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Reply:

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REPLY:

We thank Drs Arrese and Sarabia for their interest in our study.[1] While they "find the extracted data highly useful," they are concerned that "the analyzed group may represent a small subgroup of the patients we encounter in our clinical practice."[2] Moreover, they "would encourage further investigation and analysis within a larger patient population to address the limitations associated with patient selection."[2] In other words, the crucial question they ask and that any clinician confronted with new trial results is entitled to ask is, Should I change my practice in the light of this new evidence? The authors of the letter are concerned that patients might have been selected to participate in the study and that this selection may have affected the generalizability of results. The answer to the question (Should I change my practice?) depends, partly, on the type of practice and whether that practice is dogmatic or open to uncertainty. However, the authors are right that the answer also strongly depends on the type of patients who participated in the trial, and the concern that trial results may not be applicable to all or most patients encountered in practice is legitimate, highly pertinent, and generalizable to most, if not all, clinical trials.[3]

To address this concern, one must first examine the trial eligibility criteria (the criteria that defined who could be included in the trial). In that regard, CURES was pragmatic: Trial eligibility criteria were wide. However, we did not specify treatment eligibility criteria, criteria that would define who should be treated (by any method, surgical or endovascular) rather than observed. That problem remains unanswered to this day.[4]

Second, regarding generalizability, one must examine Table 1, which compares patient and aneurysm characteristics.[1] We believe not only that the CURES groups were comparable but also that trial patients were typical, if not representative of, clinical series of treated patients. They are actually similar to patients recruited in a current ongoing trial.[5] One may note that there were few patients in CURES with large (> 15mm) or posterior circulation aneurysms.[1] Thus, we cannot claim, for example, that the trial provides a general answer for these patients.

Third, to assess generalizability, one must examine the registry of patients screened for participation. For practical reasons, screening logs were not required according to the CURES protocol. However, we do have a gross estimate of the proportion of patients with Unruptured intracranial aneurysms (UIAs) recruited in CURES by examining the flow chart of patients recruited in the Comprehensive Aneurysm Management (CAM) study in 1 center that also participated in CURES. CAM is a care trial that includes both treatment and observation registries and 2 randomized trials, one of which is similar to CURES. Approximately 50% of patients ($n = 205/403$) were observed and 10% ($n = 39/403$) were treated without question, but 20 of these 39 patients were included in the trial comparing endovascular with surgical treatment (51%). One hundred fifty-nine of 403 patients (40%) were proposed for the trial comparing treatment with conservative management, and of those, 98 (62%) were randomly allocated to surgical or endovascular treatment. We believe that the design of the CAM study encouraged trial participation so that our estimates are upper boundaries, but from this single-center experience, we estimate that CURES results apply to, at most, 50% of patients with UIAs considered for treatment and to <25% of all patients with UIAs. We nevertheless believe that CURES results are the best available data to inform the care of most patients with UIAs considered eligible for surgical or endovascular treatment.

This last statement does not mean that CURES results should be integrated into a computer program comparing CURES treatment results with rupture risks in untreated patients (in observational studies of patients ineligible for treatment or for a trial) to supply a providential answer to the clinical uncertainty that concerns particular patients.[6,7]

Finally, a classic motto of clinical trial methodology is that the design should be such that trial results impact medical practice. We believe that this motto is inadequate: The clinical uncertainty transparently revealed by the existence of the trial question should rather impact practice immediately, long before trial results become available.[8] Surgical or endovascular treatment is appropriately recommended only once it has been shown beneficial to patients. In the meantime, promising (but potentially harmful) treatments should be offered in the form of a care trial designed to optimize care in the presence of uncertainty for each individual patient.[9] The preventive treatment of patients with UIAs by surgical or endovascular means has yet to be shown clinically beneficial. In that context, optimal care is a care trial. The reason CURES cannot provide a final answer regarding the best treatment is that the primary outcome was a surrogate end point, an angiographic finding at 1 year. The price to pay for this better outcome was a higher immediate risk of transient morbidity. We have yet to show whether angiographic findings translate into better outcomes for patients in the future reality of everyday life.

Back to the crucial question of should I change my practice? We believe that for many readers of this reply the answer is yes.

For clinicians who believe that observation is best for most patients, CURES showed that treatment can be performed with low morbidity (2% at 1 year). They should, at the very least, mention to their patients that treatment might improve their expectation of a good outcome in the future.

For clinicians who believe that most UIAs should be treated by clipping, CURES showed that while angiographic results may be better at 1 year with clipping, this finding has yet to be proven clinically beneficial to patients. In the meantime, clipping was convincingly shown to be associated with added transient initial morbidity.

For clinicians who believe that most patients should undergo endovascular treatment, CURES showed that angiographic results (and thus the future potential morbidity associated with rupture risks or retreatments) may negate the lesser initial treatment risks.

Both surgical and endovascular advocates should recognize that their treatments have never been shown beneficial for patients. Given the current uncertainty, we all should question our practice; we should learn to teach and practice within the context of pragmatic care trials.

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