Prevalence and natural history of intracranial aneurysms

Matthias Gawlitza

Roadmap

- Prevalence of intracranial aneurysms
- Natural history of intracranial aneurysms and their risk of rupture
  - ISUIA
  - UCAS
  - PHASES
  - Other risk factors

Prevalence

- Aneurysm rupture causes SAH
- Often affects younger patient (< 65 years)
- Important morbidity and mortality
- UK annual costs of 510.000.000 £ for SAH

Cost Eff Resour Alloc 2010; 8: 6.

„The“ meta-analysis

Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis

Monique H M Vlak, Ale Algra, Raya Brandenburg, Gabriël J E Rinkel

Lancet Neurol 2011; 10: 626–36

Background Unruptured intracranial aneurysms (UIAs) are increasingly detected and are an important health-care

Prevalence

- 68 studies, 83 study populations, 1450 UIAs in 94 912 patients from 21 countries
- Crude prevalence of uruptured intracranial aneurysms (UIA): 2.9%
- 3.2 % (95% CI 1.9–5.2) in a population without comorbidity, with a mean age of 50 years, and consisting of 50% men
- PR 0·01 (95% CI 0·00–0·12) in patients <30 years
- PR 2·2 (1·3–3·6) for women >50 years
- No higher prevalence in Japan and Finland → higher rupture risk in these populations

Lancet Neurol 2011; 10: 626–36

Risk factors for UIA

	Crude (57 studies, 69 study populations, 1353 UIA)	Age adjusted (28 studies, 33 study populations, 601 UIA)		Sex adjusted (34 studies, 39 study populations, 648 UIA)		Age and sex adjusted (26 studies, 31 study populations, 600 UIA)	
	PR	PR	Adjusted PR	PR	Adjusted PR	PR	Adjusted PR
ADPKD	8·8 (4·3–18·0)	8·1 (4·0–16·0)	8·3 (4·2–16·0)	9·4 (4·7–19·0)	8·9 (4·1–19·0)	6·2 (2·9–13·0)	6·9 (3·5–14·0)
Atherosclerosis	3·1 (1·7–5·5)	1·9 (1·1–3·6)	1·5 (0·7–3·1)	2·2 (1·2–3·7)	2·2 (1·3–3·8)	1·5 (0·7–3·0)	1·7 (0·9–3·0)
Family history*	4·8 (2·6–8·8)	3·9 (2·3–6·8)	4·0 (2·3–6·9)	4·0 (2·3–6·8)	3·7 (1·8–7·5)	2·9 (1·4–6·1)	3·4 (1·9–5·9)
Pituitary adenoma	4·1 (1·1–15·0)	2·7 (1·1–6·6)	2·6 (1·1–6·0)	2·7 (1·1–6·6)	2·6 (1·0–6·7)	1·9 (0·8–4·7)	2·0 (0·9–4·6)

Data are prevalence ratio (PR) or adjusted PR with 95% CI. The prevalence from studies of people without comorbidity or of patients with a brain tumour was used as the reference (brain tumour includes brain metastases). The calculated prevalence in a study population of people without comorbidity consisting of 50% men and with a mean age of 50 years is 3·2%, based on the model with 31 study populations. UIA=unruptured intracranial aneurysm. ADPKD=autosomal dominant polycystic kidney disease. *One or more affected relatives.

***Table 2*: Prevalence ratios per reason for investigation, adjusted for sex and age**

- PR 2·2 (1·5–3·3) for positive family history of SAH or UIA with at least two first-degree relatives compared with those with only one affected first-degree relative.

Prevalence

	Total number of aneurysms (%)
Size of intracranial aneurysm	368 (100%)
<5 mm	241 (66%)
5–9 mm	101 (27%)
≥10 mm	26 (7%)
Site of intracranial aneurysm	864 (100%)
Anterior cerebral artery and branches	154 (18%)
Medial cerebral artery	303 (35%)
Internal carotid artery including posterior communicating artery	360 (42%)
Posterior communicating artery alone	85 (10%)
Vertebrobasilar arteries	47 (5%)

93%

***Table 4*: Proportions of aneurysms by size and site**

Lancet Neurol 2011; 10: 626–36

To summarize…

- The prevalence of intracranial aneurysms is around 3 %
- The prevalence of UIA is influenced by
  - Presence of polycystic disease
  - Positive family history
  - Age
  - Sex
  - Probably atherosclerosis and tobacco
- Geographical region has no effect on prevalence
- The majority of UIA measures < 5 mm

To summarize…

- Other rare factors associated with UIA
  - MEN type I syndrome
  - HHT
  - Ehlers-Danlos syndrome type IV
  - Marfan’s syndrome
  - neurofibromatosis type I
  - aortic coarctation
  - sickle cell disease
  - Moya Moya disease
  - fibromuscular dysplasia
  - systemic lupus erythematosus

Born with a time bomb in my head ... and at 40 it exploded

By MATTHEW LITTLE
UPDATED: 00:45 BST, 28 November 2010

Share 33 View comments

The headache came from nowhere. It seized the back of my head and pulsed with a pain I had never previously experienced.

I writhed in bed or paced around in an effort to escape it ... to no avail.

It was June this year. I had been avidly watching the World Cup and the England v Germany match was coming up - but with this pain in my head I didn't care about football any more.

ANEURYSMA

Mit Spiralen gegen die Bombe im Kopf

Universitätsmedizin i[redacted] 06.06.2007, 16:42 Uhr

Der Bombenentschärfer

Mit einer neuen Technik behandelt der Neuroradiologe[redacted] lebensgefährliche Gefäßausstülpungen im Gehirn. VON BAS KAST

Santé. Anévrisme cérébral : une bombe à retardement !

Publié le 15/07/2015 à 07:01 - 1 Écouter

What are the data?

Prospective studies, >50 patients, rupture as endpoint

- ISUIA (Lancet 2003; 362: 103–10)
- UCAS (N Engl J Med 2012; 366: 2474–82)
- SUAVE (Stroke 2010; 41: 1969–77)
- Juvela *et al.* (Stroke 2013; 44: 2414–21)
- Wermer *et al.* (Stroke 2006; 37: 414–18)
- Ishibashi *et al.* (Stroke 2009; 40: 313–16)

ISUIA

Unruptured Intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment

*International Study of Unruptured Intracranial Aneurysms Investigators**

Lancet 2003; **362:** 103–10
See Commentary page 90

*Investigators listed at end of report

Correspondence to: Prof David O Wiebers, KA-MZ, ISUIA Coordinating Center, Mayo Clinic, Rochester, MN 55905, USA (e-mail: wiebers.david@mayo.edu)

ISUIA

- Prospective cohort study
- 4060 pts (1917 surgery, 451 endovascular)
- 1692 pts with 2686 UIA conservatively managed
- 1077 pts with UIA and without previous rupture
  - 410 surgery and 124 endovascular during follow-up
  - Mean follow-up: 4 years
  - 51 ruptures during follow-up
  - 41 ruptures without previous SAH
  - 10 ruptures with previous SAH

ISUIA

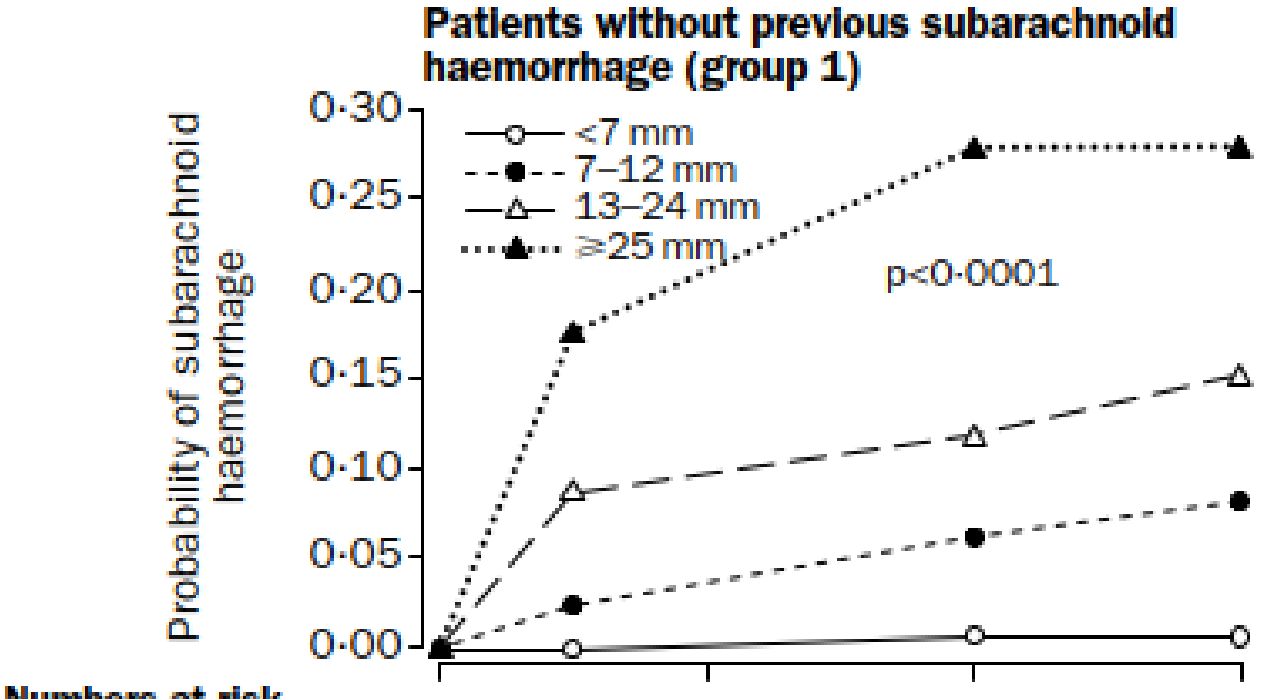
	<7 mm		7–12 mm	13–24 mm	≥25 mm
	Group 1	Group 2			
Cavernous carotid artery (n=210)	0	0	0	3·0%	6·4%
AC/MC/IC (n=1037)	0	1·5%	2·6%	14·5%	40%
Post-P comm (n=445)	2·5% n=2	3·4%	14·5%	18·4%	50%

AC=anterior communicating or anterior cerebral artery. IC=internal carotid artery (not cavernous carotid artery). MC=middle cerebral artery. Post-P comm=vertebrobasilar, posterior cerebral arterial system, or the posterior communicating artery.

Table 4: **5-year cumulative rupture rates according to size and location of unruptured aneurysm**

- Annual rupture rate of UIA <7mm: 0.1%
  - Higher rupture rates in UIA <7mm with previous SAH (p<0.0001)
- Annual rupture rate of all UIA: 0.8%

ISUIA


Patients without previous subarachnoid haemorrhage (group 1)
Probability of subarachnoid haemorrhage
0·30
0·25
0·20
0·15
0·10
0·05
0·00
<7 mm
7–12 mm
13–24 mm
≥25 mm
p<0·0001
Numbers at risk
<7mm 535 449 260 112 35
7–12 mm 304 250 129 47 14
13–24 mm 182 144 65 27 9
≥25 mm 51 46 24 9 3

ISUIA

www.centauro.it

Interventional Neuroradiology 14: 85-96, 2008

Unruptured Intracranial Aneurysms

A Critical Review of the International Study of Unruptured Intracranial Aneurysms (ISUIA) and of Appropriate Methods to Address the Clinical Problem

J. RAYMOND[1], F. GUILLEMIN[2], F. PROUST[3], A.J. MOLYNEUX[4], A.J. FOX[5], J.S. CLAIBORNE[6], J.-F. MEDER[7], I. ROULEAU[8], THE TRIAL ON ENDOVASCULAR ANEURYSM MANAGEMENT (TEAM) COLLABORATIVE GROUP

1.	Poorly defined objectives and indeterminate hypotheses	
2.	Irrelevant population of patients excluded from treatment	
3.	Selection bias at entry manifest by: (all p <.001 as compared to treated cohorts)	a. age b. Size of lesion c. History of hemorrhage from another lesion d. Location e. Multiplicity f. Symptoms
4.	Undefined observation period	
5.	Error rates and sample size not pre-specified	
6.	Excessive losses to follow-up (21% of patients followed at 4 years)	a. Excessive loss by unrelated (?) mortality (12.7%) b. Excessive loss by cross-over (32% eventually treated; reasons?)
7.	Assessment of outcome events was not blind	
8.	Exclusion of events when other potential causes for intracranial bleeding (n=31)	
9.	Exclusion of other intracranial hemorrhagic deaths (n= 19)	
10.	Exclusion of deaths of unknown cause (n= 11)	
11.	Post-hoc definition of subgroups	
12.	Arbitrary relocation of P. Com aneurysms	
13.	Inclusion of extradural lesions (cavernous lesions)	
14.	Systematic attribution to large or posterior location categories when lesions multiple (40%)	
15.	Incomplete reporting:	a. Actual numbers not provided b. Confidence intervals not provided c. Methodological obscurities

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ISUIA

- The ISUIA data are far from perfect cf selection bias
- Multiple methodological flaws
- Impression of „good data“ because of the large sample

UCAS

ORIGINAL ARTICLE

The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort

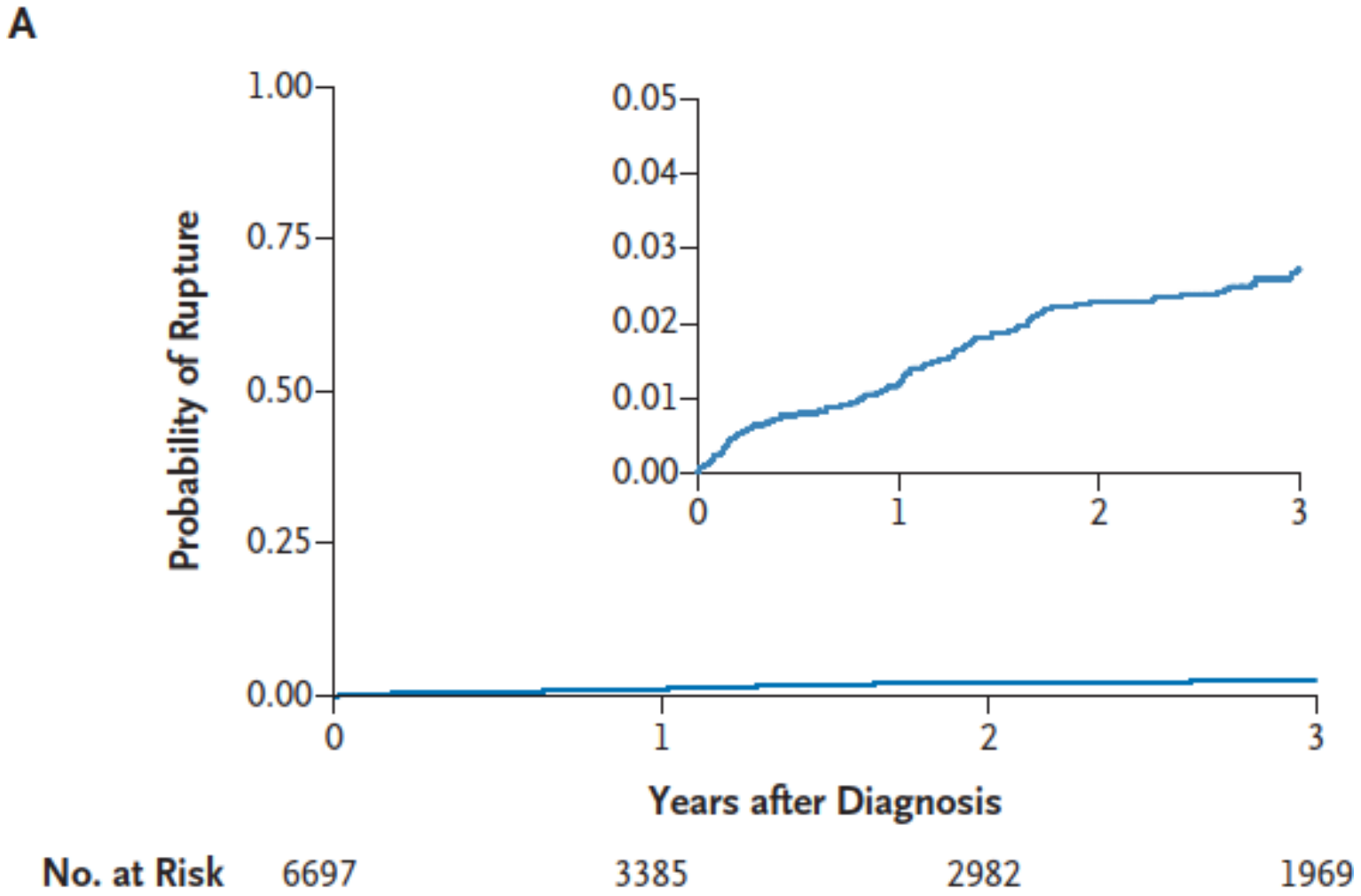
The UCAS Japan Investigators*

N Engl J Med 2012;366:2474-82.

UCAS

- Prospective cohort study
- Japan
- 5720 pts with 6697 UIA (2722 pts with 3050 IA were treated after diagnosis)
- 1696 UIA at 3 years of follow-up
- During 11.660 aneurysm years
  - 111 ruptures
  - Annual risk of rupture 0.95%

UCAS


A
Probability of Rupture
1.00
0.75
0.50
0.25
0.00
0
1
2
3
0.05
0.04
0.03
0.02
0.01
0.00
0
1
2
3
Years after Diagnosis
No. at Risk
6697
3385
2982
1969

UCAS

B

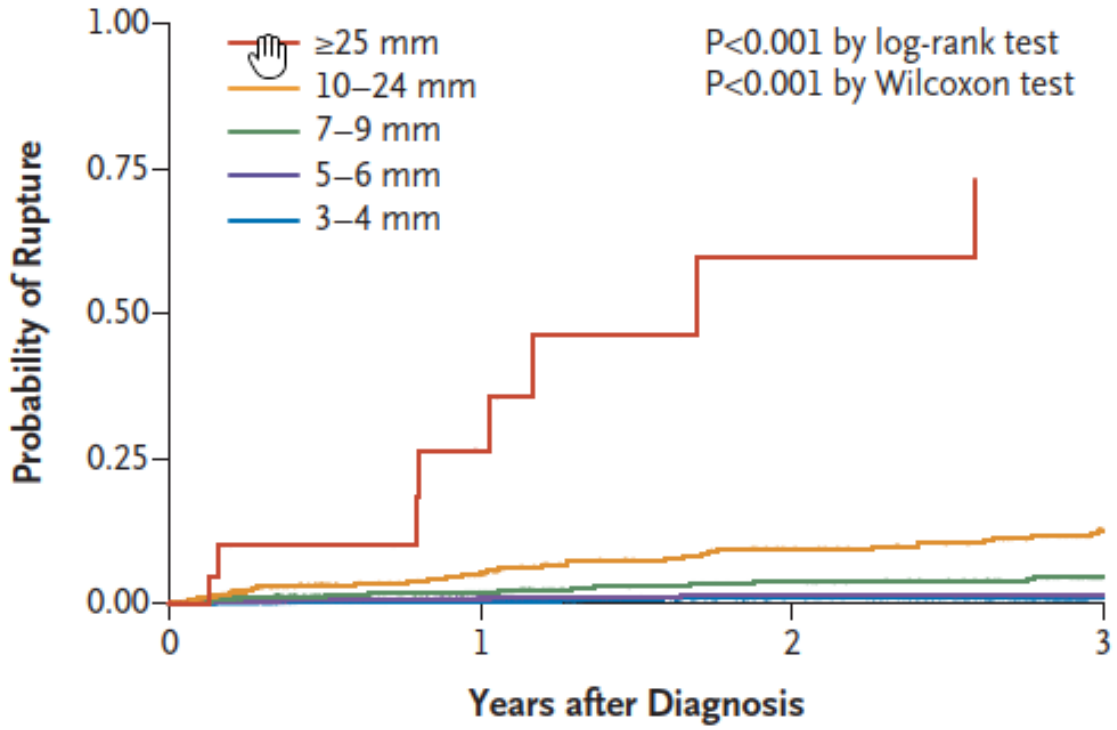
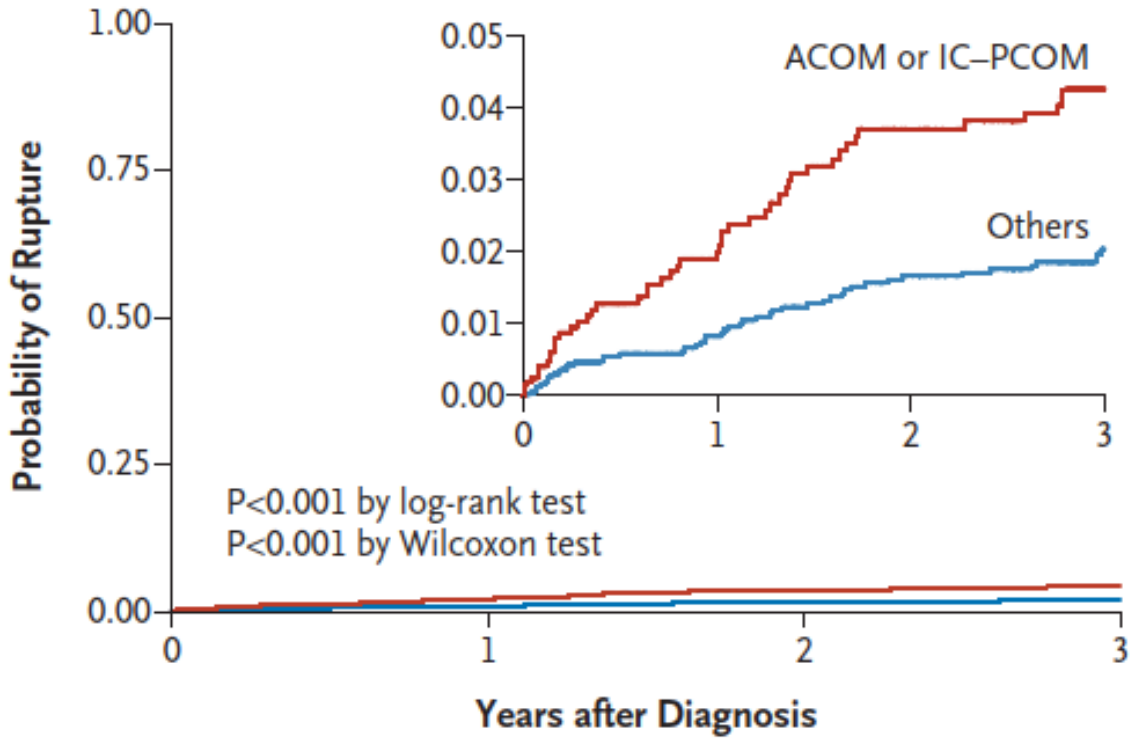


Table 2. Risk Factors Associated with Rupture of Cerebral Aneurysms.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Female sex	1.54 (0.99–2.42)	0.05
Age ≥70 yr	1.21 (0.81–1.78)	0.34
Hypertension	1.41 (0.96–2.07)	0.08
Hyperlipidemia	0.54 (0.28–1.03)	0.06
Daughter sac	1.63 (1.08–2.48)	0.02
Largest dimension of aneurysm		
3–4 mm	Reference	
5–6 mm	1.13 (0.58–2.22)	0.71
7–9 mm	3.35 (1.87–6.00)	<0.001
10–24 mm	9.09 (5.25–15.74)	<0.001
≥25 mm	76.26 (32.76–177.54)	<0.001
Location of aneurysm		
Middle cerebral artery	Reference	
Anterior communicating artery	2.02 (1.13–3.58)	0.02
Internal carotid artery	0.43 (0.18–1.01)	0.05
Internal carotid–posterior communicating artery	1.90 (1.12–3.21)	0.02
Basilar tip and basilar–superior cerebellar artery	1.49 (0.78–2.83)	0.23
Vertebral artery–posterior inferior cerebellar artery and vertebrobasilar junction	0.68 (0.16–2.87)	0.60
Other	1.48 (0.61–3.60)	0.39

UCAS

C



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UCAS

- In general, similar problems as ISUIA but larger patient and aneurysm sample
- Exclusively japanese cohort (ISUIA 90% caucasian patients)

PHASES score

Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies

Jacoba P Greving, Marieke J H Wermer, Robert D Brown Jr, Akio Morita, Seppo Juvela, Masahiro Yonekura, Toshihiro Ishibashi, James C Torner, Takeo Nakayama, Gabriël J E Rinkel, Ale Algra

Summary

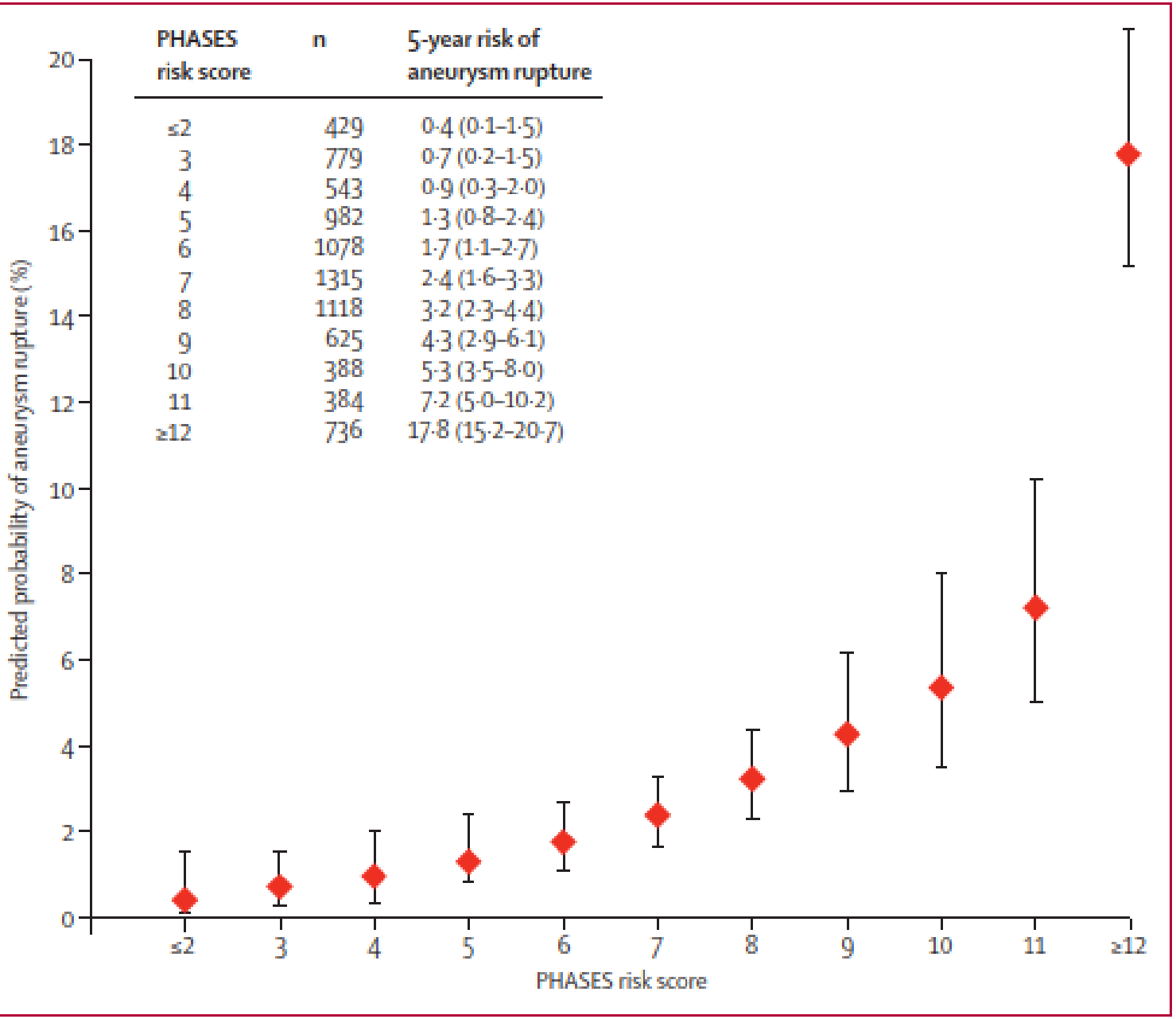
Background The decision of whether to treat incidental intracranial saccular aneurysms is complicated by limitations

Lancet Neurol 2014; 13: 59–66

PHASES score

- Pooling and analysis of 6 studies
  - ISUIA (Lancet 2003; 362: 103–10)
  - UCAS (N Engl J Med 2012; 366: 2474–82)
  - SUAVE (Stroke 2010; 41: 1969–77)
  - Juvela *et al.* (Stroke 2013; 44: 2414–21)
  - Wermer *et al.* (Stroke 2006; 37: 414–18)
  - Ishibashi *et al.* (Stroke 2009; 40: 313–16)

→ 8382 pts, 230 SAH during f/u



PHASES aneurysm risk score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
≥70 years	1
(S) Size of aneurysm	
<7·0 mm	0
7·0–9·9 mm	3
10·0–19·9 mm	6
≥20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4

Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation

Anil Can, MD
Victor M. Castro, MS
Yildirim H. Ozdemir, BA
Sarajune Dagen, RN
Sheng Yu, PhD
Dmitriy Dligach, PhD
Sean Finan, BS
Vivian Gainer, MS
Nancy A. Shadick, MD, MPH
Shawn Murphy, MD, PhD
Tianxi Cai, PhD
Guergana Savova, PhD
Ruben Dammers, MD, PhD
Scott T. Weiss, MD
Rose Du, MD, PhD

Correspondence to Dr. Du: rdu@bwh.harvard.edu

ABSTRACT

Objective: Although smoking is a known risk factor for intracranial aneurysm (IA) rupture, the exact relationship between IA rupture and smoking intensity and duration, as well as duration of smoking cessation, remains unknown.

Methods: In this case-control study, we analyzed 4,701 patients with 6,411 IAs diagnosed at the Brigham and Women's Hospital and Massachusetts General Hospital between 1990 and 2016. We divided individuals into patients with ruptured aneurysms and controls with unruptured aneurysms. We performed univariable and multivariable logistic regression analyses to determine the association between smoking status and ruptured IAs at presentation. In a subgroup analysis among former and current smokers, we assessed the association between ruptured aneurysms and number of packs per day, duration of smoking, and duration since smoking cessation.

Results: In multivariable analysis, current (odds ratio [OR] 2.21, 95% confidence interval [CI] 1.89–2.59) and former smoking status (OR 1.56, 95% CI 1.31–1.86) were associated with rupture status at presentation compared with never smokers. In a subgroup analysis among current and former smokers, years smoked (OR 1.02, 95% CI 1.01–1.03) and packs per day (OR 1.46, 95% CI 1.25–1.70) were significantly associated with ruptured aneurysms at presentation, whereas duration since cessation among former smokers was not significant (OR 1.00, 95% CI 0.99–1.02).

Conclusions: Current cigarette smoking, smoking intensity, and smoking duration are significantly associated with ruptured IAs at presentation. However, the significantly increased risk persists after smoking cessation, and smoking cessation does not confer a reduced risk of aneurysmal subarachnoid hemorrhage beyond that of reducing the cumulative dose. ***Neurology*® 2017;89:1408–1415**

Natural History of Asymptomatic Unruptured Cerebral Aneurysms Evaluated at CT Angiography: Growth and Rupture Incidence and Correlation with Epidemiologic Risk Factors[1]

J. Pablo Villablanca, MD
Gary R. Duckwiler, MD
Reza Jahan, MD
Satoshi Tateshima, MD, PhD
Neil A. Martin, MD
John Frazee, MD
Nestor R. Gonzalez, MD
James Sayre, PhD
Fernando V. Vinuela, MD

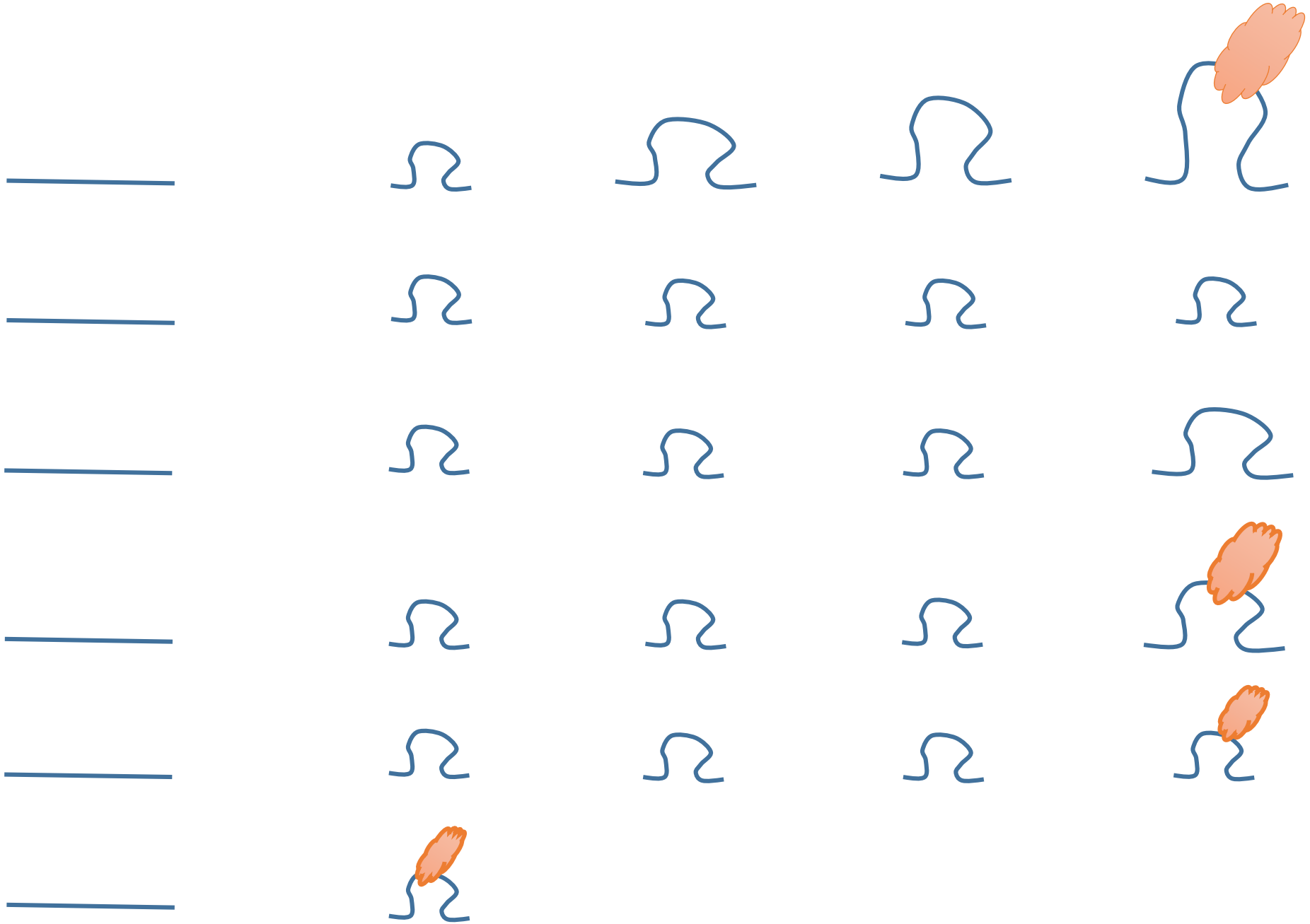
Purpose: To characterize the relationship between aneurysm size and epidemiologic risk factors with growth and rupture by using computed tomographic (CT) angiography.

Materials and Methods: In this HIPAA-compliant, institutional review board approved study, patients with known asymptomatic unruptured intracerebral aneurysms were followed up longitudinally with CT angiographic examinations. Growth was defined as an increase in one or more dimensions above the measurement error, and at least 5% volume by using the ABC/2 method.

Results:

Patients (n = 165) with aneurysms (n = 258) had a mean follow-up time of 2.24 years from time of diagnosis. Forty-six of 258 (18%) aneurysms in 38 patients grew larger. Spontaneous rupture occurred in four of 228 (1.8%) intradural aneurysms of average size (6.2 mm). Risk of aneurysm rupture per patient-year was 2.4% (95% CI: 0.5%, 7.12%) with growth and 0.2% (95% CI: 0.006%, 1.22%) without growth (P = .034). There was a 12-fold higher risk of rupture for growing aneurysms (P < .002), with high intra- and interobserver correlation coefficients for size, volume, and growth. Tobacco smoking (3.806, one degree of freedom; P < .015,) and initial size (5.895, two degrees of freedom; P < .051) were independent covariates, predicting 78.4% of growing aneurysms.

- Aneurysm rupture is often related to growth
- Rupture without growth may occur
- Growth is a non-linear process, episodes of high and low rupture risk



Adapted and modified from G. Rinkel

doi:10.1093/brain/awn187 *Brain* (2008), **131**, 2662–2665

Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case–control study

A. S. E. Bor,[1] G. J. E. Rinkel,[1] J. Adami,[2,3] H. Koffijberg,[4] A. Ekbom,[2] E. Buskens,[4,5] P. Blomqvist[2] and F. Granath[2]

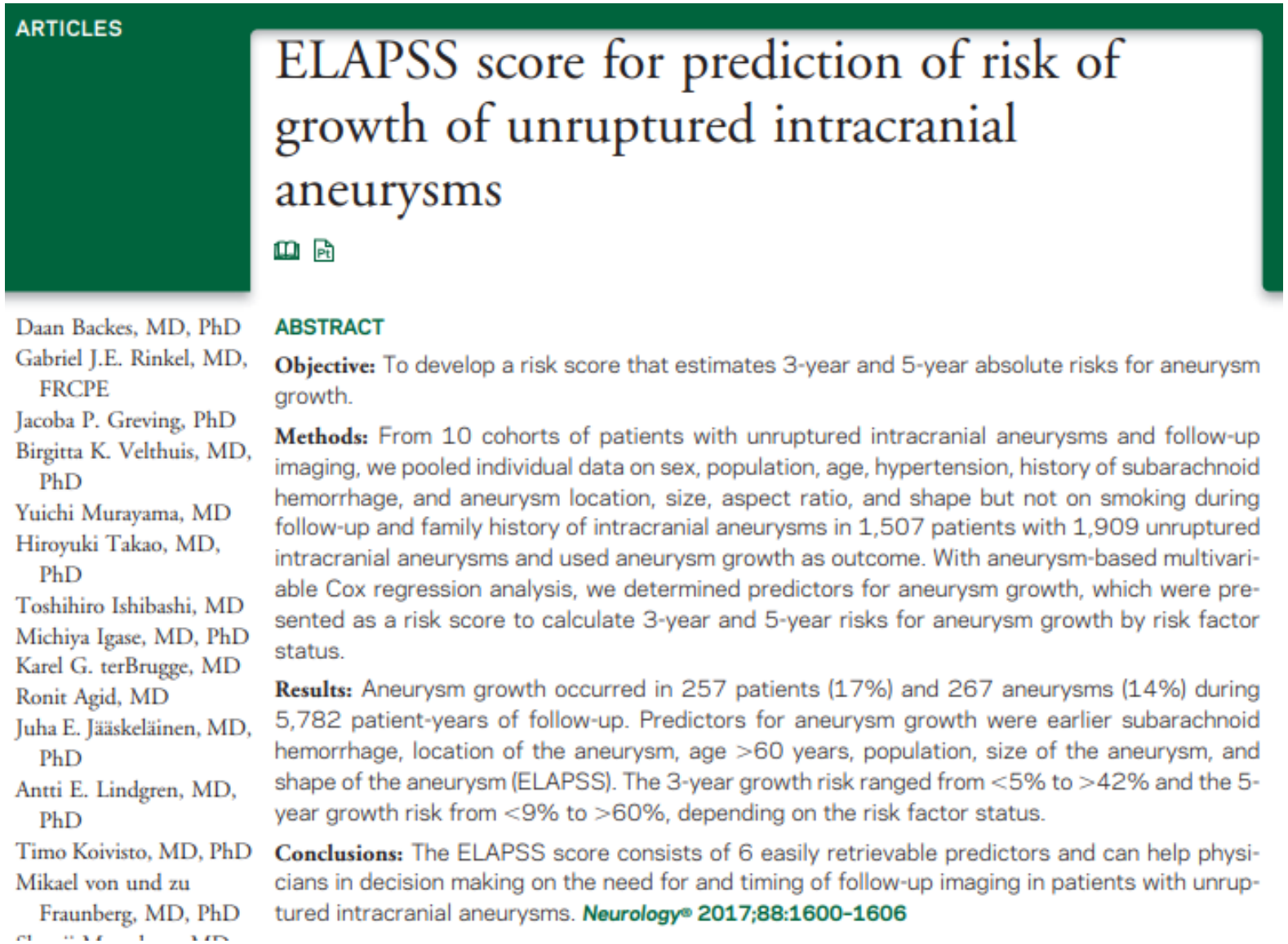
Table 1 Risk ratio of SAH according to number and type of affected relatives

	SAH patients $n = 5282$	Controls $n = 26\,402$	Odds ratio	95% CI
Number of relatives with SAH				
No affected relative	5116 (96.86%)	26 030 (98.59%)	1	Reference
1 relative	156 (2.95%)	371 (1.41%)	2.15	1.77–2.59
⩾2 relatives	10 (0.19%)	1 (0.00%)	51.0	8.56–1117*
Affected relative				
No affected relative	5116 (96.86%)	26 030 (98.59%)	1	Reference
Child	92 (1.74%)	181 (0.69%)	2.02	1.31–3.10
Sibling	46 (0.87%)	104 (0.39%)	2.40	1.72–3.34
Parent	27 (0.51%)	64 (0.24%)	2.35	1.82–3.03

To summarize

- SAH risk depends on
  - Size
  - Location
  - Previous SAH
  - Hypertension
  - Geographical region of the patient (Finland and Japan ~3 times higher rupture risk)
  - Age
  - Morphology
  - Family history
  - Tobacco smoking
  - Aneurysm multiplicity
  - Growth during follow-up

ELAPSS Score



ARTICLES

ELAPSS score for prediction of risk of growth of unruptured intracranial aneurysms

Daan Backes, MD, PhD
Gabriel J.E. Rinkel, MD, FRCPE
Jacoba P. Greving, PhD
Birgitta K. Velthuis, MD, PhD
Yuichi Murayama, MD
Hiroyuki Takao, MD, PhD
Toshihiro Ishibashi, MD
Michiya Igase, MD, PhD
Karel G. terBrugge, MD
Ronit Agid, MD
Juha E. Jääskeläinen, MD, PhD
Antti E. Lindgren, MD, PhD
Timo Koivisto, MD, PhD
Mikael von und zu Fraunberg, MD, PhD

ABSTRACT

Objective: To develop a risk score that estimates 3-year and 5-year absolute risks for aneurysm growth.

Methods: From 10 cohorts of patients with unruptured intracranial aneurysms and follow-up imaging, we pooled individual data on sex, population, age, hypertension, history of subarachnoid hemorrhage, and aneurysm location, size, aspect ratio, and shape but not on smoking during follow-up and family history of intracranial aneurysms in 1,507 patients with 1,909 unruptured intracranial aneurysms and used aneurysm growth as outcome. With aneurysm-based multivariable Cox regression analysis, we determined predictors for aneurysm growth, which were presented as a risk score to calculate 3-year and 5-year risks for aneurysm growth by risk factor status.

Results: Aneurysm growth occurred in 257 patients (17%) and 267 aneurysms (14%) during 5,782 patient-years of follow-up. Predictors for aneurysm growth were earlier subarachnoid hemorrhage, location of the aneurysm, age >60 years, population, size of the aneurysm, and shape of the aneurysm (ELAPSS). The 3-year growth risk ranged from <5% to >42% and the 5-year growth risk from <9% to >60%, depending on the risk factor status.

Conclusions: The ELAPSS score consists of 6 easily retrievable predictors and can help physicians in decision making on the need for and timing of follow-up imaging in patients with unruptured intracranial aneurysms. *Neurology*® 2017;88:1600-1606

ELAPSS Score

Figure 2 Predicted 3-year and 5-year risk of aneurysm growth

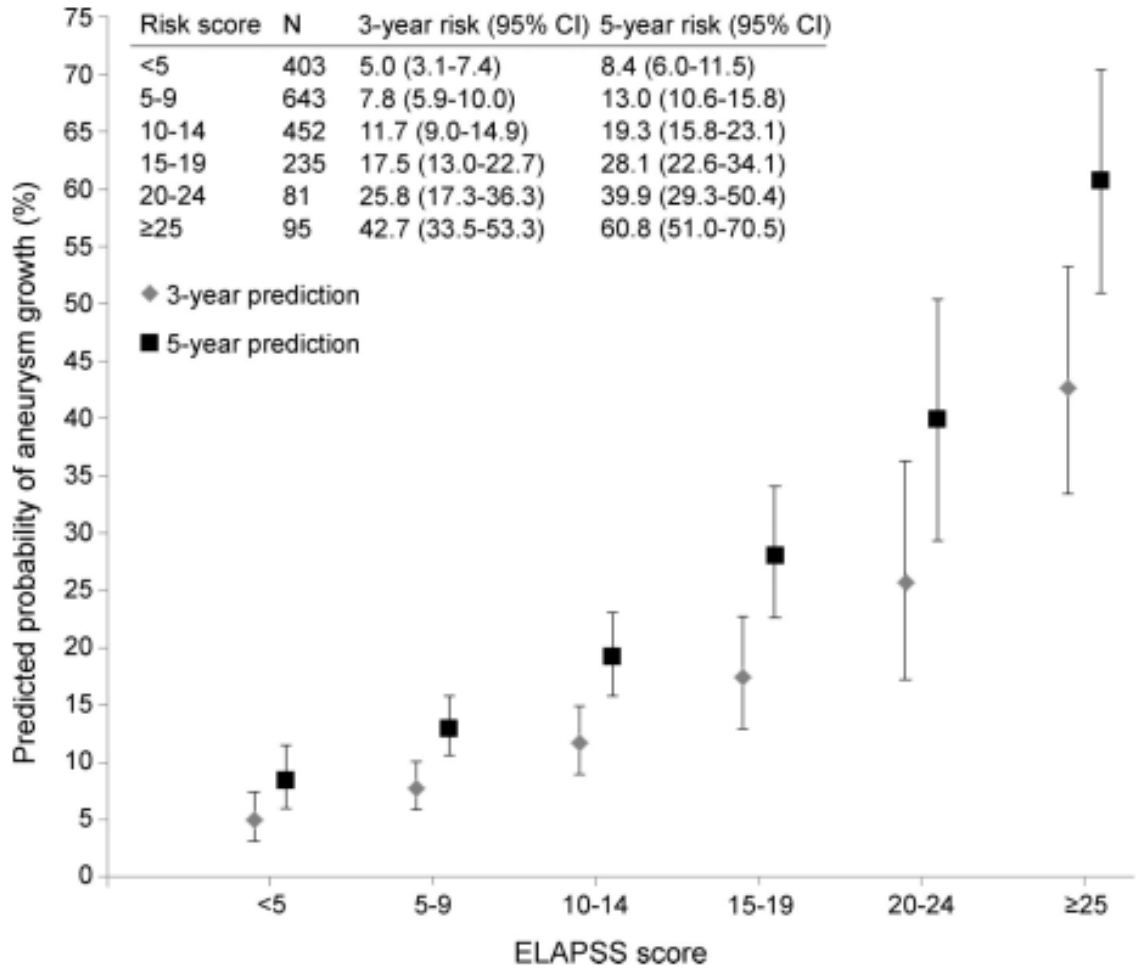


Table 3 ELAPSS score for aneurysm growth

Aneurysm growth risk score	Points
Earlier subarachnoid hemorrhage	
Yes	0
No	1
Location of the aneurysm	
ICA/ACA/ACOM	0
MCA	3
PCOM/posterior	5
Age	
≤60 y	0
>60 y (per 5 y)	1
Population	
North America, China, Europe (other than Finland)	0
Japan	1
Finland	7
Size of the aneurysm, mm	
1.0-2.9	0
3.0-4.9	4
5.0-6.9	10
7.0-9.9	13
≥10.0	22
Shape of the aneurysm	
Regular	0
Irregular	4