Editorial

On the persisting difficulty of making predictions, especially about the future

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Unruptured aneurysms are being identified with increasing frequency. A systematic review of 68 studies found 1450 unruptured aneurysms in 94,912 patients from 21 countries. The prevalence of unruptured aneurysms was 3% (95% CI 1.9%–5.2%). The prevalence increased 3% per year in 46 studies published between 1931 and 2008, but this trend was not statistically significant when the data were adjusted for sex, age, and comorbidity. I assume this means the increase in identification of unruptured aneurysms that has occurred over the years must be due partly to the increasing age of the population, given that age is a key risk factor for having an unruptured aneurysm. The increase is also likely to be due to the increasing frequency with which people undergo cranial CT and MR imaging. Otherwise, unruptured aneurysms were more prevalent with increasing age, in women, in patients with autosomal dominant polycystic kidney disease, and in those with a family history of intracranial aneurysm or subarachnoid hemorrhage (SAH). The odds ratios for some of these factors are small, so screening for aneurysms was recommended for individuals with 2 or more affected first-degree relatives, patients with autosomal dominant polycystic kidney disease, identical twins if one twin had an SAH, young patients with prior SAH (especially women), patients with multiple aneurysms, and smokers.

Unruptured aneurysms are thus fairly common. They are about 30 times as prevalent as multiple sclerosis, 10 times as prevalent as human immunodeficiency virus infection, and twice as common as fibromyalgia and chronic fatigue syndrome in the US. Regardless of what we think we know about what to do about them, treatment of unruptured aneurysms is increasing. One study found a 75% increase in admissions for unruptured aneurysms in the US between 1997 and 2006 and a 200% increase in national costs.

A fundamental question that has arisen, in part based on the controversial low rupture rates that were found in the International Study of Unruptured Intracranial Aneurysms (ISUIA), is whether all these unruptured aneurysms need to be treated. When we undertake such decision making in the management of complex multifactorial conditions, the decision depends on consideration of the risk of rupture, consequences of rupture, risk of treatment, and reduction in risk of rupture after treatment. We have data on some of these factors, but only limited understanding of others. The consequences of rupture are still dire, and while the mortality rate is decreasing, if one knew that an aneurysm was going to rupture, the decision to treat would be easy.

What about risk of rupture? Baharoglu and colleagues seek to advance our ability to predict this: which unruptured aneurysms will eventually rupture. They report one of the largest series of aneurysms analyzed by 3D rotational angiography. They studied 271 consecutive cases including 101 ruptured (170 unruptured), 135 bifurcation, and 136 sidewall aneurysms. The largest diameter, height, ratio of height to width, aspect ratio, size ratio, nonsphericity index, and inflow angles were measured. For inflow angle, an aneurysm that points directly upward, for example, from the basilar bifurcation and is in line with the long axis of the basilar artery would have the highest value possible (180°). Multivariate analysis was used to determine factors associated with the aneurysm being ruptured. Computational fluid dynamics (CFD) analysis was used to measure wall shear stress in the aneurysms at different inflow angles.

When all of the aneurysms were considered, ruptured aneurysms were associated with a higher ratio of height to width, higher size ratio, and higher inflow angle (Table 1). Dividing the aneurysms into sidewall or bifurcation types showed that for sidewall aneurysms, maximum diameter, height/width ratio, and inflow angle were higher for ruptured than for unruptured aneurysms. For bifurcation aneurysms, only nonsphericity index was associated with rupture status. Looking at Fig. 2, one sees that even for the significantly different variables, there is still a lot of overlap between the ruptured and unruptured aneurysms. This is one of the key points I take from the authors’ results and discussion. None of the individual morphometric parameters distinguish ruptured and unruptured aneurysms very well. The findings are remarkably similar to those of Richardson and colleagues published almost 50 years ago. Recent publications do not cite these authors, but they should be credited with perhaps for the first time defining the height/width ratio, the aspect ratio, and an early version of nonsphericity and reporting the role of these factors in multivariate analysis (also for possibly the first time in the medical literature) in predicting rerupture of previously ruptured aneurysms.

Baharoglu et al. also conduct a focused analysis of sidewall- and bifurcation-type aneurysms using CFD on model aneurysms of each type. This analysis is compli-
cated, but for my interpretation I assume the rupture point to be near the dome of the aneurysm, which usually is the case for the smooth types of aneurysms that are modeled. This leads me to conclude that flow velocity is not an important factor in the association with rupture status because it varies with inflow angle in bifurcation aneurysms, but inflow angle is not associated with rupture. Similarly, wall shear stress is lowest in the domes of all the sidewall aneurysms independent of inflow angle, yet inflow angle is associated with rupture status. Thus, it does not seem that the single variable, wall shear stress, is the hemodynamic explanation for rupture status. This is confirmed in Fig. 4D, where rupture status in the sidewall aneurysms, which is correlated with higher inflow angle, is associated with higher wall shear stress in the hemodynamic modeling, but in bifurcation aneurysms, the wall shear stress is several logs higher independent of inflow angle.

If there is a hemodynamic factor associated with aneurysm rupture, then that factor should be associated with rupture in any type of aneurysm. We don’t measure hemodynamic factors when we see the patient, so one use of a hemodynamic factor would be if it correlated with some morphometric or series of morphometric measurements so that the aneurysm morphometry can be used as a surrogate to tell what aneurysm will be ruptured. This is another interesting point of this paper. The morphometric factors seem to be very different depending on whether the aneurysm is a sidewall or bifurcation type. Another point is that looking at the authors’ Table 1, we see that most of the bifurcation aneurysms have anterior communicating artery (ACoA) and middle cerebral artery (MCA) locations. The mean maximum diameter of the ACoA aneurysms was almost half a millimeter smaller than that of the MCA group. We don’t know the rupture status of the aneurysms in these groups, but this would be interesting to know because the ACoA site typically is a site where most aneurysms are ruptured and the MCA is the commonest site for unruptured aneurysms. This would highlight again the authors’ contention that diameter alone is not associated with rupture status and would also suggest that there is some association with aneurysm location.

Overall, the authors have reported an excellent set of data that is very well analyzed and presented. One key limitation is that this study and most of the aneurysm CFD studies compare ruptured and unruptured aneurysms. This is not the same as what one wants to compare, which is unruptured aneurysms that never rupture and unruptured aneurysms just before they rupture. It is difficult to understand exactly why these comparisons could give different results, but comparing other vascular lesions like arteriovenous malformations in the same way seems to generate slightly different lists of factors that are associated with hemorrhage in the natural history of unruptured lesions than the factors associated with hemorrhage when comparing ruptured to unruptured lesions at first presentation. It may have something to do with how aneurysms form and rupture. One opinion is that they grow at irregular rates, with periods of no or little growth and periods of more rapid growth that may be when the aneurysm ruptures. In addition, there are probably multiple other factors contributing to aneurysm genesis, growth, and rupture that vary over time, including genetic risk factors and the environment (smoking, blood pressure, alcohol intake).

The authors briefly review their CFD results and concur with my interpretation and with prior findings in the literature, which include the disparate results with regard to wall shear stress and aneurysm rupture status. I am not very knowledgeable about aneurysm hemodynamics, but my reading about it suggests that there are numerous assumptions and variables that can influence the values of the various measurements and that these are variably accounted for in different studies. Pulsatile and laminar versus nonlaminar flow, rigid versus flexible tubes, inflow values and pressures, wall thicknesses, and the lengths and configurations of the inflow and outflow arteries that are modeled all seem to be able to influence the results.

Another consideration is that in the multivariate analysis, the authors entered morphological features that were statistically significant in the univariate analysis. While this method is commonly used, another opinion is that one should put in variables that one is interested in or that are thought to be potentially important. Just because a variable is not significant in univariate analysis does not mean it could not be in multivariate analysis, or that it is not important. It would also be useful to know who obtained the morphometric measurements, whether they were blinded to rupture status, and the inter- and intra-observer variability and reproducibility of all of the measurements.

Prior studies have identified several factors that are associated with rupture of intracranial aneurysms. In prospective studies that follow unruptured aneurysms to observe whether they rupture or not, the main factor seems to be maximum diameter, most prominently studied in the ISUIA studies. This study also suggested that pa-

### Table 1: Morphological characteristics of ruptured aneurysms and hemodynamics of increased inflow angle*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sidewall</th>
<th>Aneurysm Type</th>
<th>All Aneurysms</th>
</tr>
</thead>
<tbody>
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<td>increased H/W, increased SR, increased IA</td>
<td>increased NSI</td>
<td>increased H/W, increased SR, increased IA</td>
</tr>
<tr>
<td>hemodynamics of increased IA</td>
<td>increased flow velocity into dome, increased WSS</td>
<td>decreased flow velocity into dome, decreased WSS</td>
<td>—</td>
</tr>
</tbody>
</table>

* H/W = height/width ratio; IA = inflow angle; NSI = nonsphericity index; SR = size ratio; WSS = wall shear stress.