treatment) is used as the primary end point of a trial, it can certainly modify the indications for retreatment for the patients included in the trial knowing that the treating physician cannot be blind regarding the treatment used. TAR transfers the variability of angiographic evaluation (minimized by blinded dual core lab reading with inter- and intraobserver reproducibility assessments) toward the variability of many therapists who additionally take into consideration far more variables than just anatomy. This transfer adds great interindividual heterogeneity and additional influencing variables. MAPS investigators have identified the drawbacks related to the use of TAR to evaluate aneurysm treatment efficacy, but still their conclusion is that "target aneurysm recurrence is a promising clinical outcome measure that correlates well with established angiographic measurements." It would have been effectively surprising to learn that TAR was not well correlated with aneurysm occlusion status, which would have meant that completely occluded aneurysm or modest neck remnants have been retreated.

Defining the appropriate way to evaluate the efficacy of intracranial aneurysm treatment is certainly not simple. The best way would be the protection afforded by a given treatment against bleeding/rebleeding as the true clinical end point. However, this parameter is not feasible as bleeding/rebleeding events are exceedingly rare after aneurysm treatment even in previously ruptured aneurysms, let alone unruptured aneurysms. TAR that is overwhelmingly determined by aneurysm retreatment is certainly not a good tool as indications for aneurysm retreatment are unknown and very heterogeneous; including from one country to another, from one center to another, from one physician to another, not to mention from one day to another for the same physician. This additional heterogeneity outbalances the positive effect of the clinical relevance of TAR. Evaluating efficacy with anatomic results as a surrogate end point is certainly not perfect, but it is a relatively simple, clinically meaningful, and a far more reproducible way of doing comparison between different aneurysm treatments.

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EDITORIAL

Counterpoint—Target Aneurysm Recurrence: Measuring What Matters

C.G. McDougall, S.C. Johnston, A. Gholkar, and A.S. Turk

What Is Target Aneurysm Recurrence?

Target aneurysm recurrence (TAR) has been proposed as a measure of clinical effectiveness after aneurysm treatment. It is a composite end point that is meant to capture the clinical events that are most important to patients after aneurysm treatment, specifically aneurysm rupture and retreatment. Because sudden unexplained deaths may also be due to aneurysm rupture, such deaths are conservatively assumed to be due to aneurysmal

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hemorrhage and are included as one of the components of TAR. Thus, TAR is said to have occurred if ≥1 of the following hard end points is experienced by a patient following treatment:

1) Target aneurysm rupture
2) Sudden unexplained death
3) Target aneurysm retreatment.

This effectiveness scale was proposed in the context of the Matrix and Platinum Science (MAPS) trial, a randomized trial that enrolled 626 patients and mandated 5 years of clinical follow-up.[1] It is hoped that TAR events in MAPS can be correlated with the core laboratory adjudicated angiographic treatment results. Thus, it may be possible to better understand how angiographic outcomes predict future clinical recurrences. One-year results have been reported, and the 5-year follow-up, upon which future publications will be based, was completed in October 2014.

TAR Matters Because It Is What Patients Care About

When we treat patients with aneurysms, particularly patients who have recovered after treatment of a ruptured aneurysm, it is striking to see how traumatized many of them are, even years after experiencing an SAH. Like patients with posttraumatic stress disorder, many live with fear hanging over them, even if they are told that the chance of recurrent SAH is exceedingly rare. Recurrent hemorrhage looms in overwhelming importance in the minds of these patients, even if this worry is disproportionate to the frequency with which posttreatment hemorrhage occurs.

Retreatment is a major event for a patient. In addition to being costly, it carries physical risk, and it reminds patients that treatment is imperfect in that it provides only partial protection from future hemorrhage. Once a patient has been treated and the procedural risks are no longer an issue, rehemorrhage and retreatment are far and away the 2 events that concern patients most.

If we, in turn, care about what really matters to our patients, we must track and measure these events and strive to fully understand why they happen. Only then can we systematically address and reduce the rates of rehemorrhage and, consequently, retreatment.

Why "Adequate Occlusion" Is Inadequate

From the inception of aneurysm treatment, the immediate goal of treatment has been complete aneurysm occlusion. Long experience with surgical clipping and infrequent recurrent hemorrhages led to the dogma that surgically obliterated aneurysms rarely rebleed. Despite exceptions being reported,[2] this assumption has largely carried over to endovascular aneurysm treatment.

Although the definitions of angiographic occlusion after coiling are quite heterogeneous, the most widely used classification scale is the 3-point Raymond (Modified Montreal) scale.[3] Recognizing that "complete" aneurysm occlusion after coiling is only achieved half of the time or less,[1,4-7] we have seen creep into the endovascular literature the concept of "adequate occlusion," wherein "complete occlusions" and "neck remnants" are lumped together as "adequate occlusions." This concept is based on the intuitively attractive, but unproven, assumption that rehemorrhage is exceedingly rare in aneurysms that have neck remnants but no residual filling of the aneurysm sac. The implied converse assumption is that recurrent hemorrhage is only important (if ever) in aneurysms with residual filling.

Unfortunately, other than the Cerebral Aneurysm Rerupture After Treatment (CARAT) Trial,[8] precious few data exist to support the correlation between completeness of endovascular coiling and the risk of clinical recurrence. As CARAT investigators, we are very much aware that CARAT had major limitations. For example, aneurysm occlusion rates in CARAT were derived retrospectively from angiographic reports dictated by physicians who were self-reporting their treatment results during a period that predated uniform reporting standards such as the Raymond scale. It should be abundantly clear that these results would not be expected to correlate reliably with independent core laboratory readings, and it is unfortunate that, years later, we still lack prospective evidence reliably correlating angiographic end points with clinical outcomes. While the findings of CARAT have been widely referenced, CARAT constitutes level B evidence at best.

In the meantime, this rational-but-unproven assumption of "adequate occlusion" has been coupled with the belief that we cannot measure the clinical events that actually matter. Regardless of how intuitively attractive the angiogram is as an end point, until the evidentiary vacuum is addressed, the assumption that angiographic results correlate with patient outcomes is only a circular argument: "We believe that it matters so we measure it/We measure it so we believe that it matters." Once this potentially fatal error is accepted, the circular logic seems inescapable. Indeed, the suggestion of Pierot et al[9] that more accurate volumetric analysis of residual aneurysm filling would be an improvement perpetuates the circular argument. Only through research that shows more precisely how angiographic remnants link to the clinical events that we care about can we resolve this dilemma.

The question is further begged—what do we tell our patients who have Raymond 3 remnants? That their aneurysm occlusion is inadequate? Raymond 3 residual is very common, occurring in roughly 20%–35% of patients in multiple randomized trials.[1,4,7] Similarly, deterioration in angiographic occlusion between treatment and early angiographic follow-up is in the range of 35%–50%.[5,10] Are these patients shouldering the bulk of rehemorrhages while we reassure them by quoting low rehemorrhage rates that use the entire population ("adequate" and "inadequately" occluded) as the denominator? We do not and cannot know until we track, measure, and correlate TAR with angiographic end points.

TAR: Imperfect but Fundamental

A fair criticism of TAR is that were TAR to be widely adopted, most TAR events would likely be the result of retreatment—that is, TAR essentially equals retreatment. It is likely that, as with angiographic occlusion scales, retreatment as an end point is more likely to be internally consistent between treatment arms within a trial but less reliable when used to compare one trial with another. Because the indications for retreatment are currently unclear, practice patterns can vary widely, making comparisons between trials problematic if the principal measure is essentially the retreatment rate. Indeed, the MAPS investigators found that in North America, if the treating physician reported residual aneurysm filling (Raymond 3), retreatment was performed within the

first year in 49.2% of patients. For centers outside North America, the comparable retreatment rate was only 19.2%; but with longer follow-up, the retreatment rate for patients with Raymond 3 residual rose to 47.6%, a rate not statistically different from the North American rate (A.S. Turk, DO, unpublished data, 2014). Given that physicians in both locations behaved similarly in retreating patients with Raymond 3 residual aneurysm filling, it is not clear why retreatment was delayed at centers outside North America, but the need for longer follow-up is clear.

The most recent data from the International Subarachnoid Aneurysm Trial (ISAT), reporting follow-up extending beyond 10 years, suggest that despite older technology with questionable rates of angiographic occlusion, rehemorrhage rates are low but still roughly triple the rate seen after surgical clipping.[11] We do not know whether the recurrent hemorrhages happened only in patients with residual aneurysm filling or to what extent hemorrhages occurred in patients with "adequate occlusion." Moreover, we do not know what role retreatment— or lack of retreatment— played in preventing or permitting recurrent hemorrhage. As reassuring as it is that ISAT rehemorrhage rates are low, we must not accept the belief that rates are low enough. Truly understanding who needs to be retreated is key to driving down the rate of delayed rehemorrhage. For now, we remain in the dark regarding how to manage roughly one-third of our patients—those whom we all seem to believe have "inadequate occlusion."

It is our belief that the balance between retreatment and rehemorrhage can offset the criticism that TAR equals retreatment and that retreatment is arbitrary. Completely occluded aneurysms and tiny neck remnants are rarely retreated, so it is primarily aneurysms with residual filling (Raymond 3) that are retreated. If residual aneurysm filling is the strongest predictor of rehemorrhage, it is reasonable to expect that for a given rate of residual angiographic filling, lower rates of retreatment will ultimately lead to higher rates of rehemorrhage and vice versa.

For example, if one were to compare the MAPS with the HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS) Trial, one would observe that both trials have similar rates of residual aneurysm filling—approximately one-third of patients— but dramatically different rates of retreatment (roughly 9% for unruptured aneurysms and 14% for ruptured aneurysms in MAPS versus 3% overall in HELPS).[1,12] If the presumed inverse relationship between retreatment and rehemorrhage holds, then with time, rehemorrhages will eventually comprise a much higher proportion of TAR in centers where few retreatments are done, while centers aggressively retreating residual aneurysm filling may find that their TAR rates are almost entirely driven by retreatments. With a retreatment rate of only 3% as in HELPS, even a few rehemorrhages would result in rehemorrhage becoming a meaningful proportion of the overall TAR rate. Unfortunately, in HELPS as in many other otherwise excellent prospective trials, no attempt was made to capture rehemorrhage rates beyond the relatively short-term angiographic end points, in effect burying the impact of delayed hemorrhage.

Conclusions

Studying the balance between retreatment and rehemorrhage, specifically correlating TAR with the angiographic results, is the only viable way to address the issue of retreatment. The question is not TAR versus the angiographic results, it is how the angiographic results predict what we care about—target aneurysm recurrence.

Disclosures: C.G. McDougall—*RELATED*: *Consultancy*: I am on the Scientific Advisory Board for Covidien and a consultant for MicroVention.

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