TABLE 1. Power* of comparisons based on different sample sizes and cumulative event rates

Cumulative event rate at 10 years in RITA group (%)	Number of patients per group													
	200	300	400	500	600	700	800	900	1000	1200	1400	1600	1800	2000
12	17.7	24.2	30.7	36.9	42.9	48.6	53.8	58.8	63.3	71.2	77.7	82.9	87.0	90.2
16	23.9	33.3	42.3	50.6	58.0	64.6	70.4	75.4	79.7	86.4	91.0	94.2	96.3	97.7

RITA, Right internal thoracic artery.

*Power estimates assume: (1) recruitment over 6 years, (2) maximum duration of follow-up of 10 years, (3) 5% significance level (2-tailed), (4) analysis by log rank test.

exist. The publication is likely to influence the attitudes of cardiac surgeons and may jeopardize future better-designed and better-executed RCTs of an important question.

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References

1. Buxton BF, Raman JS, Ruengsakulrach P, Gordon I, Rosalion A, Bellomo R, et al. Radial artery patency and clinical outcomes: five year interim results of a randomized trial. *J Thorac Cardiovasc Surg.* 2003;125:1363-71.
2. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet.* 2002;359:1686-9.
3. Pocock SJ. Clinical trials: a practical approach. Chapter 10: Monitoring trial progress. Chichester: Wiley; 1983. p. 142-59.
4. Meinert CL, Tonascia S. Clinical trials: design, conduct and analysis. Monographs in epidemiology and biostatistics, Vol 8. Oxford: Oxford University Press; 1986. p. 208-31.
5. Pocock SJ. Statistical and ethical issues in monitoring clinical trials. *Stat Med.* 1993;12: 1459-69.

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Reply to the Editor:

We thank Professor Angelini and colleagues for raising several important issues in relation to our trial.¹ However, we do not agree that the conclusion of our article is misleading, and we believe that the issues raised in their letter can be simply and easily addressed.

The article presents the results 5 years after trial inception. We make that perfectly clear in the text and display the mean duration of follow-up in a graphic format with the Kaplan-Meier graphs. Pocock's concerns about the imprecision of estimates as displayed by such graphs in the presence of few events relates to the risk of conveying a visual impression of a difference where none exists. This is of moot concern in a graphic display of actual lack of difference.²

This interim analysis was not planned; it represented a response of the group of cardiac surgeons, cardiologists, intensivists, and cardiac anesthesiologists involved in the trial to the aggressively promoted view that radial artery conduits are "best," a view also strongly espoused by Professor Angelini and colleagues³ on the basis of nonrandomized data. A decision to undertake an interim 5-year graft patency analysis was made to ensure that, with the best of the data available so far, the design of the trial did not expose our patients to "unsafe surgical practice." No criteria were formally set for "stopping" the trial. The data were presented to the physicians involved in the trial and, following discussion, a unanimous decision was made to continue the study. The enrollment of 556 patients is now complete.

We agree about the importance of interim analyses for the purpose of patient safety. However, the methodology suggested by the correspondents is typically that of large multicenter drug company-sponsored trials, where major financial conflicts of interest exist. In such studies, the need for an impartial Data and Safety Monitoring Board (DSMB) is obvious. The need for a DSMB in single-center studies, where the patients are known to all physicians involved and are regularly seen in outpatient clinics, is empirically unproven.

Furthermore, the statistical criteria for action cannot, in our opinion, be sensibly taken as an absolute but must be seen within a Bayesian analysis of the pretest probability of a particular outcome being correct.⁴ We note that no gold standard exists to empirically validate the sensitivity and specificity of current statistical criteria for trial cessation. The probabilities of a difference between groups¹ approximate unity, a far cry from the extreme statistical "stopping" values as suggested by O'Brien and Fleming and the Peto-Haybittle rule to avoid a type 1 error.^{5,6}

Our study might be underpowered. However, the number of events seen in this interim group of patients may not be representative of the whole population. Furthermore, we anticipate that most of the outcome events will be seen in the latter half of the trial, and therefore, the estimation of sample size based on information from the interim analysis is inappropriate. We invite caution and consider that more interim information is needed before a recalculation of sample size is necessary. We agree that our report contains data with limited statistical power. As this was a safety analysis aimed at excluding only a major difference between the 2 groups, we believe our observations are important to the continued conduct of this and other studies, hence the publication.

All 438 patients¹ were included in the clinical outcomes analyses, which were based on an "intention-to-treat." Forty-two patients were excluded from the graft patency study: 21 were radial artery trial grafts and 21 were controls (16 right internal thoracic artery and 5 saphenous vein grafts). Two patients of the 42 refused angiography and 23 were excluded because of graft disease. In 2 patients the wrong conduit was used and in the remaining 15 patients, the correct grafts were used, al-

though the surgical technique was not as defined in the protocol. We understand the correspondents' concern about possible selection bias due to the exclusion of patients who did not receive the correct graft or in whom the surgeon did not target the correct artery. However, such decision is logical because it is not reasonable to assess the patency of a radial graft when no such graft exists. The same applies to assessing flow to a vascular bed that was actually not grafted. We consider that, in a study such as this, angiographic analysis on "per-treatment" principles is the correct approach. We further note that this decision was made a priori.

Finally, the conclusions of the article are correct given the data available. Furthermore, all the necessary information is available in detail for readers to understand the limitations that surround such conclusions. There is no attempt to mislead and whether our report will influence surgical attitudes remains uncertain. Furthermore, it is an "open verdict" and we cannot see how it could jeopardize future randomized controlled trials, given our conclusion that "the continued evaluation of the RA is justified." For our part, we are very committed to carrying out good randomized trials in cardiac surgery and will continue to do so in a branch of medicine where, relatively speaking, they are uncommon.

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References

1. Buxton B, Raman JS, Ruengsakulrach P, Gordon I, Bellomo R, Hare D, et al. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. *J Thorac Cardiovasc Surg.* 2003;125:1363-71.
2. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet.* 2002;359:1686-9.
3. Caputo M, Reeves B, Marchetto G, Mahesh B, Lim K, Angelini GD. Radial versus right internal thoracic artery as a second arterial conduit for coronary surgery: early and mid term outcomes. *J Thorac Cardiovasc Surg.* 2003;126:39-47.
4. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes Factor. *Ann Intern Med.* 1999;130:1005-13.
5. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics.* 1979;35:549-56.
6. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized controlled trials requiring prolonged observation of each patient. 1. Introduction and design. *Br J Cancer.* 1976;34:585-612.

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Reply to the Editor:

The choice between the right internal thoracic artery (RITA) or radial artery (RA) for the second coronary artery bypass conduit remains hotly debated, as evidenced by 2 recent publications in the *Journal*, one a randomized controlled trial¹ and the other a retrospective observational study.²

The interim 5-year result of our randomized controlled study suggested that the clinical outcomes of the RITA and the RA groups were similar. This differed from the conclusion drawn from the cohort study reported by Caputo and colleagues,² which suggested a clinical benefit from using the RA compared with the RITA. It is important to consider possible reasons for such an apparent difference in conclusions.

Caputo and colleagues' study² differed from the randomized trial. There was no assessment of graft patency, and they included additional end points. Obviously, cohort studies can never control for unrecognized factors. Therefore, an observational study should always be regarded as providing less reliable evidence than a randomized trial.³ This has recently been highlighted by the complete reversal of opinion as to the benefits of hormone replacement therapy once the results of randomized trials became available. One important factor that may not be well controlled in an observational study of this sort is the surgeon. The choice of graft was "entirely at the discretion of the surgeon." If some surgeons strongly preferred one type of operation, or even used it exclusively, this means that the comparison based on the observational data may suffer from bias because of confounding with the expertise of the surgeon.

Our comparison of cardiac event-free survival in the randomized controlled trial showed no significant differences, but this does not necessarily mean that the 2 studies are in conflict.

For our RA versus RITA comparison, the estimates and 95% confidence intervals (CIs) were 91% (76%-99%) for the RA group and 82% (63%-99%) for the RITA group. Because of the small numbers, these CIs are very wide and therefore consistent with a number of different possible underlying realities ("hypotheses"), namely, that the RA and RITA have the same cardiac event-free survival, that the RITA is better than the RA, and that the RA is better than the RITA. The latter is suggested by Caputo and coworkers.² Our study is not yet in conflict with this because, for example, our findings are consistent with a "true" cardiac event-free survival of 90% for the RA group and 70% for the RITA group; both of these values are in the respective CIs, and if they were the true values, which they could be, that would be consistent with Caputo and colleagues' findings.

Biologically, the left internal thoracic artery and RITA are similar and when grafted to the left anterior descending and circumflex coronary arteries⁴ have almost identical results. However, when the RITA is grafted to the right coronary system, there is a significant reduction in patency. For example, in the first 5 years of our internal thoracic artery program from 1984 to 1989, patency of the in situ RITA graft to the distal right coronary artery or its branches was approximately 75%. Because of the high graft failure rate of in situ RITA grafts when used on the right side, most surgeons, including ourselves, have favored using the RITA graft to the left system,⁵ either as a free or in situ graft. This latter strategy results in better graft survival curves that separate by 6 years.⁶ Caputo and coworkers,² on the other hand, used an in situ or pedicled graft in 94% of patients. Furthermore, 53% of the RITA grafts were attached to the right coronary or posterior descending artery where results could be less than optimal.² Therefore, although some of their analyses adjusted for the target artery and the authors thus claim that the results were not compromised, it is not clear whether adjustment was made for the type of proximal anastomoses (in situ vs free).

The clinical end point used by Caputo and colleagues² was a composite of death, myocardial infarction, repeat coronary bypass or percutaneous coronary intervention, and recurrent angina. Unfortunately, any composite outcome measure is only as