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Reply

We appreciate the commentary provided by Dr Mackey and Professor Naylor on the ARCHeR publication and the opportunity to respond.

Professor Naylor commends us on "being the only one of the 10 or so 'high-risk' [sic] stent registries to publish" results, and although we appreciate the salute, we refer Professor Naylor to the publication of the CREATE trial by Safian et al[1] several months ago, and we know of at least one other study currently in review. As a point of clarification, there have been seven high-surgical-risk registries completed in the United States since the advent of embolic protection devices.

Two specific issues are raised by Professor Naylor, one concerning statistical methodology and the other the clinical applicability of results. Regarding methodology, the noninferiority design is increasingly common where the intent is to establish a reasonable technology or technique alternative to an existing therapy (which may be preferred because of less invasiveness or cost, greater availability, and so on) and where previous literature exists to establish a control rate.[2] In addition, noninferiority trial designs are generally preferred over equivalence trials, which are unnecessarily two tailed. In the case of carotid stenting in the United States, randomization in high-surgical-risk trials was believed to likely hinder timely enrollment (as evidenced by the SAPPHIRE trial), so this alternative study design was established.

Both Professor Naylor and Dr Mackey question various components of and/or methods used for the comparator—specifically, the weighted historical control. This information was not included in our original article because of space constraints. To be clear, the methodology for the determination of a weighted historical control was established a priori in a binding contract with the Food and Drug Administration before the first patient was enrolled in ARCHeR. Once the last patient was enrolled, the 14.4% comparator was computed from the prespecified 1-year composite end point rates, which were 15% for comorbid conditions and 11% for anatomic conditions, and weighted according to the actual distribution in those categories. Although we appreciate Professor Naylor's concern with stopped trials,[3] as explained in the text of the article, ARCHeR 1 was rolled over into ARCHeR 2 to allow for the introduction of the embolic protection filter and not for clinical or outcome reasons; it did not complete enrollment by agreement with the overseeing regulatory body. Moreover, all three phases of the trial were conducted with the same inclusion and exclusion criteria, which resulted not only in their poolability, but also in a homogeneous distribution of symptomatic patients across three trials.

Both Professor Naylor and Dr Mackey go to great lengths to prove that the concept of a high-surgical-risk patient is a fallacy. It is unfortunate that leaders in the field in vascular surgery continue to beat this drum, providing in support only retrospective data from single surgeons or centers, all of which lack both rigorous neurologic audit and 30-day follow-up, which have become the standard for assessing carotid stent procedural outcomes. Previous studies have clearly demonstrated a threefold increase in apparent stroke rates with prospective neurologic evaluation, as was performed in ARCHeR.[4,5] What is not offered is the contemporary outcomes in a very similar endarterectomy cohort in the SAPPHIRE trial,[6] in which the 1-year composite end point in the surgical group was 20.1% and higher than the randomized stent cohort at every time point.

More recently, the generalizability of these results in the nontrial setting has been demonstrated in the subsequent CAPTURE registry (TCT 2006 Scientific Sessions, oral presentation. October 2006), in which the 30-day rates of adverse outcomes in more than 3500 patients tracked with neurologic audit are lower than these AR-CHeR results. In contrast, real-world mortality rates with carotid endarterectomy have been reported to be nearly three times higher than those in landmark clinical trials.[7]

Any attempt to compare data from the ARCHeR trials with a normal-surgical-risk historical cohort will be missing the point. High-surgical-risk patients not only are at increased risk for endarterectomy, but are also likely to be at increased risk for stroke as well. Data from the Asymptomatic Carotid Stenosis and Risk of Stroke group confirm that the existence of even two comorbid factors (contralateral transient ischemic attack and renal insufficiency) are associated with an increase in the 1-year event rate from 2.3% to 7.3% in patients with carotid disease.[8]

The field of vascular surgery has had more than 50 years of experience with endarterectomy, yet it has failed to conduct a single study vs medical therapy among high-surgical-risk candidates. Nonetheless, large numbers of individuals at high surgical risk undergo endarterectomy each year. It seems, then, somewhat disingenuous to suggest that carotid stenting, which compares favorably to surgery in this population, should be discarded as a therapeutic option because it has not proven any effectiveness vs medical therapy. We nonetheless agree with Dr Mackey that further study of these two therapies with both prospective neurologic evaluation and long-term follow-up will help define the need for, and utility of, carotid revascularization in this population.

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Regarding "InterGard silver bifurcated graft: Features and results of a multicenter study"

Ricco[1] recently published an article containing a meta-analysis but did not describe the techniques of the analysis. The absence of methodology stimulates the following questions: What were the inclusion/exclusion criteria for selection of the comparator studies? As presented, it is impossible to reproduce the meta-analysis or, more importantly, discern the effect of various biases.[2,3] How robust was the conclusion from the meta-analysis when possible confounding factors were considered? Various types of bias are inherent within any meta-analysis. It is a basic necessity of all meta-analyses to perform sensitivity analyses to demonstrate the robustness of results.[4,5] Did the studies in the meta-analysis report graft infection in terms of odds ratios, or did the authors extrapolate these data from reported percentages and counts? Translation of percentage and count data directly into an odds ratio without accounting for differences in follow-up duration between individual studies would introduce statistical bias. Moreover, the authors fail to state whether individual study data were weighted to derive the combined odds ratio and did not describe the calculation method used: either fixed-effect or random-effect modeling.[3] Do the wide confidence intervals for the odds ratio of the author's study (0.21 with a 95% confidence interval of 0.01-4.4) really reflect a reproducible outcome? The dashed vertical line in their Forrest plot (fig 6)[1] corresponds to no effect (odds ratio = 1.0). If the confidence interval of individual studies includes 1, then it is debatable whether any difference in the effect estimate of one treatment vs another is significant at conventional levels ($P < .05$). Finally, did the authors consider the homogeneity vs heterogeneity of individual studies used? The poolability of individual study data in the meta-analysis was not discussed, although the data in the Forrest plot (fig 6)[1] suggest that individual study data were homogeneous. Consequently, we believe that the authors should have commented on the applicability of their conclusion toward patient populations with characteristics (eg, comorbidities and risk factors) that are different from the patient populations considered.[5]

This postmarketing study has a commendable data return, considering its study type and follow-up duration, with just 2.8% patients lost to follow-up over a mean of 55 months.[1] Complete disposition of all patients from all centers through each study period would have been useful. Kaplan-Meier curves with a 3-year follow-up are presented despite a reported mean follow-up longer than 4.5 years. The low attrition rate and follow-up duration suggest that data are available to show outcomes well beyond the selected follow-up of 3 years. A rationale for limiting the survival data to 3 years would be appropriate.

There are remarkably few English-language publications on the use of silver-coated bifurcated vascular grafts.[1,6] Answers to the above methodologic and reporting issues would allow readers to better judge the validity of the stated conclusions.

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Reply

We appreciate the letter from O'Connor and Andrew concerning our article, but we want to clarify the following points concerning the methodology of the study and the meta-analysis presented in the article.

The purpose of our prospective multicenter study was to evaluate the safety, patency, and infection rate of a bifurcated aortic polyester graft coated with collagen and silver acetate. As pointed out by O'Connor and Andrew, our study had only 2.8% of patients lost to follow-up over a mean of 55 months. This result was achieved by adequate monitoring of all centers. In addition, uniformity and completeness in complication reporting was verified during on-site monitoring visits by comparing complications in charts with those in the case-report form. As usual, the Kaplan-Meier curves were used to report patient survival and primary and secondary patency up to 3 years. As pointed out by O'Connor and Andrew, follow-up was longer for some patients, and technically any survival plot can be extended right through to the longest follow-up time. However, this extension is not good statistical practice, because for any such plot the eye is drawn to the right (ie, where the plot finishes), where there is least information and greatest uncertainty. Much of the right-hand part of the plot can
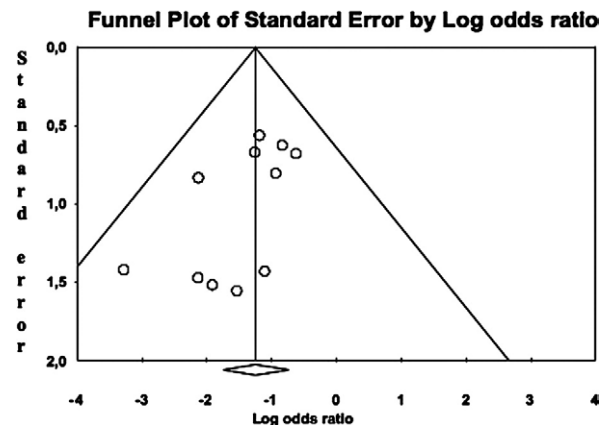

Fig. Funnel plots with graft infection log odds ratios from individual studies on the horizontal axis and standard error reflecting the study size on the vertical axis. The name *funnel plot* is based on the fact that the precision in the estimation of graft infection will increase as the sample size of component studies increases. Effect estimates from small studies will therefore scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias, as shown here with data from our studies, the plot will resemble a symmetrical inverted funnel.