Morita and colleagues present a very interesting paper about an important topic that may be particularly pertinent in Japan given that some of the highest incidence rates for subarachnoid hemorrhage (SAH) have been cited in reports from that country. There are obviously many challenges inherent in the approach of collating and combining data from several relatively small retrospective reports, as illustrated by this study and substantially acknowledged by the authors. We faced similar challenges in North America and Europe in an attempt to evaluate small retrospective studies, and our inability to provide uniform, robust results while using this approach led to the development of the International Study of Unruptured Intracranial Aneurysms (ISUIA). It is nevertheless interesting that the results of the current study indicating increased rupture risk for large, posterior circulation, and symptomatic unruptured cerebral aneurysms were very similar to the pattern observed in the ISUIA1,2 (a multivariate analysis performed in the ISUIA indicated that the increased risk associated with symptomatic unruptured aneurysms was related to the increased size of these lesions). Moreover, the overall rupture rate of 2.7% per year reported in the current study would not differ statistically from the overall rupture rates we reported from early small retrospective series from a single institution.3,4 It is difficult to evaluate the apparent cases of rupture of small aneurysms in the absence of information about which patients had prior SAH and without sufficient follow-up information to allow calculation of rupture rates. Given the substantial differences in patient populations, study design, and follow-up analyses, it is not statistically possible to compare the results of the current metaanalysis with the results of the ISUIA by using traditional probability values.

Notwithstanding the aforementioned points, the results of the study by Morita, et al., are intriguing and provide food for thought as we anticipate the results of the two ongoing prospective studies in Japan that the authors mention in their paper. A difference in risk factors and the behavior of unruptured intracranial aneurysms in substantially different genetic populations cannot be excluded.

References

RESPONSE: We appreciate Dr. Wiebers’ thoughtful comments about our systematic review. As he has emphasized, reviewing and summarizing small series is difficult because the case material, classification, follow-up methods, and study periods differ among series. Because of these difficulties, we asked the authors of each study included in our review to provide their own data reclassified according to our criteria. Most of the authors kindly fulfilled our request, and we particularly appreciate their cooperation. The strength of our study relies on their efforts, which we could request because our report is based on single-nation studies and we know each other very well. Without such a relationship with each author, we might not have been able to obtain uniformly classified data. Nonetheless, as Dr. Wiebers notes, it was still a difficult task to collect such information because some of the authors’ data were already lost—some from a change in recording style occurring during software upgrades and some because of computer breakdowns. Furthermore, some of the older raw data had not been obtained with informed consent from patients and we did not collect raw data. To carry out a multivariate analysis regarding risk factors (such as a comparison of the influence of symptomatic and larger aneurysms), we need patients’ raw data. Problems such as publication biases be-

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come more serious when assessing management results collected from surgical series. With these problems in mind, we strongly recommend that authors who wish to publish their own series of specific diseases obtain informed consent from each patient for a generalized data analysis. Authors should also keep raw data obtained in each patient with their report in a format that will not be lost. Such efforts can contribute tremendously to future scientific study. Furthermore, the method of classification, measures used to evaluate outcomes or events, and other pertinent information should be uniform. We hope that guidelines developed to direct the management of specific diseases also contain recommendations about methods of follow up and other pertinent issues. The two on-going prospective studies in Japan have been constructed to overcome the innate problems of retrospective data collection. The first study is a prospective on-line collection of data from patients with unruptured cerebral aneurysms treated in the involved institutions (Unruptured Cerebral Aneurysm Study in Japan, UCAS Japan). Each patient chose a treatment plan based on the recommendations of the attending physician, and prospective follow-up and management data are being assessed. No results about rupture risk or management outcome have yet been published. The second study is being conducted by a group of neurosurgeons at national hospitals who agreed to observe all patients harboring unruptured aneurysms with a diameter less than 5 mm (Small Unruptured Aneurysm Verification; SUAVe study). The latest publication from this group shows that, even among these small lesions, four aneurysms ruptured and the calculated rupture risk was 0.8% per year (95 confidence interval 0.2–3%). Eighteen aneurysms enlarged, seven of which were surgically treated. A location on the anterior communicating artery and the occurrence of multiple aneurysms in older women were factors affecting the rupture risk. Because the study is limited to a select group and the follow-up period is short, the confidence interval is wide and longer follow-up periods and further case involvement are required to establish acceptable data. Nonetheless, a close follow-up review with reasonable sensitivity to enlargement of the lesion has proved to be a valid method for managing small aneurysms. We hope such efforts to build valid prospective data obtained via uniform measures from multiple institutions will solve some of the mystery surrounding unruptured aneurysms and provide useful information for their appropriate treatment. This cannot be accomplished using the current retrospective analysis of data. These efforts might also be used to identify the reason for the difference in incidence of SAH between patients in Japan and those in Western countries. Nevertheless, there will still be some patients in whom detailed prospective data analysis may not clarify the optimal management strategy and a randomized controlled trial is required. The aforementioned prospective studies may help us define the group of patients best served by randomized controlled trials.

References