Questionable Interpretation of Results of ACTIVE Study on Matrix Coils by Boston Scientific

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Note: Due to an oversight, this reply did not appear with the following letter in the August issue.

Reply

We thank Drs Sluzewski and van Rooij for their criticisms of the ACTIVE Study, the results of which were published in the newsletter from Boston Scientific and referred to in an AJNR editorial (1). It is rare that new material is criticized to the point that the goal is described as more or less opposite to what was expected by the originators.

First, the criticism is perfectly right regarding the rebleed rate, which is 7% instead of 3%. The rebleed rate must be calculated among patients who presented with a ruptured aneurysm. There are several explanations for this high percentage: 1) Two patients in the ACTIVE Study presented with dissecting aneurysms and should not have been included because the treatment strategy was not adapted for such aneurysms. Thus, the rebleed rate should be 2%. This number in "absolute value" is still higher than what is reported in the literature. However, the number of patients is too small to be statistically significant. 2) Other parameters should be considered. At the time of the study, no other tools except Matrix coils were used to accomplish the treatment, which was a major limitation (this is not an excuse; it is a bias of the study and it was obviously a mistake). The large majority of patients also clearly presented with wide neck aneurysms. Additionally, the stiffness and friction of the first Matrix coils were limitations to obtaining good packing. The conjunction of these parameters might explain the lack of "completion" of the sac compared to results with bare coils (whose suppleness and shapes can be varied at latitude) and the "so-called" higher rebleed rate. However, this argument has no statistical authority.

The statement by Drs Sluzewski and van Rooij that "Apparently the Matrix coils allow residual filling of the aneurysmal sac over an unknown period of time and during this period the patient is not protected against a rebleeding" is a hypothesis, not an explanation. Their statement is based on a visual appreciation of the "packing density" after a Matrix coil treatment. However, Matrix coils carry a given percentage of radiolucent material (PGLA), and it is obvious that visual comparison with regular bare coils (regardless of the manufacturer) was not adapted. By definition, the so-called packing density will always be less with Matrix due to this percentage of transparent material.

With regard to the retreatment rate, the confusion exceeds that for the rebleed rate. Ninety-nine percent of recurrences are angiographic, not clinical. What does this mean for the patient? Worldwide, there is no agreed-upon definition of a recurrence of an aneurysm and no agreement on its incidence in patients on a long-term basis. Consequently, there is even less definition and less agreement on which recurrences should be retreated and why. This situation raises the very crucial question of why and when an angiographic recurrence should be considered for retreatment. For the time being, retreatment (with the exception of rebleeding, which is very rare) is a strictly personal decision, more or less empiric, which implies only the person who makes the decision. This comment is an important criticism, but it applies to endovascular treatment in general and cannot be used to oppose Matrix only. The ACTIVE Study was conducted 3 years ago with strict honesty. Meanwhile, and because of the information obtained from the study, the material and results have dramatically improved. We now have enough retrospective data to prove that a "Matrix effect" exists (forthcoming publications). This effect includes angiographic improvement of anatomic results on a long-term basis versus bare coils. But the real debate is based on the following: 1) Are bioactive coils, such as Matrix, bringing real clinical benefits for patients? In other words, is it necessary to use 20% to 30% more expensive materials to get a better angiographic appearance (the so-called Matrix effect) on control angiograms? The answer is yes if there is a significant benefit in terms of decreased rebleed rates during 10 or 15 years versus bare coils. If not, the answer is definitively no. Nobody knows the answer at present, but it is the duty of the medical community to find it. 2) Another very important part of this debate is to know whether we are happy enough with bare coils to the point where we decide that no further evolution is mandatory. At least we have a clear negative answer to this second stake. Matrix belongs to the future. It is a new concept that will change the results of aneurysm coiling. Even if the material (Matrix) itself disappears, the concept will persist and develop. For this reason, we have to thank the company. However, as doctors we also have to be very careful and not give way to the sirens of marketing arguments, which will never be scientific proofs. In light of the promising results during the last 3 years, we have no ethical problems in using Matrix coils. Think back to just 12 years ago, when everybody was happy with the results of microsurgical clipping of aneurysms. How many suspicious, negative, or destructive comments were made during the first 6 or 7 years of coiling aneurysms? Probably as many as the total number of aneurysms coiled from the beginning!

If we continue to behave ethically, the future of Matrix coils and other products from competitors will depend only on their intrinsic properties to benefit patients, which is fine. Nevertheless, the interventional neuroradiology community needs to reach a consensus on ways to prove superiority or inferiority of new materials independently of companies.

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We fully agree with Raymond et al (1) that "new embolic agents should first demonstrate safety characteristics that are equivalent to standard platinum coils before considering a widespread application" and "worse, their use could be associated with early rebleeding when lesions are treated after rupture" (p. 1129).

These concerns are even more important and urgent when companies of embolic agents provide us with questionable interpretations of study results. In the 2004 *Matrix Newsletter,* the results of the so-called ACTIVE Study are presented (2). Matrix coils are coated with a biologically active substance and proved to accelerate healing of intracranial aneurysms in swine, and it is concluded that these coils may prevent aneurysmal recanalization after endovascular treatment of cerebral aneurysms (3).

The first page of the newsletter states, "The ACTIVE Study represents the first prospective multicenter trial designed to evaluate the benefit of the Matrix Detachable Coil for the treatment of cerebral aneurysms and was sponsored by Boston Scientific, Neurovascular, Fremont, CA."

On the second page, it is reported that 3% of the patients treated with Matrix coils suffered a fatal early rebleeding (three of 100). On closer inspection, however, only 44 of these 100 patients were treated after aneurysmal rupture. Thus, the early fatal rebleeding rate should have been reported to be 7% (three of 44) instead of 3%. In the ISAT study (4), in which the patients were treated with standard platinum coils, 10 of 1005 patients suffered an early rebleeding after coiling of a ruptured aneurysm (1%).

Apart from the fact that this 7% of rebleeding rate after treatment with Matrix is unacceptably high, these findings are not surprising after review of the remaining part of the newsletter: it is reported that 67% of the coiled aneurysms still show residual aneurysm filling on the immediate postembolization angiogram. On the 12-month follow-up angiogram, 49% of the aneurysms show "progressive thrombosis." Apparently the Matrix coils allow residual filling of the aneurysmal sac over an unknown period of time and during this period the patient is not protected against a rebleeding.

In the evaluation of these new coils that possibly improve long-term results, the most important goal of ruptured aneurysm treatment—that is, to exclude the aneurysm from the circulation to prevent early rebleeding—is clearly ignored.

So do these new coils at least perform better in the long term than they were designed to? On page 3, the results of follow-up angiography after 12 months are discussed. In a complex and confusing way, an attempt is made to compare these findings on follow-up with historical data, but in a presentation by the company we find out that 16% of the followed patients had to be retreated with coils (5). The retreatment rate after treatment with standard platinum coils is in the range of 10% (6).

The conclusion of the ACTIVE Study should therefore not be that "the results of 1st treatment with 1st Generation Matrix Detachable Coils are favorable," but that Matrix coils offer no benefit over standard platinum coils and that these coils should not be used to treat recently ruptured cerebral aneurysms.

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