Assessing the constancy of intracranial aneurysm growth rates - Response

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Growth rates of intracranial aneurysms: exploring constancy

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Object. The annual rate of rupture of intracranial aneurysms is often assumed to be constant, but it is unknown whether this assumption is true. Recent case reports have suggested that aneurysms grow fast in a short period of time. The authors of the present report investigated the plausibility of a constant growth rate for intracranial aneurysms.

Methods. Assuming a constant aneurysm growth rate within an individual and varying rates between individuals, a hypothetical cohort was simulated. Individuals with high growth rates will display aneurysm formation and rupture at a young age; such persons disappear early from the hypothetical cohort. As a result the mean lesion growth rate varies over time. In hypothetical cohorts with different initial mean growth rates, the authors calculated age-specific incidence rates (per 100,000 person-years) of subarachnoid hemorrhage and compared these rates with population-based data on the incidence of subarachnoid hemorrhage (per 100,000 person-years).

Results. A hypothetical cohort with a mean initial growth rate of 0.18 mm/year reproduced most closely the incidence rates observed in the population. However, even for this most plausible hypothetical cohort, age-specific incidence rates in the model differed substantially and statistically significantly from those observed in the population.

Conclusions. Based on the results of this study, it is unlikely that intracranial aneurysms in general grow at a constant time-independent rate. The authors hypothesized that the actual growth process is irregular and discontinuous, which results in periods with and without aneurysm growth and with high and low risks of rupture.
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KEY WORDS • intracranial aneurysm • simulation model • subarachnoid hemorrhage

RESEARCH on the development of intracranial aneurysms has been performed in numerous fields such as hemodynamics,[18] biomechanics,[4] histology,[6] and computational fluid dynamics.[21] Although these studies have provided new information regarding factors involved in aneurysm development, the results cannot be directly related to the growth rates of aneurysms. Given that an aneurysm's size is a main determinant in its risk of rupture,[26] lesion growth rates are a key factor in the relation among aneurysm prevalence, the risk of aneurysm rupture, and the observed incidence of SAH. Although aneurysm growth has been suggested to be erratic,[12] existing models of aneurysm screening or treatment generally incorporate a constant time-independent growth rate and risk of rupture. Aneurysms that grow fast in a short period of time[14–16,30,31] are likely to have high risks of rupture for short periods of time.[11] Variable growth rates with corresponding time-variable risks of rupture will change predictions of the SAH risk over different time intervals. Evidence regarding the actual growth process may support or challenge current assumptions and perhaps evoke new screening and/or treatment strategies for unruptured aneurysms.[24,33]

Limited empirical data exist on the change in, or the consistency of, aneurysm growth rates over time. Extensive data collection on growth rates is not feasible, because it would require frequent screening—for example, with MR angiography—of large groups of healthy individuals and persons with unruptured aneurysms. Thus, insight into aneurysm growth rates can be attained only by modeling the effects of different growth rates on aneurysms sizes and SAH incidence and comparing these results with the observed incidence of SAH in an actual population. We constructed a model suitable for the simulation of individual patient histories. Drawing from a parametric distribution, aneurysm growth rates were assigned to individuals. As aneurysm formation and

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Abbreviations used in this paper: ACoA = anterior communicating artery; ASTRA = Aneurysm Screening After Surgical Treatment for Ruptured Aneurysms; CI = confidence interval; ICA = internal carotid artery; IDR = incidence density ratio; IMGR = initial mean growth rate; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; VBS = vertebrobasilar system.

rupture occur at a young age in people with high lesion growth rates, such persons disappear early from a hypothetical cohort; therefore, the mean lesion growth rate in cohorts decreases with time. We compared age-specific SAH incidence rates (per 100,000 person-years) in simulated cohorts with various initial mean lesion growth rates with the rates observed in the general population, and we determined whether a constant intracranial aneurysm growth rate could lead to the SAH incidence observed in the actual population.

Methods

Here, we provide a textual description of the constructed model; a more detailed and mathematical description of the model is given in the *Appendix*. During the selection of relevant data from the literature, we placed emphasis on the general applicability of data. Because calculations of aneurysm prevalence and rupture risk vary widely among studies and populations,[8,20] we collected estimates from either systematic reviews or multinational studies whenever available. The calculation of incidence rates, IDRs, and corresponding CIs was based on the number of actual SAH incidents and the number of person-years in which these incidents occurred.[7]

Study Model

The model defined to measure the effect of assumptions on lesion growth rates is defined as a Markov model.[22] The most relevant parameters of this model are given in Table 1. By definition, Markov models presume that an individual is in 1 of a finite number of predefined health states. All relevant events, such as rupture of an aneurysm or death from an unrelated event, are represented as transitions from one health state to another. The probabilities associated with these transitions typically depend on the characteristics of the individual under consideration. The term "(micro)simulation" refers to tracking the separate histories of individuals through the model in discrete time steps (cycles). In a dynamic simulation the characteristics of individuals not only determine the transition probabilities, but also are permitted to change over time, that is, during the simulation. We constructed a dynamic simulation Markov model in which patient age and aneurysm size changed over time. Note that because aneurysm growth rates are constant within an individual but vary between people, the risk of SAH increases differently over time for each person.

During each time cycle in the model, individuals might have died of causes other than SAH, aneurysms might have ruptured, or patients might have survived without experiencing SAH. Moreover, during each cycle an aneurysm grew according to a specific growth rate. Based on estimates in Table 1, the annual risk of SAH was derived from a continuous function relating aneurysm diameter and location to the risk of rupture. This function is depicted in Fig. 1 (for details see *Appendix*). As a result of SAH or subsequent treatment, an individual might have survived and the aneurysm obliterated by treatment or the patient might have died. Additional simplifying assumptions made with respect to the Markov model are described in Table 2.

TABLE 1

Summary of transition probabilities used in the model

Parameter	Value
overall 28-day case-fatality rate for SAH*	0.417
continuous relative risk of aneurysm rupture per mm of lesion diameter*	1.11
annual rate of rupture for aneurysms†	
2–6 mm	0.011
7–9 mm	0.023
10–26 mm	0.028
relative prevalence of aneurysms‡	
in ACoA	0.224
in MCA	0.282
in ICA	0.396
in VBS	0.098
risk of rupture per 100 person-years for aneurysms‡	
in ACoA	1.1
in MCA	1.1
in ICA	1.2
in VBS	4.4
initial mean age of persons (yrs)§	
in Scenarios 1 & 3	25 ± 10
in Scenarios 2 & 4	35 ± 10

  * Ingall et al., 2000.
  † Juvela et al., 2000.
  ‡ Rinkel et al., 1998.
  § Minimum of 0.

The Scenarios

Each simulated cohort in the model comprised 50,000 individuals, with an equal number of men and women. All individuals harbored 1 aneurysm with an initial diameter of 0 mm. Accordingly, patient age at the start of the simulation was equal to the age at which aneurysm formation began. Because aneurysms are thought to develop during early adulthood,[11,20] the initial ages of individuals were drawn from a normal distribution, with a mean age of 25 ± 10 years (mean ± standard deviation) in Scenario 1. The variation in individual (constant) lesion growth rates was obtained using a Weibull probability distribution (see *Appendix*). We simulated a large number of shapes for this distribution given that the actual variation in individual lesion growth rates in the population was unknown. For each shape we calculated the IMGR, that is, the mean lesion growth rate over all individuals at the start of the simulation. Because episodes of SAH, on average, occur more often in persons with high lesion growth rates than in those with low rates, the mean aneurysm growth rate across alive individuals will decrease as time passes, that is, over the subsequent cycles. To account for the fact that the actual age at which aneurysm formation begins is unknown, we tested the sensitivity of our results to changes in the initial age of individuals and the risk of rupture by defining various scenarios (Table 1). The risk of rupture in Scenarios 3 and 4 (Fig. 1 *lower*) was set to half that of Scenarios 1 and 2 (Fig. 1 *upper*).

Observational Data From the Literature Used to Analyze Simulation Output

We compared the outcomes in simulations with population-based data on SAH incidence rates, assum-
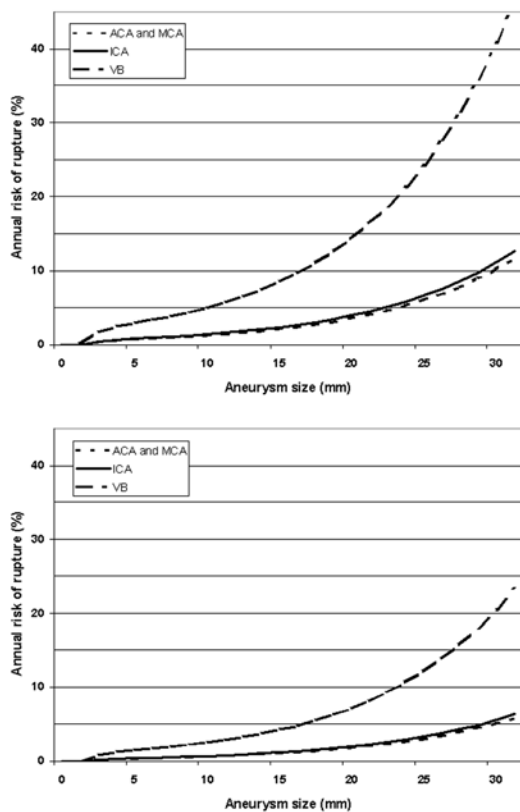
FIG. 1. Line graphs showing the continuous function relating aneurysm size and location to the annual risk of rupture for Scenarios 1 and 2 (*upper*) and 3 and 4 (*lower*). The annual risk of rupture increases smoothly and exponentially with aneurysm size. It is highest for aneurysms in the VBS (VB) and lowest for those in the ACoA (ACA) and MCA.

ing that the latter represented the true underlying process of aneurysm formation and rupture. In a multinational SAH epidemiological study, age-specific annual rates of SAH were given for 8 age categories, 25–29, 30–34, . . . , 55–59, and 60–64 years, for 11 different populations.[8] In a systematic review based on 5 autopsy and 5 angiography studies, the prevalence of aneurysms in the age categories 20–39, 40–59, and 60–79 years was provided.[20] We combined these data and calculated the age-specific annual risk of aneurysm rupture (Table 3).

To assess the similarity between the incidence patterns in the simulated cohorts and those in the actual population, we calculated the ratio of the incidence rate in the simulation and that in the actual population for the 8 age categories shown in Table 3. For all scenarios the number of person-years simulated per age category was in the range of 0.25–3.00 times the actual number of person-years reported in the literature. This finding ensures that the CIs in Fig. 2 are based on uncertainty for both the simulated and actual incidence rates.

Assessing the Correspondence Between Model Output and Actual Data

From a set of 2000 tested lesion growth rate distributions per scenario, we selected those that resulted in SAH incidence rates most closely resembling those observed in the population (see *Appendix*). Note that the best-fitting values for the initial mean lesion growth rates would accurately approximate the incidence in some (the intermediate) age categories given that the specific goal of the optimization procedure was to find such values. Moreover, incidence rates in the intermediate age categories would be approximated more accurately than those in the lowest

TABLE 2
Assumptions underlying the Markov model in this study

No.	Description
1	every individual has exactly 1 aneurysm from the initial age of a person (when aneurysm size is assumed to be = 0 mm) to his or her age at death; the probability of additional aneurysm formation was omitted, although a lesion may not be considered an aneurysm if it is, for example, <2 mm in diameter; from the perspective of a growth process, all aneurysms start as 0-mm lesions; no conceptual distinction is made btwn lesions < or >2 mm
2	aneurysm size can only increase and never decrease; it is assumed that the max (theoretical) growth rate for any aneurysm is 10 mm/yr; it is also assumed that, in general, large growth rates occur less often than small growth rates
3	no risk factors for aneurysm rupture on a person level are taken into account; person sex might affect the risk of rupture in some populations,* but this effect varies widely among populations;† other person characteristics such as genetic disposition or habits (for example, smoking) are not modeled explicitly, but different individual growth rates will account for these characteristics implicitly
4	individuals w/ SAH either survive or die due to the SAH or subsequent treatment; patients who survive the episode are assumed to have been treated for the ruptured aneurysm; these persons start the next month w/ an aneurysm size of 0 mm; because of the constant growth rates w/in individuals, the aneurysm will always start growing again (at the same rate) after a period of 12 mos following lesion treatment
5	risk of aneurysm rupture is based on the risk for asymptomatic unruptured aneurysms in persons who have not had an SAH, even though (see Assumption 4) some of the aneurysms in the model occurred in patients who had suffered an SAH & survived, & therefore may have a higher risk of rupture
6	individuals w/ SAH can become disabled; however, the model does not differentiate btwn disabled & healthy individuals in any way
7	probability of aneurysm rupture is a function of aneurysm size & location only; aneurysm shape is not taken into account; aneurysms <1 mm in diameter will not rupture; because aneurysms 2 mm in diameter have been known to rupture, a risk of rupture was included for aneurysms >1 mm in diameter
8	total number of SAH incidents is calculated; no distinction is made btwn 1st & recurrent episodes of SAH

* From Juvela et al., 2001, and Rinkel et al., 1998.
† From Ingall et al., 2000.

TABLE 3

Number of person-years, SAH incidents, and aneurysm prevalence per age category to determine the age-specific risk of rupture per person-year

Age Category	No. Person-Years Per Age Category*	No. SAH Incidents Per Age Category*	Prevalence of Aneurysm Per Age Category†	Age-Specific Risk of Aneurysm Rupture Per Person-Year in % (95% CI)
25–29	6,383,137	168	0.0135	0.194 (0.167–0.226)
30–34	4,787,353	198	0.0135	0.307 (0.267–0.353)
35–39	4,787,353	296	0.0135	0.457 (0.408–0.513)
40–44	4,787,353	402	0.018	0.467 (0.424–0.515)
45–49	4,787,353	590	0.018	0.685 (0.632–0.743)
50–54	3,989,461	593	0.018	0.823 (0.762–0.895)
55–59	3,191,569	499	0.018	0.868 (0.795–0.948)
60–64	3,191,569	532	0.022	0.758 (0.697–0.826)

* Calculated from Ingall et al., 2000.
† Rinkel et al., 1998.

and highest age categories. A constant lesion growth rate that accurately approximated the SAH incidence rate for a certain age category would also probably approximate the incidence rates reasonably well for neighboring age categories but not for more distant ones. Thus, the best-fitting values for the initial mean lesion growth rates would approximate the incidence rates reasonably well for intermediate age categories but not for age categories at the extremes, which implies the best overall fit to the observed incidence rates. The incidence rates from the model and from the observational data were bound to be similar for some age categories given our optimization procedure; therefore, we defined the criterion for the hypothesis of constant aneurysm growth to remain plausible, in one of our scenarios, as follows: all 95% CIs for the IDRs should include the value of 1 for all age categories simultaneously.

Results

Analysis of Simulation Output for Exemplary Growth Rate Distributions

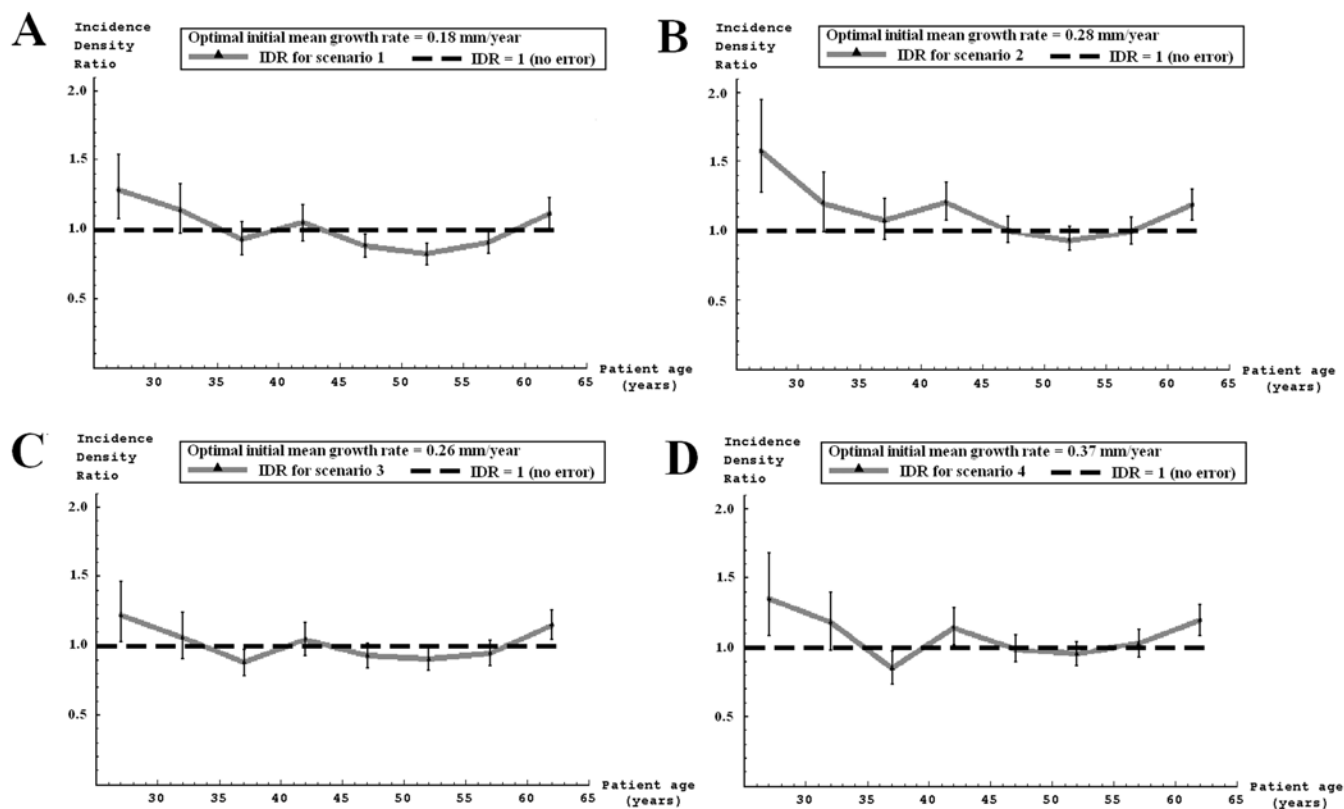Our results were based on the growth rate distribution

FIG. 2. Graphs depicting the IDRs for the SAH incidence rates for 8 age categories in the hypothetical cohort and the actual population together with their CIs. The IDRs for Scenarios 1 (A), 2 (B), 3 (C), and 4 (D) are shown. The *horizontal line* at IDR = 1 indicates the level at which the results from the simulation and the actual incidence agree perfectly.

that led to SAH incidence rates most similar to those observed in the population. As an illustration of the effects of different growth rate distributions on simulation output, the simulation outputs for 4 different distributions of growth rates in Scenario 1 are shown in Fig. 3. The mean growth rates at the start of the simulation corresponding to these 4 distributions are 0.05, 0.15, 0.50, and 1.50 mm/year. We depicted the absolute number of SAH incidents (Fig. 3A and B) and the annual risk of rupture (Fig. 3C and D). The solid black line in Fig. 3D represents the actual annual risk of rupture for different age categories observed in the population (Table 3). In addition, Fig. 4 *left* depicts the average diameter of aneurysms at the time of rupture, and Fig. 4 *right* illustrates the average diameter of unruptured aneurysms. High initial mean lesion growth rates resulted in a large number of persons with fast-growing aneurysms and thus led to a large number of SAH incidents in the first 3 decades of follow-up (Fig. 3A and C). Low IMGRs resulted in a small number of SAH episodes. The number of SAH incidents, according to patient age, more or less followed a gaussian distribution, with an increasing value as the IMGR decreased (Fig. 3B). The value of the IMGR also affected the average aneurysm size considerably. With an IMGR of 1.50 mm/year, almost all aneurysms ruptured within the first 2 decades of follow-up and had an average diameter of ~ 40 mm at that time (Fig. 4 *left*). This finding clearly was not corroborated by observations in the actual population. Figures 3 and 4 combined suggest that values for the IMGR in the range of 0.15–0.50 mm/year most accurately reproduced the SAH incidence rates observed in the population but with sizes of ruptured aneurysms much larger than those observed in clinical practice.

Analysis of Simulation Output

The IMGR that best fit actual observations was 0.18 mm/year (see *Appendix* for the optimization method used). This initial rate resulted in SAH incidence rates in the simulated cohort that were closest to those in the actual population. Corresponding IDRs are shown in Fig. 2A. Even with this best possible match, significant differences appeared between the incidence rates obtained through simulation and those observed in the population. The IDRs calculated for Scenarios 2 (mean starting age 35 ± 10 years), 3 (mean starting age 25 ± 10 years, 50% reduction in the risk of rupture compared with that in Scenario 1), and 4 (mean starting age 35 ± 10 years, 50% reduction in the risk of rupture compared with that in Scenario 1) are shown in Fig. 2B–D. The corresponding best-fitting IMGRs were 0.28 mm/year (Scenario 2), 0.26 mm/year (Scenario 3), and 0.37 mm/year (Scenario 4). Figure 2B–D indicates that the best-fitting value for the IMGR was sensitive to the initial age of individuals and to the risk of rupture. However, the different assumptions defined in Scenarios 2, 3, and 4 did not lead to a better match between results in the simulated model and those from the literature. There was no single IMGR that for each age category resulted in an incidence rate similar (that is, with overlapping 95% CIs) to that observed in the population. Figure 2 shows that in all scenarios there were statistically significant differences
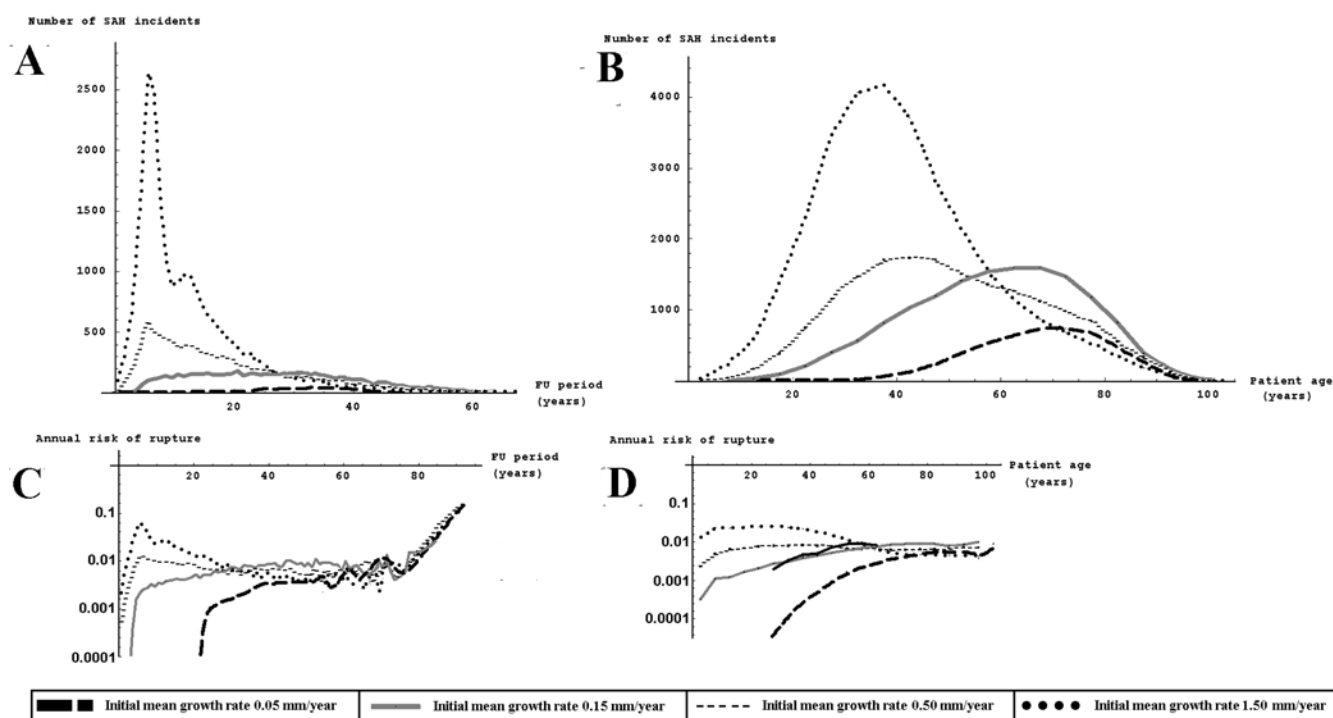

FIG. 3. Graphs depicting the number of SAH incidents during follow-up (A) and as function of patient age (B). Graphs illustrating the annual risk of rupture, on a logarithmic scale, during follow-up (C) and as a function of patient age (D), for 4 illustrative IMGRs. The *solid black line* in panel D represents the annual SAH incidence rates derived from the literature. FU = follow-up.
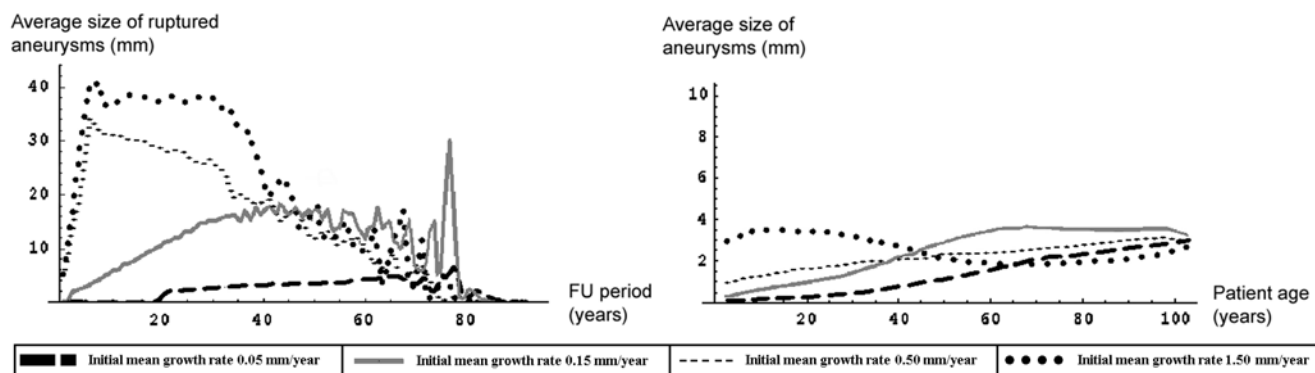
Fig. 4. Graphs showing for 4 illustrative IMGRs the average size of aneurysms at the time of rupture during follow-up *(left)* and the average aneurysm size as function of patient age *(right)*. The peaks in the *left panel* for the high IMGRs are artifacts of the simulation model. For high mean growth rates almost all aneurysms rupture in the first 40 years of follow-up and too few rupture thereafter to provide a reliable estimate of the average size of ruptured aneurysms.

between the incidence in the simulated cohort and that observed in the population.

Discussion

We did not find a constant time-independent pattern of intracranial aneurysm growth that produced lesion incidence rates and sizes similar to those in the general population. It is therefore highly implausible that intracranial aneurysms grow at a constant time-independent rate. On an individual level, periods of practically no growth can alternate with bursts of growth and high rupture risk. A period of growth can result in an episode of SAH or an enlarged but stable aneurysm. The periods without growth are probably long, because lesion growth is observed in only 1 of 4 persons with an aneurysm over a mean follow-up period of 6.7 years.[25]

Our evidence for the implausibility of a constant aneurysm growth rate is based on a modeling approach and is therefore indirect. Empirical data on aneurysm growth rates from large, prospective follow-up studies are currently unavailable, and it is unlikely that such data will be collected in the near future, if ever. Frequent imaging in a large cohort of patients with unruptured aneurysms seems infeasible and unethical. Thus, in the area of aneurysm growth rates we must rely on anecdotal data and modeling studies. Although empirical data on intracranial aneurysms are hard to collect, the notion of irregular growth is supported by empirical data on abdominal aortic aneurysms.[13]

Two recent studies have been conducted using mathematical modeling to validate the results of the International Study of Unruptured Intracranial Aneurysms.[3,9,27,32] In one of these studies it was assumed that an aneurysm grows at a rate proportional to the cubic root function of the lesion age, which results in a faster than linear (that is, constant) growth rate.[3] In the other study the authors made the basic assumption that aneurysms gain volume at a constant rate, implying that the growth rate in aneurysm diameter decreases exponentially as the diameter itself increases.[32] Although these studies remain open to considerable discussion,[29] both demonstrated irregular growth rates. Nonetheless, their outcomes diverge from observations made in

clinical practice and population-based studies. In one study the model predicted much higher estimates than those observed in the general population for the prevalence of intracranial aneurysms, incidence of SAH, and mean age at the time of SAH.[3] The other study lacked variability in aneurysm growth rates, which resulted in a risk of rupture that was independent of aneurysm size.[32] Whether fully deterministic functions of irregular aneurysm growth can provide results that are corroborated by clinical evidence is currently unclear; aneurysm growth can also be chaotic and thus unpredictable.

Several features of aneurysm development were not incorporated into our model. First, the occurrence of multiple aneurysms was not accounted for. The International Study of Unruptured Intracranial Aneurysm investigators reported that 25% of persons without a previous SAH had multiple aneurysms, but this factor was not a statistically significant predictor of subsequent SAH.[9] If rupture did occur in persons with multiple aneurysms it was usually the largest lesion that actually ruptured.[11,28] In our model this lesion would be the first aneurysm to develop, which would determine the majority of rupture risk. Accordingly, we believe that given the goal of the current study this notion can be ignored. Second, in defining the probability of death after SAH or subsequent treatment, we did not include patient age as a determinant. The age-specific risks of rupture in Table 3 could only be determined up to the age of 64 years. Nevertheless, although case fatality has been shown to differ across age groups 0–60 years and ≥ 61 years,[9,19] we suggest that the impact of ignoring the aging effects on outcome will remain marginal. After all, the majority of events occur at an age < 60 years. A third aspect that was intentionally ignored is the risk of aneurysm rupture related to lesion growth. Although aneurysm growth can directly increase the risk of rupture,[1,10,17] no quantitative data on this relation are available; however, any risk associated with aneurysm growth in the model automatically would be constant within individuals (and varying between them). This additional risk of rupture would lead to lower best-fitting growth rates and cause all hypothetical aneurysms to rupture (on average) earlier than in our present model. The decrease in the time to rupture would be high-

est in individuals with high lesion growth rates, leading to higher incidence rates at low ages and lower incidence rates at high ages in the simulated cohort. Note, however, that the incidence in the first age category for the simulated cohort is already significantly higher than the corresponding incidence in the observed population (Fig. 2). A further increase in incidence for the low age categories would therefore yield incidence rates incompatible with observations from actual cohort studies.

A fourth phenomenon that has not been taken into account is the possibility of a spontaneous decrease in aneurysm size. Although decreases in size have been reported,[11] we did not include aneurysm shrinkage in our model, because structured data for a substantial number of persons were unavailable. Omission of this process may have influenced our results, although not greatly given the rarity of aneurysm shrinkage. In summary, these 4 simplifications, used to keep our model comprehensible, are unlikely to have influenced the results considerably.

Risk factors for SAH, such as hypertension, smoking, and aneurysm shape, were not explicitly included in the model but were accounted for by the variation in growth rates between individuals in the population. Variation in growth rates leads directly to variation in aneurysm sizes between individuals and thus in variation in the risks of rupture between individuals. Persons with high growth rates, such as current smokers with hypertension, can thus be considered to have multiple risk factors, and individuals with low growth rates can be regarded as having no risk factors.

Conclusions

Our results show that a constant, time-independent growth rate of intracranial aneurysms is unlikely. Instead, growth is much more likely to be irregular and discontinuous, which leads to periods with and without growth and with high and low risks of rupture. The irregular growth of intracranial aneurysms has important implications for research, clinical practice, and screening effectiveness. In follow-up studies of unruptured aneurysms, the risks of rupture should be reported for the entire follow-up period; it is not rational to recalculate observed risks into yearly risks of rupture. As a consequence, for a particular patient with an unruptured aneurysm, data on the risk of rupture are known for only the relatively short periods of time that have been observed in follow-up studies; extrapolating remaining lifetime events from these risks is no more than guesswork. Screening of persons considered to have a risk of aneurysm growth and subsequent SAH, such as those with a family history, becomes increasingly less effective if the irregularity leads to the rapid development and rupture of aneurysms.[23]

Appendix

In this *Appendix* we discuss the details of the model, in particular, the calculations with respect to the risk of aneurysm rupture and the details of the distribution of growth rates in the model. Moreover, we explicate the iterative process by which the best-fitting growth rates (that is, the growth rates for which the hypothetical cohort most closely reproduced the incidence rates observed in the population) were determined.

We used Mathematica (version 5.1, Wolfram Research, Inc.) to implement the model. In our model aneurysm growth rates were constant within a person but varied between individuals, and thus, the risk of SAH increased differently over time for each individual. This fact complicated the use of Poisson processes as a nonstationary Poisson process must be defined for each individual to model episodes of SAH. A dynamic (micro)simulation was therefore preferred over a set of nonstationary Poisson processes, because the former requires only individual growth rates and a function for the risk of rupture based on aneurysm size, whereas the latter requires individual intensities for the risk of rupture and a function describing the manner in which these intensities should change over time.

The Model

The complete model is visualized in Fig. 5. In this figure $q_{g,x}$ is the probability of dying within the next time cycle at x years of age and of sex g.[2] The function $F_{ProbSAH}(s,l)$ represents the risk of rupture per time cycle as a function of aneurysm diameter s (in mm) and location l (where $l \in$ {ACoA, MCA, ICA, VBS}; see Fig. 1). For the overall 28-day case fatality rate for SAH and subsequent treatment, 0.417 was used,[8] and all survivors were assumed to have had successfully obliterated aneurysms. Aneurysm growth occurs every cycle in all individuals, except in persons with recently obliterated aneurysms, who have $F_{Treated}$ set to 1 for the 1st year after an SAH episode (see Assumption 4 in Table 2). All points in time and differences over time (for example, age) are measured in months. Because aneurysms can exhibit fast growth in a short period of time,[15,28] we used time cycles of 1 month in our simulation; thus, we were able to accurately determine the time of rupture and the aneurysm size at that time, even for fast-growing aneurysms. The simulation stopped when all individuals from the hypothetical cohort had died.

Annual Risk of Aneurysm Rupture

To determine the annual risk of aneurysm rupture we used the estimates from Table 1. Given the continuous relative risk of rupture per mm increase in diameter and an appropriate midpoint of 1 of the size intervals 2–6, 7–9, or 10–26 mm, it is possible to define a function that calculates the annual risk of rupture for a given aneurysm size. Using these 3 intervals, their midpoints of 4, 8, and 14 mm, and the continuous relative risk of rupture of 1.11 per mm, 3 exponential functions could be defined for this risk: F_1 through the point represented by aneurysm size 4 mm and risk of rupture 0.011 (x and y, respectively), F_2 through the point described as aneurysm size 8 mm and risk of rupture 0.023, and F_3 through the point represented by aneurysm size 14 mm and risk of rupture 0.028. Note that for the size interval 10–26 mm, the midpoint or average value of 14 mm was used, instead of 18 mm, because larger aneurysms are more rare than smaller ones. Only a single function for the risk of rupture is required; therefore, we defined the function F_{AVG} as the average of F_1, F_2, and F_3. To comply with Assumption 7 (Table 2)—that is, aneurysms smaller than 1 mm will not rupture—we set F_{AVG} to 0 for aneurysms of size s, so that $0 \leq s < 1$ mm. Finally, to ensure that the annual risk of rupture rose smoothly from 0 at $s = 1$ mm, an additional alteration was made to F_{AVG}: for aneurysms of size s, where $1 \leq s < 4$ mm, the value of F_{AVG} is multiplied by the factor $(^1/_3(s-1))^{1/3}$. The function F_{AVG} can be related to the diameter-cube hypothesis;[5] that is, the annual rupture risk of an aneurysm varies as the 3rd power of its diameter D, so that rupture risk = kD^3, where k is a constant. We calculated that for the aneurysm sizes 10–30 mm, the F_{AVG} closely resembles $kD^{2.5}$. For aneurysm diameters 1–10 mm, the F_{AVG} still represents a small risk of rupture, whereas kD^3 decreases to 0 very quickly with decreasing aneurysm diameter.

From Table 1 a hypothetical average rate of rupture for the 4 cited locations can be computed (1.95/100 person-years). Given the location l of an aneurysm, where $l \in$ {ACoA, MCA, ICA, VBS}, we denote the relative risk of rupture for that location by RR_l, with
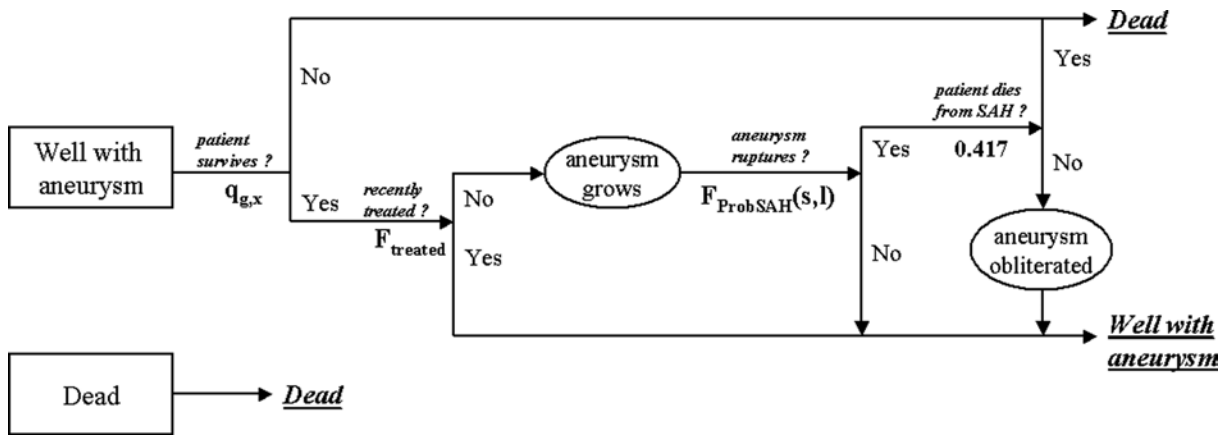
FIG. 5. Schematic showing the Markov model for the hypothetical cohort of patients. The transition probability $q_{g,x}$ denotes the mortality quotient for an individual of sex g and age x, $F_{Treated}$ indicates whether or not a particular person was treated after surviving an episode of SAH in the last 12 cycles (months), and $F_{ProbSAH}(s,l)$ denotes the risk of rupture of an aneurysm of size s mm at location l.

$RR_{ACoA} \approx 0.564$, $RR_{MCA} \approx 0.564$, $RR_{ICA} \approx 0.615$, and $RR_{VBS} \approx 2.256$. Now the function $F_{ProbSAH}(s,l)$ for an aneurysm of diameter s mm and location l is defined as follows: $F_{ProbSAH}(s,l) = RR_l \times F_{AVG}(s)$.

This function is continuous and strictly increasing for $s > 1$ mm. Furthermore, it is smooth; that is, there are no thresholds at which the risk of rupture changes abruptly (there is no 10-mm barrier).[9,17]

Distribution of Aneurysm Growth Rates

No information on the distribution of growth rates for individuals is available from the literature for reasons outlined above. From the ASTRA study we know that in a group of 610 individuals who had recovered completely from a previous SAH and undergone aneurysm clipping or coiling, aneurysm growth occurred in 25% (mean follow-up period 6.7 years).[25] In this study, growth was detected if an aneurysm had grown (on average) at least 0.5 mm in 7 years, that is, ~ 0.075 mm/year. Any aneurysm growth on average < 0.075 mm/year would not have been detected on CT angiography. Because it seems that in the majority of individuals with aneurysms these lesions do not grow and because it is known that in the minority of people with growing aneurysms the growth rates can be substantial (for example, surpassing 2 mm/year), different distributions of constant growth rates were defined for individuals who do and do not have noticeable aneurysm growth.

Growth Rate Distribution for Aneurysms Without Noticeable Growth

Within the model, aneurysms do not grow noticeably if their growth (if any) cannot be measured, that is, if they grow < 0.075 mm/year on average, as was the case in 75% of the participants in the ASTRA study. For an individual with an aneurysm that does not exhibit measurable growth, the actual growth rate is determined by drawing a random growth rate value from a uniform distribution with a minimum 0 mm/year and a maximum 0.075 mm/year. In the aforementioned 75% of participants, however, the actual aneurysm growth rate would be so small (on average 0.0375 mm/year) that the lesions probably would not reach even 1 mm in diameter, the size below which aneurysms cannot rupture in the model.

Growth Rate Distribution for Aneurysms With Noticeable Growth

Aneurysms that noticeably grow have an average growth rate of > 0.075 mm/year. For persons with these specific aneurysms a Weibull distribution was defined, depending on a shape parameter α and a scale parameter β, which represented the distribution of possible growth rates. The parameter β is a pure number (that is, it is dimen-

sionless) known as the "Weibull slope" because its value is equal to the slope of the regressed line in a probability plot. The values of the parameters α and β defining the Weibull distribution cannot be assigned any medical interpretation. The main reason for using a Weibull distribution is the flexibility with respect to the shapes this distribution can take on for different combinations of (α, β). Note that according to Assumption 2 in Table 2 all growth rates should fall in the range of 0–10 mm/year, and the probability density function of the distribution of growth rates should (approximately) be decreasing over this range. The right tail of the Weibull distribution may be infinite for some combinations of (α, β); therefore, any growth rates randomly drawn from the distribution that are > 10 mm/year are rejected, and new random values are drawn until a valid growth rate is determined. This rejection process effectively increases the probabilities of growth rates in the range of 0–10 mm/year to an extent proportional to the value of these probabilities. The result of this process is a distribution that has the same shape in the range 0–10 mm/year as the Weibull distribution. Given that the shape of the distribution of individual growth rates (that is, the form or appearance of the probability distribution curve) is unknown, a large set of (α, β) values was used, representing different shapes, to evaluate the scenarios. To define the shape of the Weibull distribution, α and β values remained in the range of 0–50. For an individual with an aneurysm that exhibited measurable growth, the actual growth rate of that lesion was determined by drawing a valid growth rate value from the Weibull distribution and adding to it the minimum measurable growth rate of 0.075 mm/year.

Determining the Aneurysm Growth Rate for Individuals

Each individual has a 75% chance of belonging to the group of persons without measurable growth and a 25% chance of belonging to the group with measurable growth. For all persons in the simulation an individual growth rate was determined as follows: a random drawing process indicated to which of the 2 groups a person belonged, and thereafter the aneurysm growth rate for an individual was determined using either the uniform distribution or the Weibull distribution, as described above.

Growth Rate Characteristics of the Hypothetical Cohort

After determining all the individual aneurysm growth rates, it is possible to calculate, for example, the mean and median growth rate for the hypothetical cohort. Note that the mean value of all individual growth rates is to be interpreted as the IMGR, that is, the mean growth rate at the start of, not throughout, the simulation process. Once the simulation process starts, individuals with high lesion growth rates

will have higher chances of dying each month (due to a higher risk of SAH) than those with a near-zero growth rate, which causes the mean growth rate to decline with time. The values used for (α, β) lead to IMGR values in the range of 0–2.5 mm/year. Although an IMGR of > 2 mm/year may seem high, remember that for all combinations of (α, β) 75% of all persons have a growth rate < 0.075 mm/year. High IMGRs are therefore caused by a small number of individuals with very high lesion growth rates (for example, on the order of 5–10 mm/year) and not by a large number of individuals with fairly high growth rates (for example, on the order of 0.5–2 mm/year).

Determining the Best-Fitting Growth Rate Distribution

The different shapes the unknown growth rate distribution can take were defined by a set of values for (α, β), with both α and β in the range 0–50. For a specific value of (α, β) the age-specific SAH incidence rates in the hypothetical cohort were compared with actual incidence rates in the population from the literature (Table 3). To assess the difference or error between this simulation output and observed incidence rates, the IDR (that is, the ratio of incidence rates) was calculated for the 8 age categories 25–29, 30–34, . . . , 55–59, and 60–64 years. Calculation of the IDR and its 95% CI was based on the number of SAH incidents observed and the number of person-years in which these incidents were observed.[7] The error for the model, given some value for (α, β), was defined as follows:

$$Err_{\alpha,\beta} = \sqrt{(IDR_{25-29} - 1)^2 + ... + (IDR_{55-59} - 1)^2 = (IDR_{60-64} - 1)^2}$$

By definition $Err_{\alpha,\beta}$ has a value ≥ 0 for all values of (α, β), with values close to 0 indicating little discrepancy between the incidence rates in the hypothetical cohort and those in the population from the literature and large values indicating a substantial mismatch. We determined the best-fitting shape of the growth rate distribution, that is, the (α, β) value for which $Err_{\alpha,\beta}$ has the lowest value, for each of the 4 scenarios in 2 steps. Step 1: A set of 1000 random values for (α, β) was constructed, with α and β in the given range. For each value of (α, β), the model was simulated and the value of $Err_{\alpha,\beta}$ was calculated. From the 20 smallest values for $Err_{\alpha,\beta}$, a range of values for the IMGR was derived for which simulation output was closest to the observed incidence rates. For Scenario 1, this range was determined to be 0.13–0.24 mm/year. Step 2: A new set of 1000 random values for (α, β) was constructed for which the IMGR value corresponding to each (α, β) combination had to fall in the IMGR range determined in Step 1. For each value of (α, β) the model was simulated, and the value of $Err_{\alpha,\beta}$ was calculated again. The values calculated for (α, β) leading to the smallest value of $Err_{\alpha,\beta}$ were accepted as the best-fitting values for (α, β). The IDRs corresponding to the best-fitting value of (α, β) were calculated.

For Scenario 1 the best-fitting value for (α, β) was found to be (20.92, 0.54), and the IDRs calculated for the 8 age categories 25–25, 30–34, . . . , 55–59, and 60–64 years were equal to 1.29, 1.14, 0.93, 1.05, 0.88, 0.82, 0.91, and 1.12, respectively. The set of IDRs for all 4 scenarios together with their 95% CIs is depicted in Fig. 2. For all scenarios the number of person-years simulated per age category was in the range of 0.25–3.00 times the number of person-years per age category in the literature (Table 3). This result ensures that the CIs for the IDRs were based on the uncertainty in both the simulation output and the incidence rates observed in the population. The number of individuals in the simulation could be increased to calculate even smaller CIs, based almost completely on the uncertainty surrounding the observed incidence rates. However, simulating more individuals would not lead to different results because the CIs for the IDRs obtained using a simulation of 50,000 individuals already failed to encompass the value of 1 in several age categories, for all scenarios.

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