COMMENTARY

Unruptured intracranial aneurysms: prospective data have arrived

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Management of the patient with an unruptured intracerebral aneurysm remains complex. Key questions are: what is the risk of rupture for a particular aneurysm and can subgroups of patients at high-risk be identified? Related questions are whether we should screen certain groups for cerebral aneurysms and, if so, how?[1] Other important considerations include whether, and how, an asymptomatic aneurysm should be treated. The prospective arm of the International Study of Study of Unruptured Intracranial Aneurysms (ISUIA), reported in today's *Lancet*, is the largest prospective study examining rupture risk of unruptured asymptomatic intracerebral aneurysms—especially in patients with no previous history of subarachnoid haemorrhage. Previous retrospective data were published by ISUIA in 1998[2] and were criticised about recruitment and selection bias—eg, the excess of small and cavernous carotid aneurysms.[3,4] Robust prospective data about rupture risk by aneurysm site and size are therefore welcome. ISUIA also provides data on treatment outcomes in unruptured aneurysms, which is timely following the recent publication of a large randomised trial that compared clipping versus coiling of ruptured aneurysms (the ISAT trial).[5]

The major controversy arising from the 1998[2] paper was the 0·05% yearly rupture rate identified by ISUIA for small anterior-circulation aneurysms in patients with no previous history of subarachnoid haemorrhage (group 1)[2] compared with that in earlier reports (0·7%[6]). This extremely low rate of rupture meant that in most instances the risks of treatment outweighed the natural history risk. In their systematic review,[6] Rinkel et al identified a total of 1145 years of follow-up in patients with asymptomatic aneurysms and no previous subarachnoid haemorrhage. There were nine ruptures: aneurysmal size could be extracted for eight of the nine and all but one were in aneurysms 10 mm or larger (Rinkel GJE, University Medical Centre, Utrecht, Netherlands, personal communication). So there was one (at most two) ruptures in small aneurysms (all sites) in group 1 patients in the systematic review, which gives an annual rupture rate for small aneurysms of 0·1% (at most 0·2%). This rate is similar to the retrospective ISUIA data.[2] By comparison, in 1077 patients in group 1 in the prospective arm of ISUIA, annual rupture risk for anterior-circulation aneurysms under 7 mm was 0% and 0·52% for aneurysms of 7–12 mm, with an overall rate for aneurysms of 12 mm or less of about 0·15%. A 7 mm cutoff agrees well with a previous study.[7] What ISUIA does not resolve is the discrepancy between the extremely low rupture risk in asymptomatic aneurysms under 7 mm, compared with the large proportion of ruptured aneurysms in this size category (61% were 5 mm or less in one recent series[8]). Rupture risk is substantially higher for larger aneurysms, posterior-circulation aneurysms (including aneurysms in the posterior communicating artery), and in patients with a history of subarachnoid haemorrhage.[2,6] The prospective ISUIA data corroborate this finding with a relative risk for aneurysms of 7–12 mm of 3·3, of 17 for those over 12 mm, of 5 for posterior-circulation aneurysms, and of 3 for group 2 (patients with previous subarachnoid haemorrhage).

Direct comparison of treatments is difficult because patients' characteristics differ between the cohorts, with proportionately more elderly patients and posterior-circulation and large aneurysms (all predisposing to poorer outcome) in the endovascular cohort. Nevertheless, for group 1 patients, combined morbidity and mortality at 1 year was 12·6% for clipping and 9·8% for coiling: a 22·2% relative-risk reduction for coiling. For group 2 patients, the reduction in relative risk for coiling at 1 year was 29·7% (10·1% *vs* 7·1%). Numbers are relatively small with wide confidence intervals, especially in the endovascular cohort. However, these results are similar to those for ruptured aneurysms in the large ISAT trial,[5] although, unlike ISAT, the treatment groups were not matched.

The retrospective study[2] was severely criticised.[3,4,9] Can we have more confidence in today's prospective data? Unquestionably yes, because a careful protocol with prospective recruitment was used—but there are still weaknesses. First, and most important, exclusion criteria were wide with no indication of the number of patients excluded. Furthermore, the regional referral institutions participating in ISUIA should see considerably more eligible patients with newly diagnosed unruptured intracranial aneurysms than are included in the study,[10] but data on recruitment rate are omitted. So how representative is the recruited study population? Second, there remains under-representation of aneurysms in the anterior cerebral or anterior communicating arteries, or both, in ISUIA compared with the population with subarachnoid haemorrhage. Aneurysms under 2 mm were arbitrarily excluded from ISUIA, although these can rupture. It is unclear why separate results for patients in groups 1 and 2 are not presented consistently throughout. Family history is asserted not to be a risk factor, yet family history is not

defined and data on degree of relationship or number of relatives affected are not indicated. So the conclusion drawn cannot be substantiated by the data presented. We would continue to advise individuals with two or more affected first-degree or second-degree relatives that they are at increased risk, with the risk concentrated in those with two or more affected first-degree relatives (especially if at least one is a sibling).[1] Data from a prospective family-risk study support our caution.[11] Mean duration of follow-up in ISUIA, at 4·5 years, may be too short to detect all the rupture risk,[7,12] but planned longer-term follow-up on the ISUIA cohort will resolve this question.

Despite these criticisms, the ISUIA prospective data are the most robust available and will be helpful to clinicians. Patients with no history of subarachnoid haemorrhage and an asymptomatic anterior-circulation aneurysm under 7 mm do not require treatment on simple analysis of risk-benefit ratio alone. This category comprises most of the group 1 patients. For other sizes or sites, ISUIA provides robust information for rupture-risk analysis. Individual risk-benefit analysis is also required for patients with a history of subarachnoid haemorrhage in whom the relative risk is 3 for small anterior-circulation aneurysms compared with group 1 patients (ie, about 0·45% a year). The patient's age will be relevant here. However, the clinical situation is more complicated than simple rupture-risk versus treatment-risk analysis. Some patients undoubtedly find quality of life adversely affected by the knowledge of an aneurysm and may require treatment of even a very-low-risk aneurysm to alleviate this considerable psychological morbidity. Other patients have additional risk factors to incorporate into the risk analysis.

If treatment is indicated on individual risk-benefit analysis, which treatment? Overall, treatment results in ISUIA reflect those in the ISAT trial.[5] Where anatomy is suitable, endovascular management seems the treatment of choice for patients aged over 50 years and in those with posterior-circulation aneurysms. For those aged under 50 with anterior-circulation aneurysms, the situation is not so clear. In these patients, treatment options and relative benefits and risks (including postcraniotomy epilepsy) must be discussed carefully with patients and relatives before elective treatment so that fully informed consent can be given.

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Who needs a defibrillator after myocardial infarction?

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Defibrillator implantation for every heart-attack survivor with an impaired left ventricle may soon be recommended. The MADIT-II study (Multicenter Automated Defibrillator Implantation Trial II)[1] recruited patients who had had myocardial infarction more than a month previously and who had left-ventricular ejection fraction of 30% or less, for randomisation to an implantable defibrillator or no device. MADIT-II found a dramatic 34% reduction in hazard of all-cause mortality overall. The follow-up averaged only 20 months, so only a modest reduction in absolute mortality of 5·6% (from 19·8% to 14·2%) was recorded at study end.

Implementation of this intervention routinely for every patient meeting the criteria would necessitate an enormous increase in the facilities for defibrillator implantation and maintenance. The cost of the devices alone (£20 000–30 000 each) is an important problem limiting their universal use in this situation. Ironically, so broad and impressive are the benefits, that strategic policy-setters—financially unable to recommend full implementation within constrained budgets and ethically unable to recommend selective implement-ation—could be tempted to ignore the MADIT-II evidence entirely.

Cost concerns would be alleviated in two ways if it were possible to stratify risk within the MADIT-II umbrella. First, some MADIT-II-type patients might not require a defibrillator, thus reducing costs. Second, since the benefit is concentrated in the remaining MADIT-II-type patients, they must have a greater benefit from the defibrillator than that seen in the MADIT-II trial overall—ie, a lower cost per life-year gained.

Although ventricular arrhythmias arise suddenly, there may be subtle electrical abnormalities that allow susceptible patients to be identified before the arrhythmia occurs.[2,3] At fast heart rates, some regions of myocardium may be unable to complete a whole depolarisation-repolarisation cycle within one beat and therefore contribute only on alternate beats, resulting in subtle alternation of the QRST sequence on alternate beats, most noticeable in the T wave.

In brief, T-wave alternans is quantified as the degree of beat-to-beat oscillation in the size of the T wave during an exercise test. Special sensitive ECG electrodes and processing algorithms are required to detect this alternation and separate it from background noise. Previous work with T-wave alternans has established that it can predict malignant ventricular arrhythmias,