Point—TAR: A Useful Index to Follow-Up Coiled Intracranial Aneurysms?

L. Pierot, J. Fiehler and P. White

AJNR Am J Neuroradiol published online 27 November 2014
http://www.ajnr.org/content/early/2014/11/27/ajnr.A4119.citation

Published November 27, 2014 as 10.3174/ajnr.A4119

Point—TAR: A Useful Index to Follow-Up Coiled Intracranial Aneurysms?

L. Pierot, J. Fiehler, and P. White

The Matrix and Platinum Science (MAPS) trial results were recently published showing that Matrix[2] coils were not inferior (and not superior) to bare metal coils (BMC) in the treatment of ruptured and unruptured intracranial aneurysms.[1] In the trial, 626 patients were enrolled in 43 investigational sites from March 2007 to October 2009. Besides being designed to compare the results of aneurysm treatment with Matrix[2] and BMC, MAPS was also designed to evaluate a composite clinical outcome measure designated as "target aneurysm recurrence" (TAR) that was defined as occurring when a patient experienced any of the following conditions after his or her initial aneurysm coiling: 1) target aneurysm (re)hemorrhage, 2) target aneurysm retreatment, or 3) death from unknown cause.

As demonstrated by previous studies, there was no significant difference between Matrix[2] and BMC regarding aneurysm occlusion (evaluated with modified 3-grade Raymond scale) by core lab evaluation at the end of the procedure and at 12 months.[2,3] There was also no significant difference in the arms with respect to change in aneurysm occlusion evaluated with a 3-grade scale (better, same, worse). Moreover, no significant difference was detected in the clinical evolution in both groups. In fact, the primary trial end point was TAR and there was no significant difference between groups (Matrix[2]: 13.3%; BMC: 14.6%; $P = .76$).

Looking in the global population at the TAR events (total: 69), 1 was an unexplained death (1.4% of the events), 4 were rupture/reruptures (5.8%), and 64 were retreatments of aneurysms that had not bled after initial treatment (92.8%). Therefore, the overwhelming majority of TAR events were retreatment not related to a rupture/rerupture. It means that the primary end point of MAPS was in fact more or less retreatment.

There were in the protocol no specific indications or even guidance for aneurysm retreatment; that was entirely at the discretion of the operator. Unfortunately, and irretrievably for TAR as a primary trial end point, indications for aneurysm retreatment are absolutely unclear and no recommendation exists detailing situations in which retreatment has to be performed. It is clear that 2 operators facing the same incompletely occluded aneurysm will frequently not have the same indication for retreatment. In their recent study regarding retreatment decisions of recurrent and residual aneurysms, McDonald et al[4] have shown that the overall interobserver variability for the decision to retreat was not more than moderate (intraclass correlation coefficient: 0.50). This observation is in line with previous analyses.[5] As outlined by MAPS investigators themselves, the rate of retreatment is quite heterogeneous from 1 series to another, with a rate as low as 3% in both arms of the HELPS trial.[6] Similarly, in a CLARITY study, retreatment rate is 3.3% in the BMC group but 9.5% in the Matrix group.[3] In the Cerecyte Coil Trial (CCT), retreatment rate was 3.5% in the BMC group and 7.7% in the Cerecyte group.[7] In MAPS, retreatment rate (not including bleeding/rebleeding cases) is 33 of 315 (10.5%) in the BMC group and 31 of 311 (10.0%) in the Matrix[2] group. Were BMC less efficacious in MAPS than in HELPS, CCT, and CLARITY, that such a high percentage of retreatment was needed (10.5% compared with 3 to 3.5% in HELPS, CCT, and CLARITY)? Or were indications for retreatment quite different in centers participating in MAPS, many of which did not participate in HELPS, CCT, or CLARITY? Is TAR therefore largely a health economy (ie, geographic) effect?

Aneurysm treatment is dedicated to prevention of rerupture (for ruptured aneurysms) and rupture (for unruptured aneurysms). Indications for treatment of unruptured aneurysms are already a matter of debate and absolutely not clear. In the same way, indications for retreatment of incompletely treated aneurysms are also not clear; retreatment should not be cosmetic (to obtain a nice angiographic result), but again to prevent the risk of rupture/rerupture. Very little is known regarding the risk of rupture/rerupture of incompletely treated aneurysms. From the International Subarachnoid Aneurysm Trial (ISAT), it seems that the risk of rerupture of coiled aneurysms is extremely low and remains so for up to 10 years.[8] From the Cerebral Aneurysm Rerupture After Treatment trial, it seems that the status for aneurysm occlusion plays a significant role with aneurysm remnant having probably a higher risk of rupture/rerupture than neck remnant.[9]

Thus, indications for aneurysm retreatment are made on a case-by-case basis based on various factors including a patient's age, initial clinical presentation, potential comorbidities determining the overall prognosis of the patient, aneurysm remnant characteristics, aneurysm dynamics over time, and feasibility and risks of retreatment. These factors will be differently evaluated from one operator to another; an "aggressive" operator (or an operator who is paid on an item of service basis rather than annual salary basis) will probably have wider indications for retreatment compared with a more "conservative" one.

Evaluating an aneurysm treatment means determining its safety and efficacy. The way safety has to be evaluated is relatively clear based on determination of complication rates. This includes rates of thromboembolic events and intraoperative rupture and evaluation of neurologic outcome with mRS or other scales at a given time after the index procedure. Evaluation of efficacy is more complicated. As the goal of the treatment is to prevent aneurysm rupture/rerupture, the best way to evaluate the efficacy of a given aneurysm treatment is certainly to determine the rate of rupture/rerupture after aneurysm treatment. However, as these events are relatively rare, large study populations and/or long follow-up periods are needed to compare the efficacy of 2 different

http://dx.doi.org/10.3174/ajnr.A4119

treatments. Accordingly, the tendency has been to evaluate the efficacy through the immediate, mid-term, and long-term anatomic results as well as recanalization rate, with the definitions of recanalization being relatively heterogeneous in the literature.[10] Several scales have been proposed to evaluate aneurysm occlusion; however, the 3-grade Raymond (or Montreal) scale is still the most commonly used in the literature.[11] Defining efficacy of aneurysm treatment through the evaluation of aneurysm occlusion is already quite debatable as the link between aneurysm occlusion status and rupture/rerupture is not completely established. However, as the risk of rupture/rerupture of a treated aneurysm is probably at its maximum in cases of aneurysm remnant, evaluation of aneurysm treatment efficacy with angiographic results and recanalization rate is probably acceptable, if not perfect. In fact, the ISAT data, where endovascular anatomic results achieved were often crude by today's standards, rather indicates that the link between occlusion and rupture is limited. The target aneurysm rebleed rate at 10 years was extremely low and in only half of that small number of cases did it lead to a poor clinical outcome.[8]

As shown before, evaluation of aneurysm treatment efficacy with TAR is essentially merely evaluating efficacy through the rate of aneurysm retreatment. As stated by the MAPS investigators, retreatment is a much more important event to the patient compared with an asymptomatic angiographic finding of residual aneurysm.

However, it is possible to evaluate aneurysm occlusion status objectively in a study singularly when an independent core laboratory is used and results have an acceptable reproducibility, whereas aneurysm retreatment decisions cannot be so objectively evaluated.[12] Moreover, volumetric measurement of aneurysm changes over time as an imaging end point can limit the variability of visual assessment.[13,14] On the contrary, aneurysm retreatment is the result of a completely subjective decision process involving the treating physician and the patient who always has the possibility to refuse the retreatment of the incompletely treated aneurysm. Moreover, as soon as TAR (retreatment) 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.

Disclosures: Laurent Pierot—*RELATED: Consulting Fee or Honorarium:* Codman, Covidien/ev3, Microvention, Sequent, Stryker. Jens Fiehler—*RELATED: Consulting Fee or Honorarium:* Acandis, Codman, Microvention, Sequent, Stryker; *Support for Travel to Meetings for the Study or Other Purposes/Speaker Beureau Activities:* Covidien/ev3, Penumbra; *UNRELATED: Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed:* Covidien. Phil White—*UNRELATED: Consultancy:* Codman, MicroVention Terumo, *Comments*: For supporting/running educational activities; *Grants/Grants Pending:* MicroVention Terumo,* *Comments*: Cofunder grant for RCT-STABILISE; *Payment for Lectures (including service on speakers bureaus):* Codman, Covidien, *Comments*: Stroke-related. *Money paid to the institution.

REFERENCES

1. McDougall CG, Claiborne Johnston S, Gholkar A, et al. **Bioactive versus bare platinum coils in the treatment of intracranial aneurysms: the MAPS (Matrix and Platinum Science) trial.** *AJNR Am J Neuroradiol* 2014;35:935–42
2. Pierot L, Cognard C, Ricolfi F, et al. **Immediate anatomical results after endovascular treatment of ruptured intracranial aneurysms: analysis of the CLARITY series.** *AJNR Am J Neuroradiol* 2010;31:907–11
3. Pierot L, Cognard C, Ricolfi F, et al. **Mid-term anatomical results after endovascular treatment of ruptured intracranial aneurysms with Guglielmi detachable coils and Matrix coils: analysis of the CLARITY series.** *AJNR Am J Neuroradiol* 2012;33:469–73
4. McDonald JS, Carter RE, Layton KF, et al. **Interobserver variability in retreatment decisions of recurrent and residual aneurysms.** *AJNR Am J Neuroradiol* 2013;34:1035–39
5. Daugherty WP, Rad AE, White JB, et al. **Observer agreement regarding the necessity of retreatment of previously coiled recurrent cerebral aneurysms.** *AJNR Am J Neuroradiol* 2011;32:566–69
6. White PM, Lewis SC, Gholkar A, et al. **Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intra-cranial aneurysms (HELPS): a randomised controlled trial.** *Lancet* 2011;377:1655–62
7. Molyneux AJ, Clarke A, Sneade M, et al. **Cerecyte coil trial: angiographic outcomes of a prospective randomized trial comparing endovascular coiling of cerebral aneurysms with either Cerecyte or bare platinum coils.** *Stroke* 2012;43:2544–50
8. Molyneux AJ, Birks J, Clarke A, et al. **The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT).** *Lancet* 2014 Oct 28. [Epub ahead of print]
9. CARAT Investigators. **Rates of delayed rebleeding from intra-cranial aneurysms are low after surgical and endovascular treatment.** *Stroke* 2006;37:1437–42

10. Benaissa A, Barbe C, Pierot L. **Analysis of recanalization after endovascular treatment of intracranial aneurysm (ARETA trial): presentation of a prospective multicenter study.** *J Neuroradiol* 2014 Jul 7. [Epub ahead of print]
11. Raymond J, Guilbert F, Weill A, et al. **Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils.** *Stroke* 2003;34:1398–403
12. Tollard É, Darsaut TE, Bing F, et al. **Outcomes of endovascular treatments of aneurysms: observer variability and implications for interpreting case series and planning randomized trials.** *AJNR Am J Neuroradiol* 2012;33:626–31
13. Ries T, Wegscheider K, Wulff A, et al. **Quantification of recurrence volumes after endovascular treatment of cerebral aneurysm as surrogate endpoint for treatment stability.** *Neuroradiology* 2011;53:593–98
14. Schönfeld M, Schlotfeldt V, Forkert ND, et al. **Aneurysm recurrence volumetry is more sensitive than visual evaluation of aneurysm recurrences.** *Clin Neuroradiol* 2014 Aug 27. [Epub ahead of print]