Letters to the Editor

The Editor welcomes submissions for possible publication in the Letters to the Editor section that consist of commentary on an article published in the Journal or other relevant issues. Authors should:

- Include no more than 500 words of text, three authors, and five references
- Type with double-spacing
- See <http://jtcvs.ctsnetjournals.org/misc/ifa.html> for detailed submission instructions.
- Submit the letter electronically via jtcvs.editorialmanager.com.

Letters commenting on an article published in the JTCVS will be considered if they are received within 6 weeks of the time the article was published. Authors of the article being commented on will be given an opportunity to offer a timely response (2 weeks) to the letter. Authors of letters will be notified that the letter has been received. Unpublished letters cannot be returned.

Radial versus right internal thoracic artery for myocardial revascularization

To the Editor:

Buxton and colleagues¹ recently reported interim results of a randomized controlled trial (RCT) of alternative conduits for the second graft in patients having coronary artery bypass grafting. They concluded that “the 5-year interim results do not support the hypothesis that the radial artery (RA) has superior patency to or is associated with fewer clinical events than free right internal thoracic (RITA) or saphenous vein (SV) grafts.” We argue below that this conclusion is misleading.

First, the paper does not present 5-year results. The last patient was recruited 2 months before the paper was received. The median duration of follow-up is not stated but from the Kaplan Meier graphs appears to be about 2.5 years. Plotting survival graphs when few patients remain at risk disguises the imprecision of the estimates at these time points.²

Second, the paper represents an interim analysis but does not state (1) whether the analysis was specified in the protocol, (2) the criteria for acting on the results of the interim analysis, or (3) whether any action has subsequently been taken. It is not clear whether the trial continues to recruit.

Interim analyses of treatment effects aim to prevent participants and other patients receiving a treatment known to be inferior.³⁻⁵ They should be specified in the protocol, together with proposed actions (ie, stopping rules).^{3,4} Interim results should be disclosed only to the Data and Safety Monitoring Board (DSMB), not to the investigators.^{3,5} If the DSMB recommends specific actions (eg, stopping the trial early), the investigators have responsibility for definitive analyses. Statistical criteria for actions are usually set at a more stringent level than for final analyses (eg, $P < .001$).^{3,5} If the DSMB concludes no action is required, disclosing interim results can prejudice successful completion of the trial.³

Third, the authors report a target sample size based on higher risks of events than were observed. For patency, the sample size is also much smaller than the target. Consequently, the analyses of patency have little power to detect the target difference. For example, with about 35 patients in each group (ie, for the comparison of RA versus RITA), the analysis had only about 28% power to detect the stated target difference. The analyses of survival free from cardiac-related events also have less power than suggested because only half the participants had reached about 2.5 years of follow-up.

We believe the target sample size is optimistic, even for the planned 10-year analysis. A relative risk smaller than the 0.33 implied by the predicted event risks is likely to be clinically worthwhile. Table 1 shows the power and sample sizes for different baseline event risks (bracketing those chosen by the authors), assuming a constant relative risk of 0.67 (our estimate of the minimum effect likely to change practice). For the tabulated baseline event rates, the rates for the comparison group would be 8% and 11%, respectively (absolute differences of 4% and 5%).

Fourth, the results may also be seriously biased. The authors excluded 40 randomized patients from the graft patency study because of the “poor quality of the randomly assigned conduit (eg, damaged during removal)” or because “the appropriate coronary artery was not grafted.” The investigators should have kept these patients in the study as damage to the conduit or inappropriate grafting are likely to affect the overall outcome for a patient and may be related to the type of graft. The decision to exclude a patient could not have been blinded to the randomly assigned conduit. The distribution of excluded patients by group is not reported.

The conclusion is stated as a refutation of the hypothesis that RA grafts have superior patency than RITA or SV grafts. This conclusion is misleading because the analyses had very little chance of detecting the target differences even if they truly

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.

Massimo Caputo, MD^a
 Barnaby C. Reeves, DPhil^b
 Gianni D. Angelini, FRCS^a
 Bristol Heart Institute^a
 University of Bristol
 Bristol, United Kingdom
 Health Services Research Unit^b
 London School of Hygiene & Tropical
 Medicine
 London, United Kingdom

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.

doi:10.1016/j.jtcvs.2003.08.049

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-