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). 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 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.

We are grateful to Gabriël Rinkel for providing information on the sizes of ruptured aneurysms in his systematic review.

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Who needs a defibrillator after myocardial infarction?

See page 125

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) 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 implementation—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.23 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,
seemingly as accurately as can formal invasive electrophysiological provocative testing.\textsuperscript{4,5}

In this issue of The Lancet, S Hohnloser and colleagues pooled individual patients’ data from these studies\textsuperscript{1-3} and selected 129 who fitted the MADIIT-II description. These investigators observe that a combined endpoint of sudden cardiac death or cardiac arrest was significantly less frequent in patients who did not have T-wave alternans. This finding may at first appear to be a justification for withholding defibrillators from MADIIT-II patients without T-wave alternans.

Should T-wave alternans be used to stratify MADIIT-II type patients? Before withholding defibrillator therapy on the basis of these data, two facts should be borne in mind. First, the MADIIT-II effect was larger than is widely appreciated. Life-span was extended, as far as can be gleaned from the report,\textsuperscript{1} by 45–50% for a notional average patient. But so clear were the results that MADIIT-II ended in less than 2 years, before even 20% of patients without defibrillators had died. Thus the observed absolute reduction in mortality was necessarily small, and, as is frequently stated, somewhat misleadingly: “18 defibrillators would need to be implanted to save 20 months of life”\textsuperscript{4}. Unjustly, this includes the full effort (and cost) of implantation yet only the first 20 months of the typical 120–month working-capacity of the defibrillator. A toll bridge would never be expected to recoup its costs within a couple of years; why should a defibrillator be expected to do so?

Second, a zero event-rate in a sample still has a finite-sized 95% confidence interval. To put it another way, even if the underlying event-rate in the general population without T-wave alternans was as high as 8%, in a sample of 35 patients (such as in Hohnloser and colleagues’ study) there will be a more than 5% chance of no events occurring, since (1–0.08)\textsuperscript{35} is about 0.054. That calculation means that a zero rate in a single sample is far from complete reassurance. What is needed is a trial in which patients meeting MADIIT-II criteria and without T-wave alternans are randomised to defibrillator or no device. Such a trial would give more substantive grounds for withholding defibrillator therapy in a subset of MADIIT-II-type patients. Until then, defibrillators could be considered a standard of care for in a subset of MADIIT-II-type patients. Until then, substantive grounds for withholding defibrillator therapy criteria and without T-wave alternans are randomised to needed is a trial in which patients meeting MADIIT-II

also in 1956, the finding of Roitt et al\textsuperscript{3} of spontaneous this activity as a thyroid-stimulating immunoglobulin. Also in 1956, the finding of Roitt et al\textsuperscript{3} of spontaneous antibodies against thyroglobulin led to the birth of the idea of autoimmune disease, with the thyroid as the first example. However, there were dark days ahead when failure to identify thyroid-stimulating immunoglobulin in all cases of Graves’ disease cast doubt on such antibodies as the mechanism for thyrotoxicosis in this condition for many years. Some of the confusion was due to differences between the use of mouse and human tissue in experiments, but much was because thyroid-stimulating immunoglobulin present at very low concentrations in serum.

It took another 33 years to clone the TSH-receptor (itself a holy grail in its day)\textsuperscript{,6,7} which led to improvements in the detection of thyroid-stimulating immunoglobulin. Challenges in the purification of sufficient quantities of TSH-receptor protein delayed progression to immunisation of mice to generate thyroid-stimulating immunoglobulin for several years, but eventually murine antibodies to the TSH receptor were generated. Sadly, none of these early mouse antibodies resembled thyroid-stimulating immunoglobulin in thyroid-stimulating capacity and none of the immunised mice developed hyperthyroidism. Increasingly ingenious technology was used, and in time immunisation regimens with transfected cells, naked DNA, or adenoviruses successfully generated thyrotoxic animals, albeit at low frequency and often in unusual strains (eg, outbred NMRI mice or Armenian hamsters). However, a high-affinity stimulatory monoclonal antibody remained elusive. Then, in 2002, three groups simultaneously reported rodent monoclonal antibodies that resembled thyroid-stimulating immunoglobulin.\textsuperscript{8,9}

The final discovery by Sanders and colleagues of a human monoclonal antibody appears to have been a triumph of scale. The isolation of thyroid-stimulating immunoglobulin from immunised rodents involved the screening of around 1000 hybridomas; in the search for a human spontaneous thyroid-stimulating immunoglobulin, 16 500 hybridomas derived from the blood of a patient with Grave’s disease had to be screened to find a single clone. How does the monoclonal antibody reported by Sanders and colleagues match up against McLachlan and Rapoport’s tests for the holy grail? Well, it clearly passes two of the five. The reported monoclonal is of IgG class, and indeed IgG, as predicted by Weetman et al in

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