportion of patients during short-term follow-up. As aneurysm growth is associated with an increased risk of rupture, the authors advocate that short-term follow-up is clinically relevant and has an important role in reducing the risk of a potential SAH.

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KEYWORDS unruptured intracranial aneurysm; growth; follow-up; risk factors; subarachnoid hemorrhage

UNRUPTURED intracranial aneurysms are present in approximately 3% of the general population and represent the most common incidentally found arterial anomaly on brain imaging.^{3,24} Current clinical management of unruptured aneurysms focuses on identifying and treating aneurysms with a high estimated risk of rupture, in order to prevent the occurrence of a subarachnoid hemorrhage (SAH). Prevention of an SAH is crucial, since it is associated with significant morbidity and mortality and frequently affects relatively young individuals.¹⁷ On the other hand, the treatment-associated risks frequently outweigh the estimated risk of rupture, especially after introduction of the PHASES score.⁷ This is particularly true for patients younger than 70 years with aneurysms of

the internal carotid artery or middle cerebral artery smaller than 7 mm, which—even when assuming a high-risk profile with hypertension and a previous SAH—harbor a small estimated rupture risk of approximately 1% per year.⁷ As a result, a considerable group of patients is managed conservatively with serial follow-up imaging.

Growth of an aneurysm during follow-up increases the risk of rupture and is therefore considered as an indication for elective treatment.²² Literature regarding aneurysm growth and rupture during follow-up shows that many neurovascular centers initially recommend short-term follow-up imaging at 6 months to 1 year after diagnosis.^{6,8,10–12,14–16,18,20,22,25} Remarkably, although short-term follow-up is routinely advised, the extent of aneurysm growth

ABBREVIATIONS ADPKD = autosomal-dominant polycystic kidney disease; SAH = subarachnoid hemorrhage.

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on such a short-term, and thus the clinical relevance of short-term follow-up, is unclear.

The primary objectives of this study were to assess the extent of aneurysm growth and rupture risk during short-term follow-up in a group of patients with conservatively treated unruptured intracranial aneurysms. In addition, the association between patient- and aneurysm-specific factors and both aneurysm growth and rupture was evaluated.

Methods

Patient Selection

The study protocol was approved by the local institutional research ethics board, and informed consent was obtained as required. Our prospectively maintained neurovascular registry was queried to identify patients with unruptured saccular intracranial aneurysms between 1998 and 2017. Patients at least 18 years old with one or more unruptured intracranial aneurysms were included. We defined short-term follow-up as follow-up imaging between 3 months and 2 years after initial evaluation. Extradural aneurysms (e.g., located in the cavernous sinus) and aneurysms that were treated during follow-up were excluded, as well as patients for whom follow-up imaging was not available.

Patient Data

Patients' medical records and a questionnaire were used to collect the following baseline characteristics: age and sex of the patient at the time of initial evaluation, as well as a history of SAH from a different aneurysm, aneurysm multiplicity, cigarette smoking, use of acetylsalicylic acid, familial intracranial aneurysms, hypertension, autosomal-dominant polycystic kidney disease (ADPKD), and alcohol abuse. If a patient did not return the questionnaire, the patient's medical record was reviewed for baseline information. Hypertension was considered present if a patient had a previous diagnosis of hypertension or used antihypertensive medication. A positive familial predisposition was considered present if at least 2 first-degree relatives experienced intracranial aneurysms or SAHs. Alcohol abuse was defined as the weekly consumption of at least 300 g ethanol. We contacted the general practitioner of patients who did not return the questionnaire to verify whether the patient was still alive and to exclude possible rupture of the aneurysm. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at our institution.⁹

Aneurysm Measurements

We measured the size of all aneurysms at baseline and at follow-up. Imaging studies consisted mostly of MRA with 3D time-of-flight sequences with 0.6-mm slice thickness, and contrast-enhanced CTA with 0.75-mm slice thickness. If patients underwent multiple follow-up scanning sessions within the interval for short-term follow-up, the most recent scan was used as the follow-up scan. We used syngo.via radiological software (version VB20A, Siemens Healthcare) to perform all measurements. An-

eurysm height, width, and neck diameter were measured. We defined height as the largest distance from the center of the neck to the tip of the aneurysm dome. Aneurysm width was measured perpendicular to the height. Aspect ratio was calculated by dividing the maximum height, measured perpendicular to the neck of the aneurysm, by the neck diameter (Fig. 1).²¹ Size ratio was calculated by dividing the maximum height of the aneurysm by the average parent artery diameter.⁴ All aneurysm measurements were performed by one author (R.M.). The findings of the researcher were always compared to the findings of the neuroradiologist who reviewed the imaging during follow-up. The measurements of enlarged aneurysms were also assessed by a second reviewer (M.W.A.). When there was a discrepancy between the assessment of the reviewer and the neuroradiologist, an experienced neuro-interventionalist (M.U.) reviewed the measurements and made a final decision.

Outcome

The primary outcomes were growth or rupture during follow-up. Aneurysm growth was defined as either an increase in size of ≥ 1 mm in at least one direction or a change from a regular to an irregular shape.¹ The latter was defined as the presence of blebs, multiple lobes, or wall protrusions, as previously described by Backes et al.² Shape assessment was performed using 3D reconstructions of the MRA and CTA images, which were previously shown to adequately assess aneurysm shape.^{5,19}

Statistical Analysis

Descriptive statistics were used to describe the baseline characteristics for the group of patients with stable aneurysms and for the group with aneurysm growth or rupture. The Student t-test or Mann-Whitney U-test was used as appropriate to evaluate differences in baseline characteristics for continuous variables. Fisher's exact test was used for categorical variables. We calculated relative risks with 95% confidence intervals to identify factors associated with an increased likelihood of aneurysm growth or rupture during short-term follow-up; $p < 0.05$ was used as the limit for statistical significance. We used IBM SPSS (version 23.0, IBM Corp.) to perform the analyses.

Results

Baseline Characteristics

A total of 206 patients with 267 aneurysms met the inclusion criteria (Table 1). Twenty-two of the 206 patients had died by the time this study was conducted. Of these, 2 patients died of an SAH outside the short-term follow-up interval, 1 patient died of an SAH from an additional previously electively coiled aneurysm, and 1 patient died suddenly, potentially due to aneurysm rupture. The remaining 18 patients died of reasons unrelated to the intracranial aneurysm. Sixty-eight percent of patients who were still alive returned the questionnaire. The median age at initial presentation was 56 years (range 28–79 years), and the median interval between diagnosis and short-term follow-up was 1 year (range 0.3–2 years). The mean aneurysm size at initial evaluation was 4.7 mm (SD 2.8 mm).

FIG. 1. Illustration of the definitions of aspect ratio and size ratio.

Aneurysm Growth

Seven of 267 aneurysms (2.6%, 95% CI 1.2%–5.6%) enlarged during short-term follow-up (Table 2). Growth was detected after a median follow-up period of 1.1 years (range 0.8–1.6 years). Five patients were electively treated after growth was detected. One patient declined treatment. The remaining patient was not offered treatment, since growth was not detected by the radiologist during follow-up. However, during this study we detected the formation of a bleb during follow-up, based on which we described the aneurysm as enlarged. Treatment-associated complications occurred in 1 patient treated with stent-assisted coiling. This patient suffered an in-stent thrombosis shortly after discharge, with persistent neurological impairment at follow-up.

Aneurysm Rupture

One of 267 aneurysms (0.4%, 95% CI 0.0%–2.4%) ruptured 10 months after initial discovery (case 2). It was an anterior communicating artery aneurysm in a 79-year-old man with a maximum diameter of 22 mm at diagnosis. The aneurysm was left untreated at initial presentation due to the patient's age in combination with extensive comorbidities and intraaneurysmal thrombosis increasing the treatment-associated risks. At the time of rupture, the maximum diameter had increased to 30 mm. The patient did not survive the rupture.

Risk Factors

Patients with aneurysm growth or rupture were older than patients with stable aneurysms (median age 64 vs 56 years, $p = 0.04$). The presence of ADPKD was statistically significant for a higher likelihood of growth or rupture during short-term follow-up (RR 8.3, 95% CI 2.0–34.7), as well as an aspect ratio > 1.6 or size ratio > 3 (RR 10.8, 95% CI 2.2–52.2), and an initial size ≥ 7 mm (RR 10.7, 95% CI 2.7–42.8).

Discussion

In this study, we found that aneurysm growth during short-term follow-up does occur in a small proportion of aneurysms (2.6%). The majority of aneurysm growth and the single aneurysm rupture occurred in aneurysms larger than 7 mm. In addition to initial size, ADPKD and

TABLE 1. Patient- and aneurysm-specific baseline characteristics

	No Growth	Growth/Rupture
Patient characteristics		
No. of patients	198	8
Median age, yrs (range)	56 (28–77)	64 (54–79)
Female sex	147 (74)	6 (75)
Previous SAH	81 (41)	1 (13)
Hypertension	89 (45)	5 (63)
Current smoking	85 (43)	3 (38)
Acetylsalicylic acid use	47 (24)	4 (50)
Multiplicity	111 (56)	2 (25)
Familial intracranial aneurysms	13 (7)	0 (0)
ADPKD	6 (3)	2 (25)
Alcohol abuse	6 (3)	1 (13)
Aneurysm characteristics		
No. of aneurysms	259	8
Initial size, mm		
1.0–2.9	76 (29)	1 (13)
3.0–4.9	108 (42)	1 (13)
5.0–6.9	44 (17)	1 (13)
7.0–9.9	23 (9)	2 (25)
≥ 10.0	8 (3)	3 (38)
Irregular shape	21 (8)	2 (25)
Aspect ratio > 1.6 or size ratio > 3	52 (20)	6 (75)
Location		
Anterior cerebral arteries*	47 (18)	2 (25)
MCA	123 (48)	4 (50)
Posterior communicating artery	18 (7)	0 (0)
Internal carotid artery	50 (19)	0 (0)
Posterior circulation†	29 (11)	2 (25)

MCA = middle cerebral artery.

Data are presented as number (%) unless indicated otherwise.

* Includes the anterior communicating artery and anterior cerebral arteries.

† Includes vertebrobasilar complex and its branches.

TABLE 2. Characteristics of unstable aneurysms

Case No.	Age (yrs), Sex	Aneurysm Location	Max Diameter at Detection (mm)	Extent of Growth (mm)*	FU Duration (mos)	Outcome
1	60, F	Basilar	8.1	1.1	19	Coiling
2	79, M	ACoA	22.0	8.0	10	Rupture
3	67, F	Pericallosal	6.3	2.8	13	Coiling
4	55, F	MCA	4.1	Bleb formation	12	Observation
5	64, F	Basilar	8.2	1.2	13	Observation
6	63, F	MCA	8.8	0.7†	12	Clipping
7	54, F	MCA	1.9	1.2	14	Clipping
8	69, M	MCA	13.1	4.9	10	Stent-assisted coiling

ACoA = anterior communicating artery; FU = follow-up; max = maximum.

* Representing the maximum extent of growth, measured in one of the 3 dimensions.

† Combined with a change in morphology.

an aspect ratio > 1.6 or size ratio > 3 were associated with an increased likelihood of aneurysm growth or rupture. Enlarged aneurysms were nearly always electively treated soon after detection. Thus, short-term follow-up facilitates the detection of around 2 to 3 high-risk aneurysms for every 100 patients with a diagnosed unruptured intracranial aneurysm.

Two other studies investigated the yield of short-term follow-up for unruptured intracranial aneurysms during a relatively short follow-up period.^{10,25} Wermer et al. evaluated the yield of short-term screening in unruptured aneurysms smaller than 5 mm that were detected during screening after an SAH or because of the presence of familial aneurysms.²⁵ They identified growth in 3 (2.4%) of 125 aneurysms during a median follow-up duration of 1.3 years (range 0.7–3.8 years). One (0.8%) previously ruptured aneurysm reruptured during follow-up of additional unruptured aneurysms. A previous history of both SAH and the presence of familial aneurysms were found to be associated with an increased risk of growth or rupture during short-term follow-up. In contrast to our study, none of the aneurysms were treated, since growth was only very small. The authors argued that, given the low occurrence of growth, and the absence of clinical consequences in their cohort, short-term follow-up is not useful. In our study, we demonstrated that considerable aneurysm growth also occurs in relatively small aneurysms, underlining the clinical relevance of short-term follow-up, also for smaller aneurysms. Inoue et al. found a lower incidence of growth in 14 (1.1%) and rupture in 4 (0.3%) of 1325 aneurysms during a median follow-up duration of 1.0 year (range 0.4–1.9 years).¹⁰ Growth or rupture regularly occurred in aneurysms smaller than 5 mm, with even 44% of enlarging aneurysms being smaller than 3 mm at initial presentation. The only variable linked to an increased risk of growth was female sex. The majority of aneurysms were treated after detection of growth. The difference in frequency of aneurysm growth between both aforementioned studies may be partially attributed to the use of different measurement protocols and criteria for aneurysm growth. Wermer et al. systematically measured aneurysms in 2 directions and noted growth as an increase of at least 0.5 mm in at least one direction, while Inoue et

al. only measured the maximum diameter, used low-resolution MRA, and consequently described aneurysms as enlarged after an increase in maximum diameter of at least 1.5 times or after a change in aneurysm morphology.

Study Strengths and Limitations

Strengths of this study include the use of a strict measurement protocol to detect aneurysm growth during a predefined short-term follow-up period. Also, all patients referred to our center with an indication for follow-up imaging are routinely recommended follow-up imaging after 1 year, limiting the risk of a selection bias among conservatively treated aneurysms in our cohort. In addition, we calculated aspect and size ratios for all aneurysms; these calculations have not been described in previous studies regarding short-term follow-up but were shown to be associated with an increased likelihood of aneurysm growth or rupture in our study. Several limitations should also be addressed. The major limitation of this study is the retrospective nature of the data collection, which can potentially lead to misclassification of patients with regard to the presence or absence of specific risk factors. For a proportion of patients, mainly those who previously experienced an SAH, change in aneurysm size was assessed using multiple imaging modalities. Recent research showed no significant inter- and intraobserver variability between CTA- and MRA-based aneurysm size measurements.¹³ This suggests that changes in aneurysm size can be accurately assessed between the two different imaging modalities. Also, although we described aneurysm growth in a relatively large cohort, we were unable to perform multivariate statistical analysis due to the small number of growing aneurysms and aneurysm rupture that occurred during follow-up.²³ Furthermore, we included patients with and without a history of a previous SAH, although the mechanisms underlying aneurysm progression may be different for these groups. However, although around 40% of the patients in our cohort previously experienced an SAH, this was not associated with a statistically significant higher likelihood of aneurysm growth.

Conclusions

Growth of unruptured intracranial aneurysms occurs

during short-term follow-up. As aneurysm growth is associated with an increased risk of rupture, we believe that short-term follow-up is clinically relevant and has an important role in reducing the risk of a potential SAH.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Molenberg, Aalbers, Uyttenboogaart, van Dijk. Acquisition of data: Molenberg, Aalbers, Uyttenboogaart. Analysis and interpretation of data: all authors. Drafting the article: Molenberg, Aalbers. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Molenberg. Statistical analysis: Molenberg. Study supervision: van Dijk.

Correspondence

Rob Molenberg: University Medical Center Groningen, The Netherlands. r.molenberg@umcg.nl.