unsound. It is possible that as longer-term data become available, or if different study end points were to be applied, different conclusions might be drawn.

The decision to stop the trial was based primarily on whether or not patients had dysphagia post-operatively. The investigators are critical in their discussion of other published series for inconsistent definitions for dysphagia, and we agree that such definition is difficult. However, the same criticism can be applied to their trial, because no definition of dysphagia is provided, nor is there a description of the methodology applied for the assessment of dysphagia. We are aware from our own follow-up of patients undergoing antireflux surgery within randomised trials[2,3] that how and who asks questions, and the scoring system which is used, can influence the apparent incidence of post-operative symptoms, such as dysphagia. Furthermore, our experience with prospective follow-up of more than 900 laparoscopic fundoplications has shown that most patients who undergo a Nissen fundoplication have some dysphagia 3 months after Nissen fundoplication.[2–4] This symptom usually subsides as more time passes, and hence we contend that a follow-up period of 3 months is too short to allow adequate conclusions about dysphagia to be made. Dysphagia is common before antireflux surgery, occurring in up to 40% of patients with gastro-oesophageal reflux disease,[2,3] and it is usually more common at 3 months after open Nissen fundoplication[5] than reported in other studies. If outcomes are looked at in another way, one could focus on the apparent doubling of complications following open surgery, and report an advantage for laparoscopic fundoplication.

While the investigators assure us of the experience of the surgeons carrying out or supervising the laparoscopic procedures, 54 patients were recruited from one institution, the remaining 49 patients were recruited from eight different hospitals over 19 months—ie, on average of one case every 3 months for each hospital. Does this figure reflect the true workload of these hospitals? If not, what proportion of patients were not recruited to the trial and why, and what operations were undertaken in these patients? Since the statistics in the trial have been carefully planned it is also surprising that the investigators do not acknowledge the possibility that they may be dealing with a type II statistical error. We are disappointed that a worthwhile opportunity to add to the literature on laparoscopic versus open fundoplication had been diminished by early and possibly unnecessary termination.

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Author's reply

Sir—The criticisms expressed above focus on four topics: the indication for antireflux surgery, dysphagia, the definition of surgical expertise and the impact of the learning curve, and statistics.

We disagree with the concern expressed about the profile of patients included in the trial. It is our consistent experience that patients referred for surgery are all on proton-pump inhibitors, which is one reason for the absence of oesophagitis, while on the other hand it is becoming more and more obvious that at least 50% of patients with gastro-oesophageal reflux disease (GORD) have no oesophagitis to start with.[1] Normal sphincter pressure does not exclude GORD. About 50% of all reflux episodes are due to transient lower oesophageal sphincter relaxation and coincide with a normal basal sphincter tone.[2] We understand the surprise about the number of patients without pathological reflux on 24-h pH monitoring. It was, however, recognised in the 1980s that 24-h pH monitoring is only the gold standard if combined with symptom indices. All these patients had a proven association between symptoms and reflux, assessed by symptom index[3] or symptom association probability,[4] and responded well to surgical treatment.

The proportion of patients with dysphagia in the laparoscopic group is indeed higher than the mean rate of dysphagia in the overview by Perdikis and colleagues.[5] The upper limit in the literature is higher than the 12% in our series. The seven patients in our study lost weight, needed reintervention, and were classified as having severe dysphagia, whereas other instances of dysphagia were transient. Repeat dilatation was unsuccessful. We think that the length of the wrap is of limited importance, since in the open group, with a wrap of 3–4 cm length, only transient dysphagia was observed. Geometry, inadequate mobilisation, and torsion may be far more important, but very difficult to quantify or be objective about. The use of an intraluminal bougie is a personal preference and not supported by all surgeons. Both dysphagia and reflux control, which are of international standard (over 90%) in our study, should be included in the audit on the outcome of antireflux surgery. We can not compete with the large series by the Mayo Clinic/Jacksonville, Seattle, Los Angeles, and the Adelaide groups. We realise that a large series from one institution should not be confused with results reported from multicentre trials.

It has been pointed out that ours is a pragmatic trial and that the learning curve has not been satisfactorily defined. There is not only a learning curve, but also a maintenance curve and this should, of course, also be defined in the discussion about who is a specialist surgeon. In the discussion, we do not go any further than that the need for changing the informed consent and related ethical considerations prompted us to stop the trial in its original form. The information presented in our study is sufficient to suggest that the open procedure is superior. We are currently collecting the 2-year follow-up data and a cost-effectiveness analysis is in its final stage of evaluation. We expect to provide important answers to remaining questions. We realise that our data are specifically pertinent to surgical daily life and possibly mainly relevant for the vast majority of centres with (relatively) limited experience and a referral pattern leading to 20 to 50 antireflux operations per year. This is also shown to be the critical volume to obtain good results for oesophageal resection and Whipple's procedure. If lack of experience and technically improper surgery are key factors, this would have affected both arms. For clinical practice, we feel that a multicentre trial is at least as valuable as a study done in one institution, which has different implications for

clinical practice and is apparently considered more appropriate for the UK, the USA, and Australia. Our study may be of limited impact for large institutions but is very relevant for most centres with intermediate volume. It is obvious that we do not accept the reported percentage of dysphagia as it stands and we are currently carrying out an extension of the randomised controlled trial that we stopped.

Data in our study are consistent with a relative risk of 8·8 (p 0·02) in favour of the open repair, which rules out the possibility of a Type II error.

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Heparin *vs* aspirin in acute ischaemic stroke

Sir—In their study E Berge and colleagues (April 8, p 1205)[1] addressed a very important issue concerning the role of aspirin or anticoagulant therapy in the early management of patients with acute stroke. Unfortunately, their study was not able to confirm whether anticoagulation with a low-molecular-weight heparin was superior to 160 mg aspirin in preventing recurrent stroke or improving clinical outcome. The International Stroke Trial (IST)[2] and Chinese Acute Stroke Trial (CAST)[3] together needed to enrol about 40 000 patients to confirm the small but important benefit of aspirin in preventing recurrent stroke. Subgroup analysis of patients with atrial fibrillation treated with unfractionated, fixed-dose heparin in the IST did not show a net benefit for this treatment. Therefore, it is not surprising that Berge and colleagues report a negative result given that only 449 patients were enrolled into their study.

Stroke is a heterogeneous condition, with great variation in clinical outcome depending on many factors including the site and size of the infarct. Antiplatelet or anticoagulant therapy may only produce a small treatment effect and the biological effects of these agents are rather variable. There is evidence that patients who have a stroke while on aspirin have residual platelet aggregation, which can be suppressed by higher doses of aspirin.[4] A given dose of aspirin may produce different degrees of platelet inhibition in different individuals and similarly, a given dose of heparin may produce variable degrees of anticoagulation. Therefore, there are many variables that may confound the result of a clinical trial, but such confounding can be overcome by randomising very large numbers of patients (as in IST or CAST) or a more homogeneous group of patients (eg, those with middle cerebral artery infarcts), and trying to ensure a uniform biological effect of the drug used.

The present trial was small, doses of dalteparin (200 IU/kg/day) and aspirin (160 mg) were used which, although used in other trials, are still somewhat arbitrary, and no measure of the biological effect of these drugs was undertaken. As it is easy to measure the degree of anticoagulation and is becoming possible to accurately measure platelet function,[5] we would argue that future trials should include a measure of anticoagulant or antiplatelet activity rather than using an arbitrary dose of either drug. It would be more difficult to recruit patients to such trials, but they are more likely to produce useful answers.

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Vitamin D deficiency and tuberculosis

Sir—Robert Wilkinson and colleagues (Feb 19, p 618)[1] report the results of a case-control study on the association of vitamin D deficiency and vitamin D receptor polymorphisms with the susceptibility of tuberculosis. Although an interesting concept, I question whether the data they present really support the conclusion that polymorphisms in the vitamin D receptor gene contribute to the susceptibility of tuberculosis when considered in combination with 25-hydroxycholecalciferol deficiency. According to their table,[1] the odds ratio (OR) associated with 25-hydroxycholecalciferol deficiency (irrespective of vitamin D receptor genotype) was 2·9. According to their table 3, the OR associated with having both a "non-tt" genotype and 25-hydroxycholecalciferol deficiency was nearly equal to that for deficiency irrespective of genotype (OR=2·8). A reasonable interpretation of this observation is that the association between 25-hydroxycholecalciferol deficiency and tuberculosis is independent of vitamin D receptor polymorphisms. In other words, the effect of having both a non-tt genotype and 25-hydroxycholecalciferol deficiency could be attributed to 25-hydroxycholecalciferol deficiency alone. Proper analysis and interpretation of the joint effect of two putative risk factors on a disease is a complex issue that warrants careful attention by anyone who wants to undertake a study such as that by Wilkinson and colleagues.[2,3] Furthermore, even the simple ORs associated with 25-hydroxycholecalciferol deficiency presented by Wilkinson and colleagues may be misleading. In their table 1, when calculating the OR associated with 25-hydroxycholecalciferol deficiency (serum concentrations $\leq$10 nmol/L), they included in the reference group those with serum concentrations of more than 10 nmol/L and those whose serum concentrations were undetectable. This leads to an under-estimation of the simple association of 25-hydroxycholecalciferol deficiency with susceptibility of tuberculosis. If those with undetectable concentrations had very low concentrations, they should clearly be included in the not more than 10 nmol/L (deficient) group. If, on the other hand, the investigators think that undetectable concentrations indicate some sort of