Editorial

Unruptured aneurysms

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I thank Dr. Wiebers and coworkers and Dr. Dumont and colleagues for their interest in our study and in the natural history of unruptured aneurysms. Unfortunately, the editorial by Wiebers, et al., included misinterpretations that are consequences of careless and hasty reading of our paper. It is also very important to remember that a large sample size does not negate a poor study design. Inappropriate inclusion criteria for patients in the retrospective arm of the International Study of Unruptured Intracranial Aneurysms (ISUIA) may have led to a considerable systematic bias that cannot be corrected by any kind of statistical methods.

Our study included 142 (not 141) patients, of whom 131 or 92% (not 135 or 96% as mentioned by Wiebers, et al.) had suffered a prior subarachnoid hemorrhage (SAH) at the time of the diagnosis of their unruptured aneurysms. The follow-up status for our patient population was complete for all 142 patients, not just for 57. These 57 patients were those who were still alive between 1996 and 1998 and were admitted to the outpatient department for evaluation of their aneurysms with computerized tomography (CT) angiography. Four other elderly patients were interviewed by telephone using the same structured questionnaire; all the other patients had died by that time. As mentioned in our article, these patients had been followed prospectively until their death (also after the 1993 report) and were also evaluated several times before their death in our previous studies and in interviews conducted during our prospective follow up.

Our study showed that cigarette smoking, aneurysm size, and patient age (inversely) increased independently and significantly the risk for bleeding of an unruptured aneurysm. In addition, angiographic follow-up studies indicated that cigarette smoking, and possibly also female sex and patient age, inversely, hasten the growth of preexisting aneurysms, making them prone to rupture. Female sex and smoking also increase the risk of aneurysm formation. Our study population (142 patients with a total follow-up time of 2575 person-years, mean follow-up duration 18.1 years/patient, in one center with a defined patient catchment area) differs from the retrospectively selected (no prospective follow-up data have been shown for conservatively treated patients) patient population of the ISUIA (1449 patients with 12,023 person-years, mean follow-up duration 8.3 years/patient, in 53 centers) because of our longer follow-up time and better inclusion criteria. There was also no surgical selection and there were no patients with unruptured aneurysms who were lost to follow up in our study. Our annual rupture rate of 1.3% (95% confidence interval [CI], 0.9–1.7%) was similar to all other previously published patient series (1–3%) but significantly higher (p < 0.0001) than in the ISUIA (0.3%, 95% CI 0.2–0.4%), indicating that there may be a serious systematic bias due to failures of inclusion criteria and/or follow up in the ISUIA.

Our annual rupture rate was also significantly (p < 0.01) higher than that in Group 2 patients of the ISUIA. A higher incidence of SAH in Finland (13–16/100,000/yr) cannot necessarily explain this difference.

Our clinic was the only neurosurgical center in Finland until the late 1960s. Between 1970 and 1975, our center in Helsinki was responsible for neurosurgical services for 88% of the Finnish people and, between 1975 and 1978, for 60%. Therefore, we should speak about the Finnish Study of Unruptured Intracranial Aneurysms instead of the Helsinki Study. Helsinki is not a typical single-referral neurological tertiary center with a highly selected patient population as is typical for many neurosurgical clinics in the United States, but is instead a center responsible for all neurosurgical services only in a defined geographical area. Between 1956 and 1978, there were approximately 4.5 million inhabitants of Finland. In that time frame, 1552 aneurysm operations were performed in Helsinki. Only 142 patients with unruptured aneurysms were followed because most patients with multiple lesions were treated conservatively because of uncertainty over which aneurysm had bled. These patients were immediately excluded from our study because in case of a later SAH they would have to be excluded because of uncertainty about the source of the bleed. The number of patients with incidental or symptomatic aneurysms also remained low because lumbar puncture is essential for exclusion of major or minor SAH in the case of normal findings on CT scans. Virtually all cases of truly unruptured aneurysms diagnosed in our catchment area were included in our study. The lack of this kind of strict inclusion criterion may well explain why incidental or
symptomatic unruptured aneurysms that are 10 mm or larger have previously been shown to have an unexpectedly high rupture rate (6%/year),12 which is even higher than the rebleeding rate (3%/year) of a ruptured aneurysm 6 months after the last bleed. Therefore, I suspect that some of those unruptured aneurysms may in reality have been ruptured ones.

In Helsinki, patients with unruptured aneurysms diagnosed before 1979 were never treated surgically.3-5,9,11 Dr. Wiebers underestimates the significance of our patient population of working age, which is the most important group with unruptured aneurysms for which the ISUIA cannot recommend many treatment options, because these kinds of patients were mostly excluded because of the surgical treatment of their aneurysm. This factor also gave us a possibility for a real long-term prospective follow up of patients with unruptured aneurysms without surgical selection of cases and with no missing cases during the follow-up period. Our first patients have been presented in case reports,1,3 but the results of patient series have been repeatedly published since 1970 with improved use of statistics, including Cox regression models with time-dependent covariates, as the number of patients and follow-up years increased.4,5,8,9 Of our 142 patients, 13 were diagnosed in the 1950s, 51 in the 1960s, and 78 in the 1970s. Rupture rates did not differ significantly according to the decade in which the diagnosis was made, although patients with aneurysms diagnosed in the 1950s were younger and were more likely to be cigarette smokers. Of 33 patients with a subsequent SAH, 17 had lesions that were diagnosed during the CT era (1978 or later in Finland), and the risk of rupture among them was similar to that in lesions diagnosed before the CT era. Contrary to the assumption of Wiebers and colleagues, neither CT nor magnetic resonance imaging can reliably demonstrate whether just the unruptured aneurysm has bled, as indicated by our two patients who suffered SAH from a de novo aneurysm. Ruptured lesions were diagnosed accurately by using lumbar puncture, CT scanning, repeated angiography, surgery, and/or autopsy, leaving only a very few unresolved cases.9,10 Our study is therefore not an outdated or antique one. Furthermore, CT scanning does not necessarily reveal all aneurysm ruptures.7

When our paper was published in 1993, 27 (19%) of our 142 patients had suffered a SAH from a previously diagnosed unruptured aneurysm, and by the last follow-up evaluation 33 (23%) had suffered an SAH.8,9 The 34th patient (a nonsmoking woman who was 71.8 years of age) suffered a severe SAH in February 2000 (after a follow-up period of 23.7 years) from an unruptured anterior communicating artery aneurysm 4 mm in diameter. This lesion had been diagnosed in 1976 and had a similar appearance on a CT angiographic study performed in 1997. This aneurysm had grown after 1997 and bled for the first time in 2000. Unruptured aneurysms always seem to grow more or less before they bleed, and small aneurysms can increase in size and rupture even decades after their diagnosis,3,10 contrary to the assumption of Wiebers, et al., who had no systematic angiographic follow-up data. In our study, the exact cause of almost all subsequent SAHs was confirmed by autopsy or surgery, and the increase in size of an unruptured aneurysm with or without the presence of a secondary sac was verified. A CT scan is not sufficient for that purpose.

Patients in the ISUIA were collected from the era when unruptured intracranial aneurysms began to be treated surgically. The retrospective part of the follow-up study did not include all patients who received conservative treatment, who were also very likely to be older and sicker than those who were excluded due to surgical treatment. Patients either included or excluded in the ISUIA do not represent the same general baseline population, and a comparison of the patient population in the ISUIA with historical controls of totally different populations is erroneous. The ISUIA investigators could not have proven that those patients with no follow-up review have had a risk of aneurysm rupture of 0.3% per year. Because of excluded patients, the ISUIA cannot be a representative cohort for the natural history of unruptured aneurysms. Even the total number of patients with unruptured aneurysms in the ISUIA centers has remained unspecified.

Contrary to general expectations, patients in the retrospective part of the ISUIA were clearly older than those in the prospective part, although medical and surgical treatments have become significantly more intervention oriented during the last 30 years, with older patients in poorer condition examined and treated more actively nowadays. Thus, in the case of nonselection, patients in the prospective part should have been significantly older than those in the retrospective part of the study.

In the 1970s and 1980s surgery for unruptured aneurysms had begun to be performed increasingly in most neurosurgical centers,8,9 leading to a broad selection of the patients in the retrospective cohorts. Very likely, younger adults and cigarette smokers with unruptured aneurysms have more often undergone surgery soon after diagnosis than have elderly patients, leading to exclusion of those who had an increased risk of aneurysm rupture. Excluded younger patients are also more likely to be cigarette smokers, because cigarette smoking is more prevalent among young people, including patients with SAH, according to several previous studies.9 This population may have had an increased risk for SAH because cigarette smoking seems to increase the growth rate of an unruptured aneurysm, making it prone to bleeding.10

There are several reasons for exclusion of patients in retrospective studies: death or relocation, treatment of ruptured or unruptured aneurysms at another institution, unwillingness by patients to take part in a study, or impatience with follow-up visits. The retrospective cohort of the ISUIA may yield considerably biased results because the follow up was not complete and, because of exclusion criteria, the vast majority of patients cannot be enrolled in the study. Inclusion criteria mandating that patients be willing to take part in the study and that their original angiograms be available were unbelievable and a significant source of systematic bias. Copies of angiograms for patients who had died or who had undergone surgery elsewhere than in the primary center because of a subsequent SAH were less likely to be available for retrospective review. This kind of potential bias cannot be estimated afterward. Patients (especially cigarette smokers) may also have been unwilling to take part in the ISUIA. In addition, there was a high proportion of missing data for smoking status in that study. All patients with ruptured lesions should also have been checked to verify whether the aneurysm had been previously diagnosed elsewhere. Incomplete follow up of patients leads to a more likely inclusion.