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

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Summary

Background **The decision of whether to treat incidental intracranial saccular aneurysms is complicated by limitations in current knowledge of their natural history. We combined individual patient data from prospective cohort studies to determine predictors of aneurysm rupture and to construct a risk prediction chart to estimate 5-year aneurysm rupture risk by risk factor status.**

Methods **We did a systematic review and pooled analysis of individual patient data from 8382 participants in six prospective cohort studies with subarachnoid haemorrhage as outcome. We analysed cumulative rupture rates with Kaplan-Meier curves and assessed predictors with Cox proportional-hazard regression analysis.**

Findings **Rupture occurred in 230 patients during 29 166 person-years of follow-up. The mean observed 1-year risk of aneurysm rupture was 1·4% (95% CI 1·1–1·6) and the 5-year risk was 3·4% (2·9–4·0). Predictors were age, hypertension, history of subarachnoid haemorrhage, aneurysm size, aneurysm location, and geographical region. In study populations from North America and European countries other than Finland, the estimated 5-year absolute risk of aneurysm rupture ranged from 0·25% in individuals younger than 70 years without vascular risk factors with a small-sized (<7 mm) internal carotid artery aneurysm, to more than 15% in patients aged 70 years or older with hypertension, a history of subarachnoid haemorrhage, and a giant-sized (>20 mm) posterior circulation aneurysm. By comparison with populations from North America and European countries other than Finland, Finnish people had a 3·6-times increased risk of aneurysm rupture and Japanese people a 2·8-times increased risk.**

Interpretation **The PHASES score is an easily applicable aid for prediction of the risk of rupture of incidental intracranial aneurysms.**

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Introduction

Intracranial aneurysms occur in around 3% of the population,[1] which means around 15 million inhabitants of the European Union have an unruptured intracranial aneurysm. Owing to the rising availability of brain imaging, the number of incidentally discovered aneurysms is increasing.[2] Rupture of intracranial aneurysms results in aneurysmal subarachnoid haemorrhage, a subset of stroke that has high case fatality and morbidity, and occurs at a relatively young age compared with other types of stroke.[3–5] In patients with unruptured aneurysms, the decision whether to treat is often not straightforward. Preventive treatment of intracranial aneurysms carries a risk of combined treatment-related fatality and morbidity of up to 5%.[6] Neurosurgical treatment has a higher risk of complications than does endovascular treatment,[7] but the risk of rupture after endovascular treatment is slightly higher than after surgery, with annual rupture rates of 0·2% according to a large systematic review.[6] The risks of treatment have to be balanced carefully against the risk of rupture.[8] However, prediction of the risk of rupture is difficult.

Many prognostic factors for aneurysm rupture have been proposed.[9] Risk factors for subarachnoid haemorrhage include aneurysm size and aneurysm site, with higher risks for larger aneurysms and aneurysms in the posterior circulation.[10–14] Multiple aneurysms,[12] female sex,[9] young age,[11,12] history of subarachnoid haemorrhage,[13] and cigarette smoking[11] have been suggested as risk factors in some studies, but not in others. Moreover, estimation of absolute risk of aneurysm rupture in a patient based on combination of risk factors is complex and a clinical risk score for aneurysm rupture does not exist. Ideally, one would be able to calculate the risk of aneurysm rupture on the basis of readily available data for patient and aneurysm characteristics.

We undertook a pooled analysis of individual patient data from prospective cohort studies in which data were reported for the natural history of unruptured aneurysms and risk factors predicting rupture. The aim was to establish predictors of aneurysm rupture in patients with unruptured intracranial aneurysms and to provide a risk prediction chart that allows physicians to easily determine the 5-year risk of aneurysm rupture on the basis of a set of routinely assessed patient and aneurysm characteristics.

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Methods

Search strategy and selection criteria

We did a systematic search in PubMed and Embase, up to July 25, 2013, to retrieve all relevant studies on risk of rupture of unruptured aneurysms. In brief, we used the keywords "(intracranial aneurysm(s) OR cerebral aneurysm(s)) AND (risk of rupture OR aneurysm rupture OR risk factors OR rupture OR unruptured OR subarachnoid hemorrhage) AND (follow-up OR natural history OR natural course)" (appendix). We selected studies that: (1) included 50 or more patients with unruptured intracranial aneurysms, (2) studied the natural course of unruptured intracranial aneurysms and studied risk factors for aneurysm rupture, (3) used a prospective study design, and (4) had aneurysm rupture (aneurysmal subarachnoid haemorrhage) as an outcome.

See Online for appendix

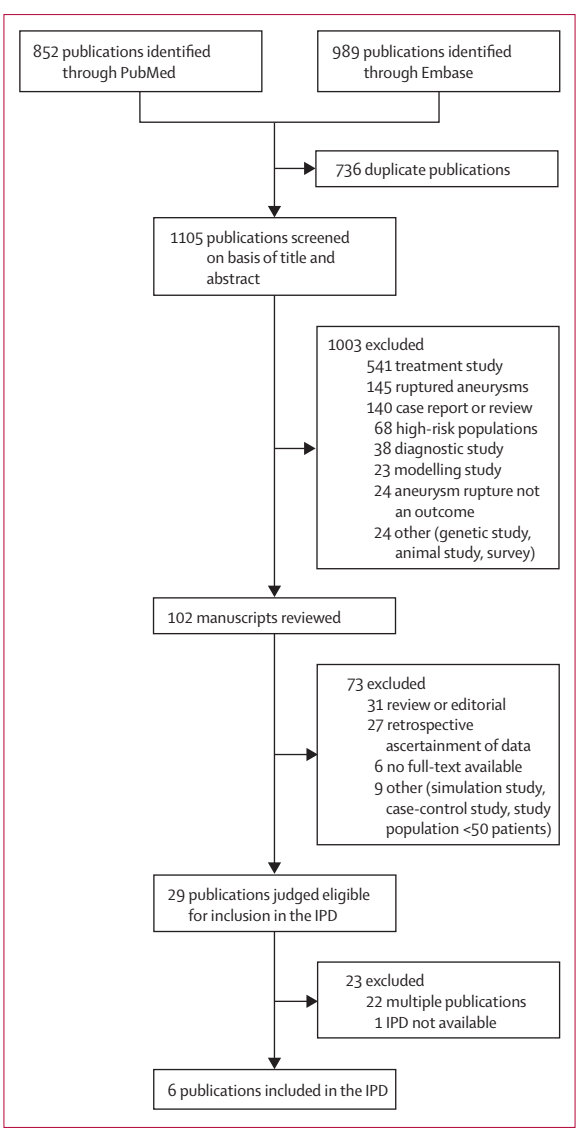

Figure 1: **Flowchart**
IPD=individual patient data.

There were no date or language restrictions other than the requirement for an abstract in English in case of foreign language journals.

One author (JPG) checked the titles and abstracts of the identified publications to select studies potentially meeting the inclusion criteria. Two authors (JPG and MJHW) independently reviewed full-text copies of the selected publications to decide which met the inclusion criteria. Of 1105 potentially relevant publications, 102 were retrieved for more detailed evaluation (figure 1). 29 publications (based on seven different cohort studies) met our inclusion criteria. Of the seven eligible cohorts, six research groups provided us with their individual patient data;[10–15] for one cohort on 111 patients we could not retrieve data.[16]

Study populations

The International Study of Unruptured Intracranial Aneurysms (ISUIA) is a large multicentre, prospective cohort study done in 60 centres in the USA, Canada, and Europe.[10] The cohort without aneurysm treatment included 1691 patients who were included between 1991 and 1998 and were followed up annually with the use of a standardised questionnaire. Patients were eligible for enrolment if they could care for themselves (modified Rankin scale <3). Patients could undergo surgical clipping or endovascular intervention at the investigator's discretion.

In Finland, 142 patients with 181 unruptured intracranial aneurysms were diagnosed between 1956 and 1978 and followed up thereafter.[11] In this long-term, single-institution cohort study, most (92%) patients harboured additional aneurysms discovered in the diagnostic work-up of another ruptured aneurysm. Follow-up evaluation was accomplished primarily by questionnaires filled in during telephone interviews with the patients or close relatives every 10 years.[11,17–20] Information about all patients was also acquired from the medical records of other hospitals and general practitioners to corroborate the accuracy of the data concerning diseases, medicines, and blood pressure. Autopsy reports and official death certificates of the patients were examined. Patients did not undergo surgical clipping or endovascular treatment during the first 25 years of follow-up.

The Small Unruptured Aneurysm Verification Study (SUAVe study) is a multicentre, prospective study done by 12 centres in Japan.[12] The baseline examination (between 2000 and 2004) included 374 patients. All incidentally found unruptured saccular aneurysms less than 5 mm in diameter were registered and followed up at 6, 12, 18, 24, 30, and 36 months and yearly thereafter. All patients were interviewed by contributors to the study, at each participating centre, who filled out a structured checklist. Patients could undergo surgical clipping or endovascular intervention at the investigator's discretion, if aneurysms enlarged by 2 mm or more in diameter or developed a bleb during the course of observation.

In Japan, 703 patients with 889 unruptured intracranial aneurysms were referred to one centre between 2003 and 2006.[13] Patients with fusiform or dissecting aneurysms and patients with less than 6 months' follow-up were excluded (102 patients with 118 unruptured intracranial aneurysms). Patients with aneurysms larger than 5 mm were regarded as potential candidates for treatment; 242 aneurysms were treated. The remaining 419 patients with 529 aneurysms elected conservative management, and CT angiography follow-up was obtained every 6 months.

In the Netherlands, a short-term clinical and radiological follow-up study was done by two centres in patients with a history of subarachnoid haemorrhage or familial intracranial aneurysms in whom an aneurysm of 5 mm or smaller was detected at screening but not treated.[15] The baseline examination (between 2002 and 2004) included 93 patients. Follow-up CT or MR angiography was done after 1 year. Patients did not undergo surgical clipping or endovascular treatment.

The Unruptured Cerebral Aneurysm Study of Japan (UCAS Japan) is a large, multicentre, prospective cohort study.[14] The baseline examination (between 2001 and 2004) included 5720 patients with newly identified, unruptured saccular aneurysms 3 mm or larger in diameter. Follow-up data for patients' clinical status were recorded through either direct interview or telephone contact at 3, 12, and 36 months and yearly thereafter. Patients could undergo surgical clipping or endovascular intervention at the investigator's discretion.

The general characteristics of the six cohort studies included in the pooled analysis are reported in table 1 and the appendix. 57 patients who were included in both SUAVe and UCAS were excluded from the SUAVe cohort, leaving 8382 patients for analysis.

Data collection

The data requested for each patient included the following at baseline: date of inclusion, age, sex, history of subarachnoid haemorrhage, smoking status, hypertension status (defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or use of antihypertensive drugs), number of aneurysms, maximum diameter of aneurysms, aneurysm location; and during follow-up: occurrence of a rupture, date of occurrence, date of a surgical or endovascular intervention, date of death, date of last follow-up assessment, and whether the patient was lost to follow-up. All data were thoroughly checked for consistency (logical checking and checking against the original publications). A few issues were queried with the responsible investigator or statistician, and all were resolved.

We classified the location of the aneurysm as the internal carotid artery, posterior communicating artery, anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery), middle cerebral artery, or posterior circulation (including the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery).

Statistical analysis

Information was available for 98% of the potential predictors (range 93–100%) and for 100% of the outcome measure. Missing data were imputed for smoking, hypertension, and aneurysm location within each cohort with the linear regression method (multivariable analyses) available in SPSS. One study did not provide data for smoking and hypertension.[13] To assign values for these missing data, we did single imputation using all relevant prognostic factors and outcome from the pooled dataset. A sensitivity analysis was done by excluding participants for whom data were missing.

Follow-up data for patients were censored at the time of an aneurysm rupture, death, the last follow-up assessment, or at the time of surgical or endovascular aneurysm treatment. We analysed rupture risk per patient. When a patient had multiple aneurysms, the largest of these aneurysms, along with its location, served to categorise the patient. Additionally, we did an aneurysm-based analysis. Kaplan-Meier curves were used to examine the

	Country	Recruitment period	Inclusion criteria	Imaging used to assess initial aneurysm characteristics	Number of patients	Mean age (range; years)	Patients with a history of SAH	Median follow-up (range; years)	Number of SAHs during follow-up	Patients treated during follow-up
ISUIA[10]	USA, Canada, and Europe	1991–98	Saccular aneurysm ≥2 mm, mRS <3	Conventional angiography	1691	55 (10–90)	615 (36%)	9·0 (0–15)	59	534 (32%)
Juvela et al[11]	Finland	1956–78	Non-fusiform, non-mycotic aneurysm	Conventional angiography	142	41 (14–60)	131 (92%)	21·0 (0–52)	34	3 (2%)*
SUAVe study[12]	Japan	2000–04	Saccular aneurysm ≤5 mm, mRS <3	MRA, CTA, DSA	374	62 (23–90)	36 (10%)	3·2 (0–20)	7	10 (3%)
Ishibashi et al[13]	Japan	2003–06	Saccular aneurysm	CTA	419	60 (17–86)	14 (3%)	2·1 (0–22)†	19	0
Wermer et al[15]	Netherlands	2002–04	Non-fusiform aneurysm ≤5 mm	CTA, DSA	93	50 (19–69)	77 (83%)	2·2 (0–15)†	1	0
UCAS[14]	Japan	2001–04	Saccular aneurysm ≥3 mm, mRS <3	MRA, CTA, DSA, conventional angiography	5720	63 (23–98)	187 (3%)	1·0 (0–9)	111	2722 (48%)

SAH=subarachnoid haemorrhage. mRS=modified Rankin scale. MRA=magnetic resonance angiography. CTA=CT angiography. DSA=digital subtraction angiography. *Three patients were treated after follow-ups of 24·4–25·9 years. †These prospective cohort studies included a retrospective component, in case an aneurysm was already present before the start of follow-up (Ishibashi et al,[13] n=17; Wermer et al,[15] n=40).

Table 1: **Cohort studies of untreated unruptured aneurysms included in our pooled analysis**

5-year absolute risk of aneurysm rupture for each potential predictor. Restricted cubic spline functions and graphs were used to establish whether continuous variables (age, aneurysm size) could be analysed as linear terms or needed transformation.[21] An age-squared term was found to be significant in the prediction model. Predictors of aneurysm rupture were studied with Cox proportional hazard regression models with stratification for cohort. Predictors were considered for entrance in the multivariable regression model irrespective of their univariable association with aneurysm rupture. The full model was simplified with a backward selection procedure (exclusion if p>0·20). We visually inspected the log minus log plot for each predictor and detected no deviations from the assumption of proportional hazards. Model performance was examined by determination of the model's discrimination and calibration. Discrimination of the model, which is expressed as a concordance (*c*) statistic, indicates to what extent the model distinguishes between patients who do and do not rupture during follow-up. The *c* statistic has a theoretical range between 0·5 and 1·0, but it typically ranges from 0·60 to 0·85 for prognostic models.[21] Calibration is the agreement between the predicted risks and the observed risks of rupture and was assessed with the calibration plot and Grønnesby and Borgan test.[22]

Prognostic models derived from multivariable regression analysis are known to overestimate regression coefficients, which results in overestimated predictions when applied in new patients.[23,24] Therefore, we internally validated our model with bootstrapping techniques, and the entire modelling process was repeated in each bootstrap sample.[24] A shrinkage factor was estimated from the bootstrap validation procedure and we shrank the regression coefficients to provide improved predictions for future patients.[23] The bootstrap procedure was also used to estimate the *c* statistic corrected for overoptimism.

	Rupture (n=220)	No rupture (n=8162)
Patient characteristics		
Women	161 (73%)	5530 (68%)
Age		
<40 years	26 (12%)	406 (5%)
40–49 years	24 (11%)	982 (12%)
50–59 years	34 (15%)	2205 (27%)
60–69 years	55 (25%)	2656 (33%)
≥70 years	81 (37%)	1913 (23%)
Hypertension	115 (52%)	3522 (43%)
Ever smoker	76 (35%)	2621 (32%)
Previous SAH	50 (23%)	1010 (12%)
Number of aneurysms		
Single	167 (76%)	6722 (82%)
Multiple	53 (24%)	1440 (18%)
Geographical region		
North America and European countries other than Finland	57 (26%)	1695 (21%)
Japan	129 (59%)	6327 (78%)
Finland	34 (15%)	140 (2%)
Aneurysm characteristics*		
Size at time of detection		
<5·0 mm	57 (26%)	3839 (47%)
5·0–6·9 mm	27 (12%)	2099 (26%)
7·0–9·9 mm	38 (17%)	1213 (15%)
10·0–19·9 mm	62 (28%)	851 (10%)
≥20·0 mm	36 (16%)	160 (2%)
Location		
Anterior cerebral arteries	41 (19%)	1525 (19%)
Internal carotid artery	83 (38%)	3091 (38%)
Posterior communicating artery	56 (25%)	1185 (15%)
Other internal carotid artery	27 (12%)	1906 (23%)
Middle cerebral artery	54 (25%)	2773 (34%)
Posterior circulation	42 (19%)	773 (9%)

Data are n (%). Ten patients with rupture of an aneurysm that was not the largest are included in the reference group (no rupture). SAH=subarachnoid haemorrhage. *Aneurysm size and location of the largest unruptured aneurysm at the time of aneurysm detection are shown.

***Table 2*: Baseline characteristics of all patients in the six cohorts**

	Univariable	Multivariable*
Female sex	1·2 (0·9–1·7)	..
Age		
Age (per 5 years)	0·6 (0·4–0·7)	0·7 (0·5–0·9)
Age squared	1·0 (1·0–1·0)	1·0 (1·0–1·0)
Hypertension	1·6 (1·2–2·0)	1·4 (1·1–1·8)
Ever smoking	0·6 (0·4–0·8)	..
Previous SAH from other aneurysm	0·7 (0·5–1·0)	1·4 (0·9–2·2)
Multiple aneurysms	1·3 (0·9–1·7)	..
Size of aneurysm		
<5·0 mm	Reference	Reference
5·0–6·9 mm	1·1 (0·7–1·7)	1·1 (0·7–1·7)
7·0–9·9 mm	2·7 (1·8–4·0)	2·4 (1·6–3·6)
10·0–19·9 mm	5·3 (3·7–7·7)	5·7 (3·9–8·3)
≥20·0 mm	14·3 (9·4–21·8)	21·3 (13·5–33·8)
Aneurysm location		
Anterior cerebral arteries	1·6 (1·1–2·5)	1·7 (1·1–2·6)
Internal carotid artery	0·6 (0·4–0·9)	0·5 (0·3–0·9)
Posterior communicating artery	2·4 (1·7–3·5)	2·1 (1·4–3·0)
Middle cerebral artery	Reference	Reference
Posterior arteries	2·5 (1·6–3·7)	1·9 (1·2–2·9)
Geographical region		
North America and European countries other than Finland	Reference	Reference
Japan	2·0 (1·4–2·9)	2·8 (1·8–4·2)
Finland	2·4 (1·5–4·1)	3·6 (2·0–6·3)

Data are hazard ratio (95% CI). SAH=subarachnoid haemorrhage. *The initial regression coefficients were adjusted for overfitting with a shrinkage factor of 0·95.

***Table 3*: Univariable and multivariable Cox regression analysis of predictors of aneurysm rupture risk in patients with unruptured intracranial aneurysms from the pooled data from six cohorts**

We derived the 5-year aneurysm rupture risk for an individual patient with a given risk factor status by applying the hazard ratios to the pooled data (appendix). A risk prediction chart was generated on the basis of the combination of risk factor levels and the corresponding risk of 5-year aneurysm rupture. All subgroups with an estimated 5-year risk greater than 15% were categorised as very high risk (>15%), since our risk prediction model tends to overestimate risk in these small subgroups (4% of the population). Additionally, we presented a risk score with scores based on the regression coefficients in the final Cox proportional hazards model.[25] Analyses were done with IBM SPSS Statistics (version 20.0) and R 2.15.2 software.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 2 shows the baseline characteristics of the 8382 patients with 10 272 unruptured intracranial aneurysms from the six cohort studies that were included in the pooled analysis. Mean age was 60 years (SD 12) and 68% of the patients were women. Rupture occurred

A Populations from North America and European countries other than Finland

Size	No hypertension, no history of SAH: Aneurysm location				Age	Hypertension, no history of SAH: Aneurysm location				Age	Both hypertension and history of SAH: Aneurysm location			
	ICA	MCA	ACA	Pcom/ posterior		ICA	MCA	ACA	Pcom/ posterior		ICA	MCA	ACA	Pcom/ posterior
≥20 mm	7	13	>15	>15	≥70 years	10	>15	>15	>15	≥70 years	14	>15	>15	>15
10·0–19·9 mm	2	4	6	7		3	5	8	9		4	7	11	13
7·0–9·9 mm	1	1	3	3		1	2	3	4		2	3	5	6
<7 mm	0	1	1	1		0	1	1	2		1	1	2	3
≥20 mm	5	9	15	>15	<70 years	7	12	>15	>15	<70 years	10	>15	>15	>15
10·0–19·9 mm	1	2	4	5		2	3	6	7		3	5	8	9
7·0–9·9 mm	1	1	2	2		1	1	2	3		1	2	3	4
<7 mm	0	0	1	1		0	1	1	1		0	1	2	2

B Japanese population

Size	No hypertension, no history of SAH: Aneurysm location				Age	Hypertension, no history of SAH: Aneurysm location				Age	Both hypertension and history of SAH: Aneurysm location			
	ICA	MCA	ACA	Pcom/ posterior		ICA	MCA	ACA	Pcom/ posterior		ICA	MCA	ACA	Pcom/ posterior
≥20 mm	>15	>15	>15	>15	≥70 years	>15	>15	>15	>15	≥70 years	>15	>15	>15	>15
10·0–19·9 mm	5	10	>15	>15		7	13	>15	>15		10	>15	>15	>15
7·0–9·9 mm	2	4	7	8		3	5	9	11		4	8	13	15
<7 mm	1	2	3	4		1	2	4	5		2	3	6	7
≥20 mm	13	>15	>15	>15	<70 years	>15	>15	>15	>15	<70 years	>15	>15	>15	>15
10·0–19·9 mm	4	7	11	13		5	9	15	>15		7	13	>15	>15
7·0–9·9 mm	2	3	5	6		2	4	6	8		3	5	9	11
<7 mm	1	1	2	3		1	2	3	3		1	2	4	5

High risk
Intermediate risk
Low risk
Very low risk

Figure 2: **Risk prediction charts for aneurysm rupture**
(A) Populations from North America and European countries other than Finland. (B) Japanese population. The number in each cell refers to the predicted risk (%) for aneurysm rupture within the next 5 years. Colour coding refers to the risk of rupture, not to the trade-off between the risk of rupture and risk of treatment. ICA=internal carotid artery. MCA=middle cerebral artery. ACA=anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery). Pcom=posterior communicating artery. posterior=posterior circulation (including the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery). SAH=subarachnoid haemorrhage.

in 230 patients during 29 166 person-years of follow-up (median 2·9 years; range 0–52 years); in 220 patients, a single or the largest aneurysm ruptured. The observed 1-year risk of aneurysm rupture was 1·4% (95% CI 1·1–1·6) and the 5-year risk was 3·4% (2·9–4·0). The Kaplan-Meier curve showed that the rate of rupture decreased during the first 5 years of follow-up (appendix).

Table 3 presents the results from a multivariable Cox proportional hazards model. Age, hypertension, history of subarachnoid haemorrhage, aneurysm size, aneurysm location, and geographical region were independent predictors of aneurysm rupture. Sex, smoking at baseline, and presence of multiple aneurysms were excluded from the model, because of their limited predictive value (p>0·20). After shrinkage of the coefficients, the *c* statistic of the final model was 0·82 (95% CI 0·79–0·85). The Grønnesby and Borgan test was not significant (p=0·07), indicating a good overall fit (appendix). We visually inspected the log minus log plot for each predictor and detected no deviations from the assumption of proportional hazards. As a sensitivity analysis, we did all analyses in a subset of data with no missing covariate data for hypertension and aneurysm location (n=7776) and found similar results. Additionally, we did an aneurysm-based analysis and the results were essentially the same.

Figure 2 shows the risk charts. In study populations from North America and European countries other than Finland, the predicted 5-year absolute risk of aneurysm rupture ranged from 0·25% in individuals younger than 70 years without vascular risk factors and with a small-sized (<7 mm) internal carotid artery aneurysm to more than 15% in individuals aged 70 years or older with hypertension, a history of subarachnoid haemorrhage, and a posterior circulation aneurysm of giant size (>20 mm). By comparison with populations from North America and European countries other than Finland, Finnish people had a 3·6-times increased risk of aneurysm rupture and Japanese people a 2·8-times increased risk. The formulae and coefficients are shown in the appendix. A simple risk score, PHASES, is presented in table 4, which can be used in combination with figure 3 to obtain approximate predictions for individual patients.

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

To calculate the PHASES risk score for an individual, the number of points associated with each indicator can be added up to obtain the total risk score. For example, a 55-year-old North American man with no hypertension, no previous SAH, and a medium-sized (8 mm) posterior circulation aneurysm will have a risk score of 0+0+0+3+0+4=7 points. According to figure 3, this score corresponds to a 5-year risk of rupture of 2·4%. SAH=subarachnoid haemorrhage. ICA=internal carotid artery. MCA=middle cerebral artery. ACA=anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery). Pcom=posterior communicating artery. posterior=posterior circulation (including the vertebral artery, basilar artery, cerebellar arteries, and posterior cerebral artery).

Table 4: **Predictors composing the PHASES aneurysm rupture risk score**

Discussion

We have developed a practical risk score (PHASES) that predicts a patient's risk of aneurysm rupture on the basis of a set of routinely assessed patient and aneurysm characteristics. We found that the largest amount of prognostic information was contained in six predictors: age, hypertension, history of subarachnoid haemorrhage, aneurysm size, aneurysm location, and geographical region. Sex, smoking status at time of aneurysm detection, and presence of multiple aneurysms had no important effect on the risk of rupture.

Reliable identification of prognostic factors for aneurysm rupture has been difficult, because the number of aneurysm ruptures during follow-up in most individual studies was too small for valid analyses.[10–13] By reanalysing data from six prospective cohort studies, we were able to include 8382 patients, of whom 230 had a subarachnoid haemorrhage during follow-up. This large number of haemorrhages enabled us to undertake multivariable analyses. To our knowledge, this study is the first to attempt to reliably predict the risk of aneurysm rupture for an individual patient on the basis of a set of easily available patient and aneurysm characteristics.

Obviously, risk scores will be more reliable if they include predictors that are already well established risk factors for aneurysm rupture. Aneurysm size and aneurysm location are such risk factors.[10–14] We found that sex, presence of multiple aneurysms, and smoking status had no added value for the prediction of aneurysm rupture when other risk factors were accounted for. This finding does not mean that these factors are not important risk factors for aneurysm rupture in isolation,

but, instead, these factors have no added value to the prediction of aneurysm rupture beyond the six predictors used in our risk score. Importantly, for smoking status we only had data for smoking at the time of aneurysm detection, and not for smoking status during follow-up (except for one cohort study[11]). The absence of a risk effect of smoking on aneurysmal rupture might therefore be accounted for by a change in smoking status after aneurysm detection. Moreover, our data should not be interpreted as a neutral effect of continued smoking during follow-up on risk of rupture. Similarly, we do not have data for blood pressure management during follow-up, so no conclusions can be drawn about presence or absence of high blood pressure during follow-up on risk of rupture. Other factors might predict aneurysm rupture, such as family history of subarachnoid haemorrhage[26] or aneurysm growth,[27] but these factors were not consistently available in our studies. Moreover, growth can only be measured during follow-up and is therefore not a characteristic available at baseline.

Our study has some limitations. First, we did patient-level analyses, and in patients with multiple aneurysms we used only the characteristics of the largest unruptured aneurysm in the analysis. Nevertheless, in the case of aneurysm rupture during follow-up, in all but ten patients the largest aneurysm ruptured. Second, some values were missing in our database. Regression imputation was used to predict missing values with information from all potential predictors and outcome. Both theoretical and empirical support is growing for the use of imputation methods instead of traditional complete case analysis.[28] We repeated all analyses in a subset of data with no missing covariables for hypertension and aneurysm location and found similar results. Third, although this model has been validated internally, it has not yet been validated externally in another population. However, this validation is currently impossible to achieve because we captured almost all published data for aneurysm rupture that are available worldwide. Fourth, different imaging modalities were used to assess the initial aneurysm characteristics and different methods of measuring aneurysm size were used across studies. Fifth, although the follow-up in most cohorts was accurate, instances of subarachnoid haemorrhage might have been missed or the aneurysm listed as the cause of the haemorrhage might have been incorrect. Such misclassification might have resulted in less accurate predictions and the overall risk of rupture might be higher if haemorrhages have been missed. Sixth, a potential for selection bias exists in this study. For example, in ISUIA and UCAS Japan many patients received treatment during follow-up. Some patients might have received treatment because of an increase in aneurysm size or the development of new symptoms, both of which are associated with increases in rupture rate. Therefore, patients with aneurysms that might have been likely to rupture were removed from the cohort,

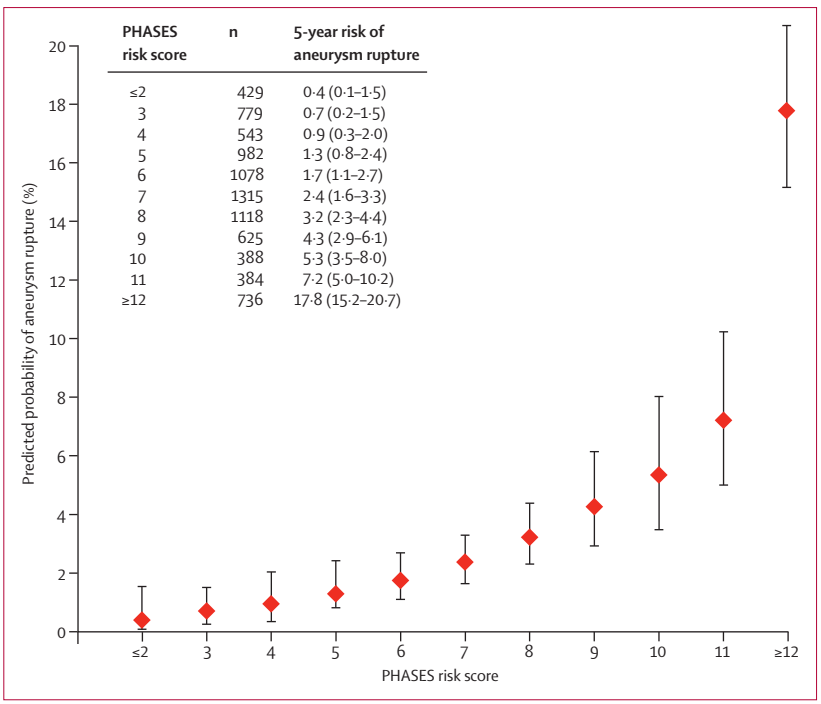

Figure 3: **Predicted 5-year risk of aneurysm rupture according to PHASES score**

despite the original intent to treat conservatively. These types of selection bias definitely affected the calculation of the risk of rupture. However, a pure natural history study is now impossible to undertake. Only the Finnish cohort was recruited during a period when unruptured aneurysms were not treated, and these patients were not operated on during the first 25 years of follow-up.[11] This factor might explain partly the increased rupture rate in the Finnish cohort. However, incidence of subarachnoid haemorrhage is higher in Finland than in other western countries and is probably caused by increased risk of aneurysm rupture.[19] Finally, the prediction holds true only for the first 5 years after aneurysm detection. This risk cannot be extrapolated over the patients' remaining lifetime, because risk of aneurysm growth and rupture are not constant over time.[29]

An important strength of our study is the large number of patients with an unruptured intracranial aneurysm from which the model was derived. Second, the natural history studies took place in several different countries, improving external validity. Third, all included studies were prospective cohort studies with careful follow-up. Fourth, the predictors in our model are well defined, easily measured clinical variables. Furthermore, both patients with previous subarachnoid haemorrhage from another aneurysm and patients with incidentally found aneurysms were included. Therefore, our risk chart seems to have broad applicability in prediction of aneurysm rupture in various populations.

Our proposed risk prediction chart, based on easily available patient and aneurysm characteristics, could

support physicians in their assessment of the risk of aneurysm rupture and serve as a valuable aid in the clinical decision as to whether preventive occlusion of the aneurysm is warranted. Further studies are needed on validation of the score, improved prediction of risks of surgical and endovascular treatment for an individual patient, and risk of aneurysmal rupture beyond the first 5 years after detection. The current risk prediction chart provides the physician and the patient with a good starting point for discussing the pros and cons of the therapeutic options.

Contributors

JPG, MJHW, GJER, and AA were involved in the design of the study. RDB, JCT, AM, TN, SJ, MY, TI, MJHW, and GJER collected data. JPG and AA were involved in the statistical analyses. JPG drafted the paper, and all authors reviewed and commented on the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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