good as its weakest end point because all outcomes are treated as having equal value. It is no surprise that the composite end point used by Caputo and colleagues is largely dependent on the presence of recurrent angina, which is responsible for 31 of 43 clinical events in the RITA group and 10 of 15 clinical events in the RA group. There were no objective criteria set for diagnosing "recurrent angina," which is always a difficult end point to assess in clinical trials. The clinical wisdom and validity of assigning the same statistical weight to angina and death defy common sense, because most patients would value the 2 quite differently.

The duration of follow-up in the study of Caputo and colleagues² is short, a median of 1.8 years for the patients receiving a RITA graft and only 1.5 years for those receiving an RA graft. It is clear that this is a short-term study result and thus more likely to reflect perioperative factors rather than the development of graft disease.⁷ The study is too short to make any long-term conclusions. In our randomized trial,¹ the number of patients who had reached 5 years follow-up was relatively small, and therefore longer-term conclusions are also limited. A more appropriate conclusion for the study of Caputo and colleagues would be that, in the short term, the RITA used as an in situ pedicle graft to the right coronary system seems to result in an inferior clinical outcome when compared with the RA.

Caputo and colleagues² attempted to control analytically for confounding factors. In the Cox proportional hazards model for mortality, this means they were attempting to adjust for other explanatory variables with very small effective sample sizes (1 death in the RA group and 5 deaths in the RITA group). Such an analysis is ambitious, to say the least. An alternative form of analysis, which would probe the comparability of the groups in terms of their profiles, would be to use the propensity score approach.⁸ This would model the surgeon's choice of operation in terms of explanatory variables at the time of the operation. It could show that there are non-comparable subsets of the patient groups and would more generally permit an analysis that more closely mimicked a randomized trial than analyses based on modeling the outcomes in terms of all the explanatory variables.

In light of these observations, we believe that a more balanced conclusion should have highlighted the limitations of using composite outcomes to increase statistical power and raised the possibility that an in situ RITA graft placed in the right coronary system, at least in the short term, might result in inferior results. It should have also emphasized that these observations cannot be extrapolated to include free RITA grafts (used in only 6% of patients) or in situ RITA grafts placed in the left system, where many remain patent for more than 20 years.

There are satisfactory existing data to guide current surgical practice, but obviously the long-term results from trials of prospectively randomized patients are required.

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Reply to the Editor:

In this issue, Buxton and colleagues comment on 2 recent articles in the *Journal* reporting evidence about the effects of choosing the right internal thoracic artery (RITA) or radial artery (RA) for the second arterial conduit for bypass grafting. The 2 articles reported interim results of a randomized controlled trial (RCT)¹ and a non-randomized study (NRS).²

Buxton and colleagues advance several alternative explanations to reconcile the apparently conflicting findings of the two studies: (1) There were differences in study design, that is, the greater susceptibility, in general, of observational data to bias. (2) Specifically, there was the possibility of inadequate control in the observational study for differences between groups in graft site and grafting strategy. (3) There was a short duration of follow-up in the observational study. (4) A composite outcome (survival free from cardiac-related events) was used in the observational study. (5) The findings are, in fact, consistent with one another given the imprecision of the findings of both studies.

In the absence of data from well-conducted RCTs with sufficient duration of follow-up, it is not possible to distinguish between these options; the last one is, arguably, the most parsimonious. As we stated,² such a trial is the only way to answer the question, and Buxton and colleagues agree with this point of view. However, the stated suggestions raise a number of methodologic points that may be of interest to readers.

The respective merits of RCTs and NRSs are debated almost as "hotly" as those of the RITA and RA.³ If an NRS of an intervention suggests useful benefits for patients, the intervention should be further investigated in an RCT whenever possible. RCTs and NRSs differ primarily with respect to their susceptibility to selection bias, leading to potential confounding.³ In an NRS, the likely direction of confounding can be inferred by inspecting the distribution of prognostic factors across groups. If patients who received the apparently more beneficial intervention had more favorable prognostic characteristics, then the finding may be explained by con-

founding; “adjusting” the results (whether by stratification, conventional multiple regression modeling, or regression modeling of propensity scores) can never wholly remove the effect of confounding, although adjustment would be expected to weaken the effect estimates (ie, move the estimates closer to no benefit). However, if patients who received the apparently more beneficial intervention had less favorable prognostic characteristics, then the finding is unlikely to be explained by confounding; “adjusting” the results will still not wholly remove the effect of confounding, but adjustment would be expected to strengthen the effect estimates (ie, move the estimates further away from no benefit).

RITA and RA grafts may be used to revascularize different sites (circumflex or right coronary) and in different ways (in situ or pedicle grafts). In our observational study, we recognized that grafts to the right coronary artery are more prone to failure and carefully controlled the analysis for site of graft. However, we did not control for the specific ways in which the conduits were grafted. Whether one should do so depends on the extent to which a surgeon’s preferred grafting strategy is attributable to the properties of the conduit being grafted. We regard differences in the way that the two conduits are grafted as aspects of the overall strategies of using the RA or RITA as arterial conduits.

The power of survival analyses is a function of the number of events observed (eg, deaths or cardiac-related events). The number of events is increased both by the number of subjects and the duration of follow-up. Despite a median duration of follow-up of only approximately 1.5 years in the NRS,² compared with 2.5 years in the interim analysis of the RCT,¹ the former analysis of survival free from cardiac-related events had considerably more power.

It is not clear to us why using a composite outcome should invalidate the findings of the NRS or why Buxton and colleagues criticize this practice, because they used it themselves (they reported cardiac event-free survival and mortality alone, as we did). In our study, the cardiac-related “event” of recurrent angina was assigned with reference to the findings of exercise tolerance tests in exactly the same way for both groups, thereby minimizing bias as far as possible. Combining events hierarchically is the recognized way to analyze mul-

tipl events that may be attributable to the underlying condition and that may be affected by the interventions being compared. This practice has been used in the analysis of many internationally renowned RCTs, for example, combining mortality and nonfatal myocardial infarction^{4,5} and mortality and heart failure.⁶ It is likely to be important when mortality is rare, or when mortality does not reflect outcomes that are important to patients⁷; there is presumably no argument that recurrent angina matters to patients. The issue of key importance is the avoidance of differential bias in the assessment of events. Results are typically shown for events in a hierarchy of severity, for example, actuarial survival and cardiac event-free survival. Participants in a study who die should not be censored or omitted from analyses of cardiac event-free survival, except in special circumstances.

There is a danger that research groups become entrenched in their views about the likely answer to a research question before appropriate evidence becomes available. We emphasize that this is not our position and that we were careful in our criticism⁸ of the interim report of the RCT¹ to restrict our comments to technical points. It is perhaps unfortunate that the two articles appeared at a similar time. Before performing our retrospective analysis, we had no prior expectation that the RA would be better; rather, we were concerned to ensure that patients receiving RA grafts were not being disadvantaged, as suggested by many other researchers. We believe that our observational analysis suggests that using the RA instead of the RITA may have benefits for patients, and that the benefits may be large; these are exactly the circumstances in which the surgical community should collaborate to perform a definitive RCT.

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Methylene blue as drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass

To the Editor:

The excellent article written by Leyh and colleagues motivated this letter.¹ We hope to share some of our extensive experience with methylene blue (MB). It is important to observe that Leyh and colleagues examined the results of MB therapy for norepinephrine refractory vasoplegia “after cardiopulmonary bypass (CPB),” although this kind of situation may happen before and even during CPB.

Our ongoing laboratory experiments have proved the usual safe doses of MB in regard to possible endothelium dysfunction. We have performed studies in porcine arteries (coronary, renal, superior mesenteric, and hepatic), rabbit aortas, and canine femoral arteries. By comparing sham animals with animals that received intravenous (IV) MB, we found differences only in intermediary concentrations in dose-response curves to the calcium ionophore