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

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into the brain is still unclear, possibly through its external and ventricular surfaces and the perivascular spaces.

PET imaging with the Pittsburgh compound (PiB-PET) has shown that shorter sleep duration is associated with higher amyloid brain burden.[7] Other studies have shown that unfragmented sleep reduces the risk of Alzheimer disease (and decreases the development of neurofibrillary tangles) and diminishes normal age-related cognitive decline.[8] Apnea is another factor that prevents adequate sleep consolidation and though it was thought to affect mentation by vascular effects on the brain, the worse cognition associated with it could be caused by interruptions of the glymphatic system function. Of course, one's inability to consolidate sleep is multifactorial and includes comorbidities and genetic and environmental factors among others. Perhaps information gathered by personal fitness devices on the sleep patterns of millions of users will shed more light onto the relationship between sleep and successful aging. Over 60% of all adults report trouble sleeping at night, thus the implications of the relationship between sleep and cognition are staggering.

Regardless of any scientific evidence, sleep is a hot item and even a new, short e-novella by famous (and very good) author Karen Russell deals with the subject.[9] In this short book, America experiences an epidemic of insomnia and a large corporation decides that sleep is a commodity. Healthy sleepers are urged to "donate" their sleep to those less fortunate. The fact that sleep is indeed a commodity is now being used by industries successfully. Personal fitness and activity tracking devices generated over US $290 million last year in sales and this is expected to double soon. Today, there are so many brands that manufacture these personal fitness devices that choosing one is difficult, particularly if one did not sleep well the night before.

So, what did I learn about my sleep in the last 2 months of wearing my Up24 band? Well, only good news. I fall asleep faster and sleep longer than I thought and have longer periods of deep sleep than others in my "team" (yes, you cannot only compete for the most activities but also for the most and best sleep). I have also become more aware as to how much people care about how I well sleep: hotels offer me better mattresses, more pillow choices, high-efficiency sheets and pillow covers, mood lightning and soothing sounds, calming pulse-point oils, and some will even call before I go to sleep to remind me to turn my electronic devices off (the blue wavelength light these devices emit affects the secretion of melatonin more powerfully than any other type of light). Airlines lagged behind hotels and now that, at least in business class, the food is improving, they are concentrating on sleep and offering natural-fiber bedding, flat-bed seats, noise-cancellation headphones, and "radio" stations with only white noise. Why the industry is doing all of this is not clear to me and in a recent article in the *New York Times*, the executive director of the Harvard Medical School Division of Sleep Medicine said, "Sleep is the enemy of capitalism, you can't produce or consume when you're asleep."[10] In the same article, Dr. Sanna also says that we need to stop thinking of sleep as a commodity and a lifestyle choice, but rather as the third pillar of health together with diet and exercise. Could it be that living and sleeping better and longer is becoming more important than just accumulating stuff? I do not think so, but tonight I will go to sleep earlier hoping that it will help me be a smarter and healthier neuroradiologist tomorrow.

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EDITORIAL

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 (bet-

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ter, 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 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 (re-

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

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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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