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Comparison of 2 Approaches for Determining the Natural History Risk of Brain Arteriovenous Malformation Rupture

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Estimating risk of intracranial hemorrhage (ICH) for patients with unruptured brain arteriovenous malformations (AVMs) in the natural course is essential for assessing risks and benefits of treatment. Traditionally, the survival period starts at the time of diagnosis and ends at ICH, but most patients are quickly censored because of treatment. Alternatively, a survival period from birth to first ICH, censoring at the date of diagnosis, has been proposed. The authors quantitatively compared these 2 timelines using survival analysis in 1,581 Northern California brain AVM patients (2000–2007). Time-shift analysis of the birth-to-diagnosis timeline and maximum pseudolikelihood identified the point at which the 2 survival curves overlapped; the 95% confidence interval was determined using bootstrapping. Annual ICH rates per 100 patient-years were similar for both the birth-to-diagnosis (1.27, 95% confidence interval (CI): 1.18, 1.36) and the diagnosis-to-ICH (1.17, 95% CI: 0.89, 1.53) timelines, despite differences in curve morphology. Shifting the birth-to-diagnosis timeline an optimal amount (10.3 years, 95% CI: 3.3, 17.4) resulted in similar ICH survival curves ($P = 0.979$). These results suggest that the unconventional birth-to-diagnosis approach can be used to analyze risk factors for natural history risk in unruptured brain AVM patients, providing greater statistical power. The data also suggest a biologic change around age 10 years influencing ICH rate.

arteriovenous malformations; intracranial hemorrhages; risk factors; survival analysis

Abbreviations: AVM, arteriovenous malformation; CI, confidence interval; ICH, intracranial hemorrhage; SD, standard deviation.

Much attention has focused recently on the wisdom of treating unruptured brain arteriovenous malformations (AVMs) (1, 2). Although rare, brain AVMs are an important cause of intracranial hemorrhage (ICH) in young adults. Brain AVM cases are technically challenging and resource-intensive to manage with the available therapeutic modalities (surgery, radiosurgery, or embolization). Currently, treatment decisions are based on weighing the risk of invasive treatment against the risk of spontaneous ICH in the untreated natural course. However, relatively few risk factors for ICH exist, and the uncertainty of risk-benefit has led to an ongoing randomized clinical trial of unruptured brain AVM for testing whether best medical therapy has better outcomes than procedural intervention (http://clinicaltrials.gov/ct/show/NCT00389181). Because of the complexity of AVM treatment and a wide range of expert opinions, it is unlikely that a single clinical trial can settle all of the questions related to management strategies. Thus, observational studies will still be needed to identify factors that influence ICH risk in the natural history course, a critical part of both individual patient management decisions and planning of future clinical trials.

A fundamental challenge in studying longitudinal risk of ICH is that it is exceedingly difficult to achieve large sample sizes with sufficient numbers of outcome events to study risk factors; many patients are censored shortly after diagnosis for treatment, resulting in short follow-up times. Furthermore, brain AVM is a rare disease and the ICH event rate in the natural course is low—approximately 2–4 events per 100 patient-years (typically presented as 2%–4% per year) after diagnosis (3–8). However, approximately 50% of patients initially present to medical attention with an ICH,

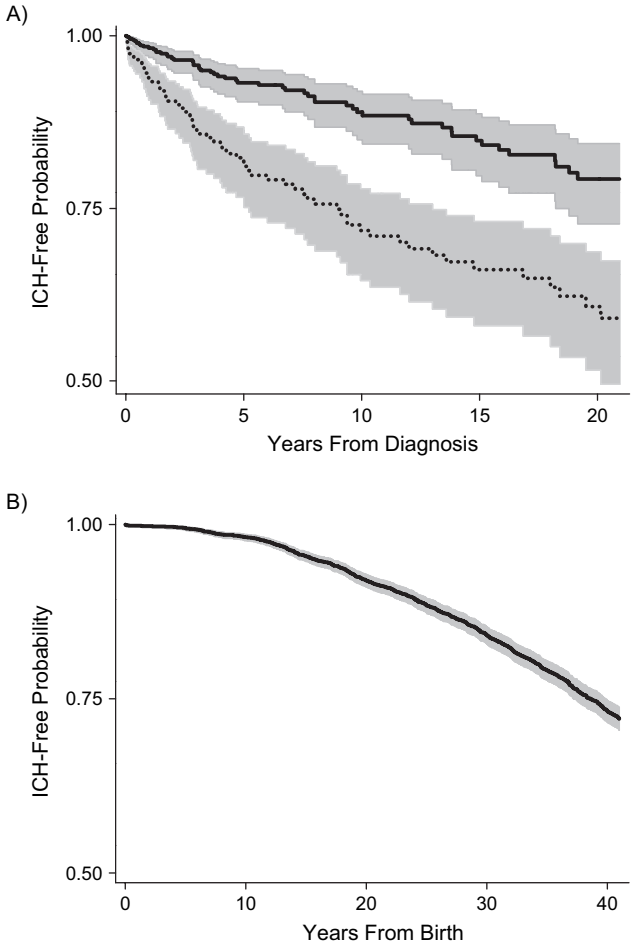

Figure 1. Examples of Kaplan-Meier intracranial hemorrhage (ICH)-free survival curves and 95% confidence intervals (shaded regions surrounding curves) among patients with brain arteriovenous malformations, Northern California, 2000–2007. A) Prospective diagnosis-to-ICH timeline, censoring at first treatment, death, or last follow-up. The curves are stratified by initial hemorrhagic presentation; the lower (dashed) line represents patients who presented to medical personnel with an ICH, and the upper (solid) line represents patients with non-ICH presentations. This is the traditional approach that assesses hemorrhage risk after diagnosis (3, 4, 11). Thus, the lower line represents time to recurrent ICH, and the follow-up time after diagnosis for these persons was excluded from further analysis. B) Retrospective birth-to-diagnosis timeline, censoring at diagnosis. By definition, none of the arteriovenous malformations among patients in this analysis have ruptured yet, so this curve should correspond to the upper line in Figure 1A.

and ICH presentation is the strongest predictor of future ICH in the clinical course, necessitating invasive treatment (3, 4). Additional biomarkers are needed to identify patients who, although their AVMs are initially unruptured, may still be at high risk for ICH, since there is a wide range of natural history risks associated with particular radiographic characteristics (3, 4).

Identification of risk factors for ICH, either clinical (3, 4) or genetic (9, 10), has traditionally used time from diagnosis to ICH for Kaplan-Meier survival analysis, as shown in Figure 1A (4). Use of time from an enrollment or index date to an ICH event has also been explored (11). Such models are the most valid and assumption-free, as patients are prospectively followed for ICH events, starting at diagnosis and censoring at treatment, death, or last follow-up. However, several groups of investigators have also reported ICH rates based on a calculation method that presumes the AVM to have been present from birth and a constant hemorrhage rate throughout a patient's life (7, 8, 12). In these ''birth-to-ICH'' analyses, the period at risk begins at birth, and the event is first ICH either at presentation (diagnosis) or after diagnosis but before treatment. The time scale in this type of analysis is age, and it will yield a survival curve like the one shown in Figure 1B. The retrospective birth-to-ICH approach has a number of pitfalls, including the assumption that the lesion is congenital, assumptions regarding ascertainment over a long period of time, and potential survivorship bias. However, this time scale has the advantage of allowing survival methods to be used in a population of patients with much longer follow-up times and greater ICH event rates.

To date, there have been no rigorous comparisons of survival approaches using different timelines for natural history studies of brain AVM, although *qualitatively* the ICH rates seem similar for unruptured AVM patients: approximately 1–2 events per 100 patient-years (3–8, 12). Therefore, our purpose in this analysis was to *quantitatively* compare ICH rates in unruptured brain AVM patients using the 2 survival analysis approaches.

MATERIALS AND METHODS

Study population

We used a data set similar to that used by Kim et al. (4) and updated data for cases accrued through July 2007. Briefly, patients with brain AVM were identified through either the University of California, San Francisco, medical center or the Kaiser Permanente Medical Care Program of Northern California. Cases were ascertained at the University of California, San Francisco, medical center beginning in January 2000, using an active surveillance system of all medical and surgical services involved in brain AVM management. Kaiser Permanente cases were ascertained through computerized searches of all inpatient and outpatient databases from 2000–2006, with vital status updated through 2007 (11, 13). The study was approved by institutional review boards at both the University of California, San Francisco, and Kaiser Permanente.

Statistical analysis

We performed Kaplan-Meier survival analysis using longitudinal data from 1,581 brain AVM patients. Two timelines were constructed for each patient before and after diagnosis, as illustrated in Figure 2. In the birth-to-diagnosis timeline, patients enter the at-risk period at the date of birth and are censored at the date of diagnosis (Figure 2, gray bars). In the diagnosis-to-ICH timeline, the at-risk period starts at diagnosis and patients are censored at the date of first treatment, death, or last follow-up (Figure 2, black bars).

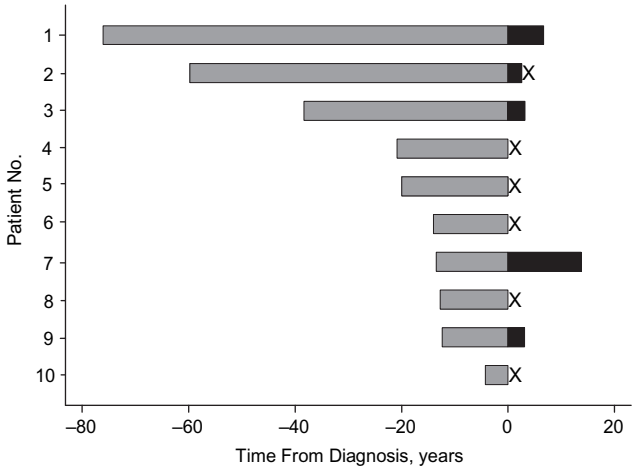

Figure 2. Natural history timelines for patients with brain arteriovenous malformations (AVMs) before and after diagnosis, Northern California, 2000–2007. We present timelines for 10 cases to show the components of the 2 timelines used in the survival analysis. Cases are ordered by time from birth to diagnosis in descending order. In the birth-to-diagnosis timeline (gray bars), patients enter the at-risk period at the date of birth and are followed until the date of diagnosis, at which point they either present to medical personnel with an intracranial hemorrhage (ICH) event (X) or do not. In the diagnosis-to-ICH timeline (black bars), patients enter the at-risk period at the date of diagnosis and are followed until they experience an ICH event (X) or a censoring event (treatment, death, or last follow-up). The diagnosis-to-ICH analysis is restricted to patients whose brain AVMs are unruptured at diagnosis to make the analysis comparable to the birth-to-diagnosis analysis, where everyone's AVM is unruptured at birth.

Table 1. Characteristics of 1,581 Patients With Brain Arteriovenous Malformations, Northern California, 2000–2007

Characteristic	No. of Patients[a]	%	Mean (SD)
Gender			
Male	764	48	
Female	817	52	
Race/ethnicity			
Caucasian	916	59	
Hispanic	277	18	
Asian/Pacific Islander	163	10	
African-American	121	8	
Other/unknown	78	5	
Age at AVM diagnosis, years	1,581		36.89 (18.26)
AVM size, cm	828		3.06 (1.71)
Venous drainage			
Superficial only	570	55	
Superficial + deep	266	26	
Deep only	194	19	
Eloquent location[b]			
Yes	305	61	
No	196	39	

Abbreviations: AVM, arteriovenous malformation; SD, standard deviation.

[a] Numbers in some sections do not total 1,581 because of missing data.

[b] Eloquent regions of the brain are defined as those that affect neurologic function and, if injured, result in a disabling neurologic deficit.

By definition, everyone in the birth-to-diagnosis timeline has an unruptured AVM until medical presentation (disease discovery), at which point they either have an ICH event (indicated by the X's in Figure 2) or do not. Patients with ruptured brain AVMs at diagnosis (lower line in Figure 1A) were excluded from the diagnosis-to-ICH analysis, since their risk of new ICH is well-known to differ from that of unruptured patients. Unruptured brain AVM patients are then prospectively followed in the diagnosis-to-ICH timeline for a first ICH event, as illustrated by the upper line in Figure 1A.

We performed standard Kaplan-Meier survival analysis for each timeline, and the survival curves were plotted on the same graph. The overall annual ICH rates were calculated using the general formula (number of patients with ICH event)/(total number of patient-years of follow-up) $\times$ 100 for each timeline separately, as described above. ICH rates per 100 patient-years were also calculated per decade for each timeline separately.

To determine the optimal point at which the 2 survival curves were similar, we used Cox regression analysis to calculate the time-shift which made the hazard ratio for comparing the 2 timelines as close as possible to 1.0. Follow-up time preceding the start time for each shifted birth-to-diagnosis timeline was dropped from the survival analysis. We used robust standard errors to account for the fact that a subset of patients was included in both timelines. The 95% confidence interval for the optimal time-shift was determined using 200 bootstrap samples. We checked the Cox proportional hazards assumption on the basis of Schoenfeld residuals, which use the χ^2 test to evaluate whether the hazard ratio comparing the birth-to-diagnosis timeline with the diagnosis-to-ICH timeline is changing over time.

RESULTS

Descriptive statistics for the 1,581 brain AVM patients are shown in Table 1. Approximately 52% of the patients were female, and 59% were Caucasian. The mean age at AVM diagnosis was 36.9 years (standard deviation (SD), 18.3), and 47% of patients initially presented with an ICH. Overall, 794 brain AVM patients experienced a first ICH event during 62,939 patient-years of follow-up (mean = 39.8 years; SD, 19.5). The mean follow-up for the birth-to-diagnosis timeline was 36.9 years (SD, 18.3) (time before diagnosis), which is much longer than that for the traditional diagnosis-to-ICH timeline of 5.8 years (SD, 8.8) (time after diagnosis). This is also reflected in the much wider 95% confidence intervals surrounding the diagnosis-to-ICH timeline for unruptured brain AVM patients in Figure 1A (upper line) and the tighter 95% confidence intervals surrounding the birth-to-diagnosis timeline in Figure 1B.

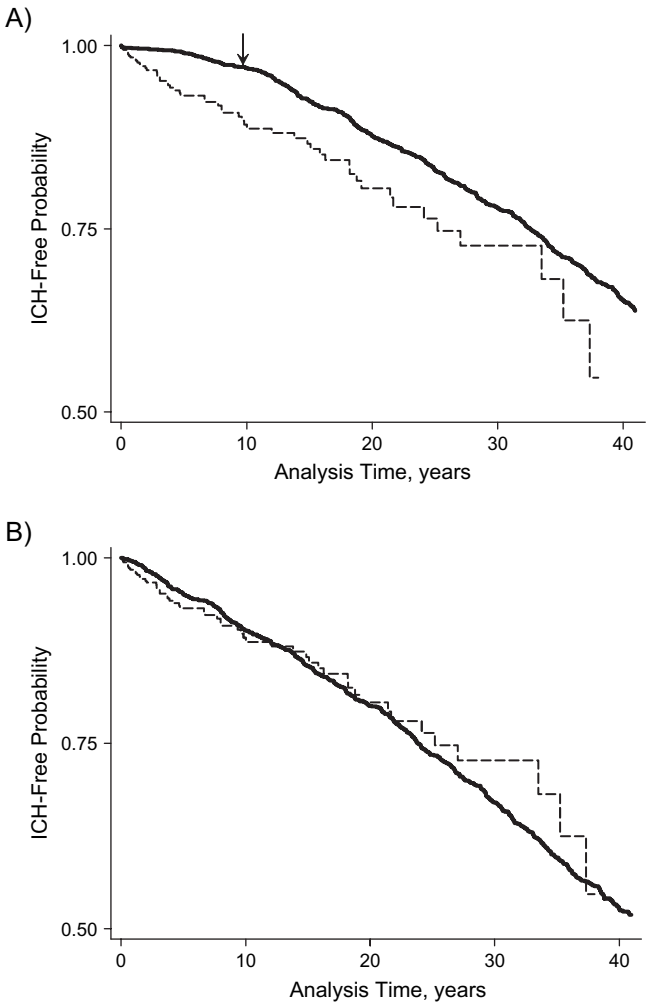

Figure 3. Kaplan-Meier intracranial hemorrhage (ICH)-free survival curves for patients with brain arteriovenous malformations, comparing 2 timelines: birth to diagnosis (solid line) and diagnosis to ICH (dashed line), Northern California, 2000–2007. Table 2 shows numbers of patients at risk in each decade of follow-up, by timeline. A) Note that the morphology of the birth-to-diagnosis curve changes around 10 years of age, as indicated by the arrow. B) Shifting the birth-to-diagnosis timeline to the left by 10 years (dropping 79 people with ICH or a censoring event at less than 10 years) results in overlapping survival curves. The diagnosis-to-ICH timeline is unchanged from that shown in panel A.

Figure 3A shows the hemorrhage-free survival curves for each timeline; the number of patients at risk during each 10-year interval is listed in Table 2. In the birth-to-diagnosis timeline, 740 ICH events occurred during 58,320 patient-years of follow-up, yielding an annual ICH rate of 1.27 events per 100 patient-years (95% confidence interval (CI): 1.18, 1.36). In the diagnosis-to-ICH timeline, there were 54 ICH events during 4,622 patient-years of follow-up, resulting in an annual ICH rate of 1.17 events per 100 patient-years (95% CI: 0.89, 1.53). Thus, ICH rates calculated using the 2 timelines were similar, although the 2 curves were significantly different (hazard ratio = 1.79, 95% CI: 1.34, 2.40; $P < 0.001$). However, the survival curve for the birth-to-diagnosis timeline appeared flat in the first few years of life, and qualitatively, the morphology of the curve appeared to change around 10 years of age, at which point the slopes of the 2 survival curves looked parallel (marked by the arrow in Figure 3A).

Table 2 shows the ICH rates per decade for each timeline separately. If one ignores the first 10 years in the birth-to-diagnosis timeline, the rates in the 2 timelines appear comparable. The ICH rates for both timelines appear to be increasing with age, consistent with previous studies in which age was associated with an increased risk of ICH (3, 11). To test this more formally, we performed a time-shift analysis of the birth-to-diagnosis timeline, starting the at-risk period at 10 years, which dropped follow-up time for 79 people. The hazard ratio comparing the 10-year-shifted birth-to-diagnosis timeline with the diagnosis-to-ICH timeline was 1.02 (95% CI: 0.77, 1.36) and was no longer significant ($P = 0.897$), as reflected in the overlapping survival curves shown in Figure 3B. The P value from the proportional hazards χ^2 test comparing the Schoenfeld residuals with time was not statistically significant ($P = 0.371$), indicating that the Cox proportional hazards assumption was not violated. Thus, in our study, the bleed rates in previously unruptured brain AVM patients were similar both before and after diagnosis when we shifted the birth-to-diagnosis timeline by 10 years.

To find the optimal shift in the birth-to-diagnosis timeline, we repeated the time-shift analysis varying the birth-to-diagnosis start time from 1 year to 25 years. The best fit was found at 10–11 years of age, where the hazard ratio comparing the 2 curves was approximately 1.0. The exact time shift was found to be located at age 10.3 years, with a bootstrapped 95% confidence interval ranging from 3.3 years to 17.4 years, confirming our qualitative observation.

DISCUSSION

We made 2 novel findings in this study. First, the estimated annual ICH rates were approximately similar in the 2 timelines. Second, the morphology of the curves was suggestive of a biologic change around age 10 years that influences ICH rate in the natural history course of brain AVM. We found that the rate of ICH per 100 patient-years was 1.27 (95% CI: 1.18, 1.36) in the birth-to-diagnosis timeline and 1.17 (95% CI: 0.89, 1.53) in the diagnosis-to-ICH timeline for unruptured AVM patients. These ICH rates were similar to those reported in recent natural history studies using the diagnosis-to-ICH (3–8) or birth-to-first-ICH (7, 8) timelines. The annual ICH rate per 100 patient-years in studies using the diagnosis-to-ICH timeline ranged from 0.9 in unruptured AVM patients with no risk factors (i.e., no deep venous drainage or deep location) (3) to 3.1 in a study from Kyoto, Japan (5). For the birth-to-ICH timeline studies, the annual initial ICH rate was 1.9 per 100 patient-years in 315 brain AVM patients undergoing stereotactic radiosurgery at 1 medical center (7) and 1.5 per 100 patient-years in 73 Spetzler-Martin grade IV or V patients referred to another center for treatment (8). Our results agree and suggest that, at least in the aggregate, AVMs that have not yet ruptured

Table 2. Rates of Intracranial Hemorrhage per 100 Patient-Years Among Patients With Brain Arteriovenous Malformations, by Type of Timeline and Decade of Follow-up, Northern California, 2000–2007

Birth-to-Diagnosis Timeline						Diagnosis-to-ICH Timeline					
Decade, years	No. of Patients	No. of ICH Events	P-Y at Risk	Rate of ICH	95% CI	Decade, years	No. of Patients	No. of ICH Events	P-Y at Risk	Rate of ICH	95% CI
0	1,581	49	154.98	0.32	0.24, 0.42						
10	1,502	139	139.31	1.00	0.84, 1.18	0	795	35	28.47	1.23	0.88, 1.71
20	1,252	131	110.49	1.19	1.00, 1.41	10	162	11	11.77	0.93	0.52, 1.69
30	954	141	80.83	1.74	1.48, 2.06	20	74	5	4.61	1.09	0.45, 2.61
40	653	122	51.91	2.35	1.97, 2.81	30	24	3	1.26	2.39	0.77, 7.41

Abbreviations: CI, confidence interval; ICH, intracranial hemorrhage; P-Y, patient-years.

have *new* bleeding rates that are approximately similar both before and after patients come to medical attention.

Interestingly, the slopes of the 2 survival curves had the closest resemblance if there was a 10.3-year shift in the birth-to-diagnosis timeline, suggesting that the AVM either 1) was not present before age 10 years or 2) was present but was biologically inactive prior to this age. Brain AVMs are commonly presumed to be static congenital lesions resulting from early embryonic maldevelopment. However, there are surprisingly few empirical data to support this assumption. Brain AVMs are biologically active lesions, as demonstrated by reports of AVMs that grow or regress (reviewed by Du et al. (14)), recur after angiographically confirmed complete resections (15–22), or appear de novo (14). Pediatric AVM cases are often identified after hemorrhagic presentation, although the risk of ICH during the natural course after diagnosis does not seem to differ from that of adults (13). However, most cases of recurrence occur in children (23), and there is some evidence suggesting that these cases represent more biologically aggressive lesions, with higher levels of angiogenic factors, such as vascular endothelial growth factor, compared with nonrecurrent AVMs in pediatric or adult specimens (14, 24). It is intriguing that the slope of the birth-to-diagnosis survival curve changes around the time of puberty, when hormone levels are changing dramatically in adolescents; however, we are not aware of any data linking hormone levels with an increased risk of ICH, and gender is not a significant risk factor.

Identifying risk factors for ICH in the natural history course requires use of complex time-dependent endpoints. A relevant issue for the traditional diagnosis-to-ICH timeline analysis is whether patients who come to attention early in the course of brain AVM pathogenesis may have a long time to ICH, while those who are diagnosed late after pathogenesis may have a very short time to ICH. A standard survival analysis based on person-years of follow-up would give unbiased estimates of risk if we assumed that: 1) AVMs are present over a long period prior to diagnosis (e.g., from birth); 2) AVMs persist in a steady state in which the ICH rate per year is relatively constant; and 3) there is no survivorship bias. If the rate varied over time or the length of time in which an AVM was present prior to discovery was differentially associated with ICH risk factors, this would be more problematic. However, it seems reasonable to assume that the former rather than the latter exists, at least for patients with unruptured brain AVMs, based on the similarities in ICH rates and survival curves after shifting of the birth-to-diagnosis timeline.

A limitation of the current study is that we did not evaluate the effect of risk factors on ICH rates using the 2 timelines, since only data on baseline characteristics at presentation were available. Potentially time-varying factors would not be available for the birth-to-diagnosis analysis, limiting direct comparison between the 2 timelines; the best example would be AVM size, which would be dynamically changing if these lesions in fact grow in size over the natural history period. Further, our study may have been subject to selection bias, since AVM cases were ascertained at a large referral center and an integrated health-care organization, which may not be representative of the general population. However, Kaiser Permanente membership characteristics are representative of the Northern California population covered (25), and our ICH rates for patients with unruptured AVM are similar to other published series from single referral institutions covering different geographic areas.

The main advantage of using the birth-to-diagnosis timeline to estimate natural history risk of ICH in brain AVM patients is evident from our results demonstrating longer follow-up times and greater numbers of ICH events. The birth-to-diagnosis timeline is natural history information that each patient brings with him or her at medical presentation but is traditionally ignored in the diagnosis-to-ICH timeline. In the diagnosis-to-ICH timeline, follow-up is limited mainly because patients are censored shortly after diagnosis due to treatment, making it difficult to accrue a large number of ICH events with which to study risk factors in a longitudinal setting. The concept of using age as the time scale rather than time in the study in cohort studies is not new and has been advocated and discussed in detail by several authors (26–28). A major difference in our application is that the diagnosis of brain AVM patients and subsequent study enrollment may be triggered by some biologic mechanism rather than randomly, as in an epidemiologic cohort study of disease-free persons.

In conclusion, the 2 approaches for estimating ICH rate in previously unruptured brain AVM patients gave similar results, especially when the timeline for birth to diagnosis was started at 10 years of age. These results suggest that we can use the unconventional birth-to-diagnosis timeline as an alternative to analyzing natural history risk for patients with unruptured AVM, even if the data cannot directly address the lifetime risk of AVM rupture. An unexpected finding was data suggestive of a biologic change around 10 years of age that influences ICH rate.

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