ischemia by 41% (!), the number of patients with >60 min of transient myocardial ischemia decreased by 10% and silent episodes by 5%.

These data all suggest a reduction in transient myocardial ischemia when heparin is added to aspirin. However, the differences did not reach statistical significance, probably because of the small sample size. The authors speculate "that 260 patients would be needed to give sufficient power (85%) to show a 70% reduction in transient myocardial ischemia." According to our calculations, to achieve a similar power to show a more realistic 25% reduction, a sample size of 910 patients would have been needed. The authors' own data actually do suggest a reduction of this magnitude. In our opinion, to expect a 70% reduction in ischemia incidence from the addition of heparin to aspirin, a treatment modality in itself of proved efficacy, was quite unrealistic.

Too small a sample size in randomized controlled trials having negative results seems to be a common error according to data published recently in *JAMA* (3). Of 102 such studies, only 16% and 36% had sufficient statistical power to detect a 25% or 50% relative difference, respectively.

We believe that the authors' data do not support their conclusion that heparin plus aspirin is no more effective than aspirin alone in unstable angina pectoris. In fact, their data suggest but do not prove that heparin plus aspirin is more effective. To draw definitive conclusions, a substantially bigger study involving ~1,000 patients would be required.

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Reply

Bodo et al. raise a point that should be asked when any comparison of different treatment strategies indicates the treatment modalities in question to be the same with respect to predefined end points. They suggest that an inadequate sample size may be responsible for our finding that combination therapy with heparin and aspirin was no different than aspirin alone in reducing the incidence of transient myocardial ischaemia in patients with unstable angina. We welcome the opportunity to defend our sample size calculation.

The sample size was based on the expected incidence of transient myocardial ischemia and the effects of heparin and aspirin on transient myocardial ischemia. We indicated in the report that the calculations were made on the basis of data from the study by Serneri et al. (1) in which the effects of heparin, aspirin and alteplase on myocardial ischemia were compared in patients with unstable angina. Using continuous ST segment Holter monitoring they compared the effects of these treatments on the frequency of angina, number of silent ischemic episodes, total number of ischemic episodes and total duration of ischemia. Their results indicated that treatment with heparin reduced anginal episodes by 94%, silent ischemic episodes by 71%, total ischemic episodes by 78% and total duration of ischemia by 81%. In contrast, aspirin had no significant effect. The typical odds reduction for recurrence of angina with heparin versus other treatments was 66% (SD 6.4%) for days 0 to 3 ($p < 0.0013$). On the basis of these results we believe that our original power calculation was reasonable. We estimated that 260 patients would be required to show a 70% reduction in transient myocardial ischemia with heparin and aspirin compared with aspirin alone, assuming a 20% incidence of transient ischemia in patients treated with aspirin, giving a power of 85%. Because some patients will be included who, in retrospect, will be diagnosed as having myocardial infarction, we increased the sample size by a further 10%. We believe that it is reasonable to expect a 70% reduction in ischemia with the addition of heparin because that is supported by the data from Serneri et al. (1).

As Bodo et al. indicate, the sample size of any trial should be carefully inspected, but they should not be drawn into making statements about treatment guidelines by interpreting data "trends" when statistical significance is not reached. For example, they make several comments about the data in Table 2 from which they suggest that combination therapy is superior to aspirin. To state that the number of patients with transient myocardial ischemia was 25% less in the combination group is misleading when the absolute numbers of patients were 31 in the aspirin group versus 27 in the heparin and aspirin group—a difference of 4 patients. Similarly, the other variables mentioned by Bodo et al. are particularly influenced by one patient in the aspirin group who contributed 1,360 min of transient ischemia, which constituted >25% of the total ischemia in that group. We highlighted the point in the text of our article. Consequently, we believe that Bodo et al. have no basis for suggesting that our data indicate that heparin and aspirin therapy is superior to aspirin alone.

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Early Repair of Tetralogy of Fallot and Ventricular Arrhythmia

It has been suggested that in patients with tetralogy of Fallot, occurrence of late ventricular arrhythmias and possibly sudden death would decrease if surgical correction is performed early in life. The work of Joffe et al. (1) has attempted to address this important issue. This study describes the long-term follow-up results in 29 patients after repair of tetralogy of Fallot.

"Early" versus "late" repair of tetralogy of Fallot is not clearly defined in published reports. Nevertheless, "early" commonly implies complete repair at the time of, or even before, development of the need for palliative surgery, which usually occurs during the first year of

life (2). Patients in the Joffe et al. study are younger overall than most of the previous studies on the subject of arrhythmias and tetralogy of Fallot. However, most of these patients had undergone a previous palliative surgery (Blalock-Taussig shunt, 62%), and all of them were >1 year old (mean age 4, range 1.2 to 7.7). The timing of operation, therefore, was not "early" for a significant number of these patients, and the question of potential long-term benefits of early repair remains unanswered.

The authors have classified the patients into two groups: 21 with "uncomplicated" and 8 with "complex or repeated" operations. This approach is unprecedented in previous large studies; the available rates of prevalence and incidence of ventricular arrhythmia are obtained from patients with tetralogy of Fallot as a whole. Therefore, the low prevalence of ventricular arrhythmia in the Joffe et al. "uncomplicated" group should not be compared with the higher rates in previous studies that include both the "uncomplicated" and "complex" patient groups. In the patients in the Joffe et al study, the overall prevalence of late ventricular arrhythmias was 28%, which should not be considered "rare."

The prevalence of significant ventricular arrhythmias after tetralogy of Fallot repair has been shown to increase with time, and most studies with long-term follow-up (up to 28 years) show a prevalence of ~40% to 45% (3,4). The Joffe et al. study also demonstrates the effect of passage of time on detection of ventricular arrhythmias: 14% of patients had significant ventricular arrhythmias at early compared with 28% at late follow-up. However, the authors concluded that this difference was not significant because statistical comparison between the two groups yielded a p value >0.1. A higher p value may have been due to small numbers and a low statistical power (type II error). It is likely, therefore, that the patients in the Joffe et al. study had the same outcome as those with later repair. Furthermore, as the authors correctly point out, one of the still unsettled controversies regarding patients with tetralogy of Fallot is that ventricular arrhythmias may be a part of the natural history of the disease rather than secondary to operation. The long follow-up period (mean of 11.8 years) of the study, for which the authors should be commended, is still not long enough to rule out this possibility (the oldest patient evaluated was 21 years old).

We, therefore, believe that it is premature to draw any valid conclusions from the study by Joffe et al. regarding the potential benefits of "early" correction of tetralogy of Fallot in the prevention of late ventricular arrhythmias.

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Reply

In Joffe et al (1) we reported that late ventricular arrhythmias were less common after "early" repair of tetralogy of Fallot and when repair was "uncomplicated." As Fallah and Mehta point out, although our patients were younger than the series reported from the early surgical era, many still had a two-stage approach to their repair, with initial palliation. No long-term data have been published using ambulatory electrocardiographic (ECG) monitoring in patients who underwent primary repair in infancy, but follow-up standard ECG data support our conclusion that early repair is likely to be beneficial (2).

We classified our patients into "uncomplicated" and "complex" repair groups to illustrate the difference in prevalence and progression of ventricular arrhythmia in these two groups. The lower prevalence in the uncomplicated repairs is of interest in terms of etiology of late arrhythmia. We do not make direct comparisons between the prevalence of arrhythmia in our prospective study and those of earlier retrospective reports.

Fallah and Mehta state that the prevalence of significant ventricular arrhythmia after tetralogy of Fallot repair increases with time. This has not been demonstrated because no prospective data have been reported. They fall into the trap of assuming that because ventricular arrhythmias are common in older patients with long follow-up after repair, they are increasing with time. The group that we studied was indeed small, and we cannot be confident that with increasing time there may not be an increase in arrhythmia in both groups during even longer follow-up. However, we emphasize that the references Fallah and Mehta quote do not address the issue of increasing incidence of arrhythmia with follow-up, as they suggest (3,4).

We and others (5,6) have previously published data that suggest that late ventricular arrhythmia may be part of the natural history of tetralogy of Fallot as a result of myocardial damage in the uncorrected heart rather than secondary to operation. This natural history is interrupted by correction, and it is hard to see how longer postoperative follow-up would address this issue, as Fallah and Mehta imply.

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