


European consensus conference on unruptured brain AVMs treatment (Supported by EANS, ESMINT, EGKS, and SINCH)

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Received: 14 February 2017 / Accepted: 13 March 2017 / Published online: 7 April 2017
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Abstract In December of 2016, a Consensus Conference on unruptured AVM treatment, involving 24 members of the three European societies dealing with the treatment of cerebral AVMs (EANS, ESMINT, and EGKS) was held in Milan, Italy. The panel made the following statements and general recommendations: (1) Brain arteriovenous malformation (AVM) is a complex disease associated with potentially severe natural history; (2) The results of a randomized trial (ARUBA) cannot be applied equally for all unruptured brain arteriovenous

malformation (uBAVM) and for all treatment modalities; (3) Considering the multiple treatment modalities available, patients with uBAVMs should be evaluated by an interdisciplinary neurovascular team consisting of neurosurgeons, neurointerventionalists, radiosurgeons, and neurologists experienced in the diagnosis and treatment of brain AVM; (4) Balancing the risk of hemorrhage and the associated restrictions of everyday activities related to untreated unruptured AVMs against the risk of treatment, there are sufficient

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indications to treat unruptured AVMs grade 1 and 2 (Spetzler–Martin); (5) There may be indications for treating patients with higher grades, based on a case-to-case consensus decision of the experienced team; (6) If treatment is indicated, the primary strategy should be defined by the multidisciplinary team prior to the beginning of the treatment and should aim at complete eradication of the uBAVM; (7) After having considered the pros and cons of a randomized trial vs. a registry, the panel proposed a prospective European Multidisciplinary Registry.

Keywords Unruptured brain AVM · Arteriovenous malformation · Consensus Conference · EANS · EGKS · ESMINT · ARUBA

In 2014, ARUBA, a randomized trial comparing interventional therapy and medical management of unruptured brain arteriovenous malformations (uBAVMs) [23] concluded that the natural history of uBAVMs is better than any form of treatment. This may have resulted, intentionally or by chance, in significantly altered treatment decisions for uBAVMs.

Although the ARUBA Study is internally valid, it has been the object of many criticisms by the scientific community [5, 11, 18, 20] because of its perceived lack of external validity as its message does not match the results of many published reports [3, 7, 12, 14–16, 24, 30, 31, 33, 36, 37, 39, 40] and the experience of the clinicians dealing with uBAVMs. The main criticisms relate to the wide heterogeneity of treatment modalities, the absence of subgroup analyses, the lack of details on the results of specific treatments, an insufficient follow-up period (less than 3 years) for the anticipated time to benefit from treatment, a small patient population, and the bias related to the high-stakes and irreversible consequences influencing the decision to be randomized. These biases, associated with a contentious interpretation of the results, lead to an assumption that cannot be generalized to all uBAVM and to all treatment modalities.

As these conclusions are not shared by most of the physicians who treat uBAVMs, it was widely felt that there was the need to overcome the dilemma created by the publication of this study.

For this reason, we decided to carry out a Consensus Conference on AVM treatment at a European level, involving the three European societies dealing with the treatment of this disease: the European Association of Neurosurgical Societies (EANS), the European Society of Interventional Therapy (ESMINT), and the European Society for Radiosurgery (EGKS). These societies were instrumental in the selection of the participants.

The preparatory work and the conduction of the Consensus Conference were coordinated by a neurologist and

methodologist from the Mario Negri Institute, an internationally renowned Italian Research Institute.

There were 24 participants (Table 1). In the 6 months preceding the date of the Consensus Conference, a questionnaire survey was undertaken with the participants to explore the therapeutic strategies for patients with uBAVMs (with indications and contraindications) based on their background and experience.

The meeting was held in Milan on December 1, 2016. The purpose was to discuss, jointly, directions and methods of treatment of uBAVM with the aim of producing a shared document. The meeting was conducted following the questions posed in the survey. The first few questions regarded the general opinion of the participants concerning the results of the ARUBA Study. A more detailed discussion followed on single aspects of the treatment of uBAVMs dealing with the particular problems and nuances of each of the three therapeutic options (surgery, radiosurgery, endovascular treatment). At the end of the meeting, a joint document was written.

All the participants of the meeting have checked the present final paper again.

General questions addressed for the management of uBAVMs

- Is your experience in accordance with the main message of the ARUBA Study, i.e., that unruptured AVMs have a better prognosis if not treated?

All the participants affirmed that the message of the ARUBA Study cannot be generalized to all unruptured

Table 1 Participants (with affiliation) to the consensus conference

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AVMs and to all the treatment modalities. The biases of that study are well known and have been described in many publications.

- Do you think that some unruptured AVMs have to be treated?

All the participants answered positively. Some uBAVMs are difficult and dangerous to treat, but some of them can be treated with low risk.

Single aspects on the risk of bleeding and the treatment of uBAVMs:

- Do you think that there are elements that increase the risk of bleeding in an unruptured AVM?

According to the survey, the panel answered that aneurysms (95%), venous patterns (75%), and location (35%) of the uBAVMs were, in decreasing order, associated with a higher incidence of bleeding.

According to a recent review of the literature, no clear risk factors for bleeding can be identified. According to some reports [1, 10, 21], size and infratentorial location are the two most common factors associated with bleeding. However, there was no general agreement on the results of these studies and the panel concluded that, at present, no definite risk factors for bleeding have been identified. Importantly, also, no factor whose absence protects the patients from bleeding has been identified.

- Is eloquence a contraindication to treatment?

Eloquence was considered a serious problem only for surgery, as two (9%) endovascular radiologists accounted size more relevant than eloquence.

For surgery, eloquence is the main concern. In their Surgical Grading Scale, Spetzler–Martin consider eloquence as one of the main issues [35, 36]. Eloquence is a relevant issue also in the Supplementary Grading Scale by Lawton [17]. Large size and deep venous drainage can affect eloquence thorough the involvement of the deep white matter.

For two (9%) surgeons, eloquence is not an issue for Spetzler–Martin grade 1 or 2 malformations while it becomes a problem for those in grade 3 or higher [26].

All the panelists agreed that a limited visual deficit can be compensated, with a small impact in terms of quality of life, to be taken into account in proposing a treatment to the patient.

Eloquence was considered by all panelists a strong suggestion to choose radiosurgery rather than other treatment modalities.

- Is young age a contraindication to treatment?

In the survey, younger age was not considered a reason to withhold treatment by all the participants and surgery was suggested by 85% of the panel [9, 28, 32].

Although the panel agreed that treatment complications may overcome a future risk of bleeding, it concluded that in a young person's life expectancy is long and in low-grade malformations the risk of bleeding for the rest of their life is far superior than the complications of treatment. Moreover, children will compensate a mild deficit more easily than adults. Literature reports that for low-grade AVMs the cross-over between serious neurological complications due to treatment vs. natural history is under 5 years [3, 5].

It was pointed out that knowing to have an AVM is an important limitation in a patient's quality of life and that at least one-third of patients with an uBAVMs are not asymptomatic. They can have severe headache or epilepsy. Moreover, the risk of surgical or endovascular treatment is probably lower in young patients than in older people. Radiosurgeons suggested that Gamma Knife (GK) for malformations in young patients appears to be more effective than in older people, and 96% of the panel disagreed with the option of waiting for a treatable uBAVM to bleed before suggesting treatment.

- Is old age (>65 years) a contraindication to treatment?

In patients over 65, treatment was considered contraindicated by most of the panel because the risk of treatment can outweigh the risk of bleeding. Most (84%) of the panel agreed that only a life expectancy over 20 years could be a prerequisite for treatment. However, radiosurgeons suggested that as radiosurgery is a low-risk treatment, it can be suggested also at an older age.

- Is small size a contraindication to treatment?

Small malformations are less susceptible to the risks of treatment and have a greater chance of being cured [17, 33].

All three modalities of treatment can be used, but there was general agreement that a multidisciplinary discussion has to be performed prior to the treatment, with the aim of defining the best strategy to obtain a complete cure with lower risks.

As a general rule, 67% of the panel agreed that in a small non-eloquent uBAVM, surgery is preferable (with or without previous embolization), 22% indicated Gamma Knife, and 11% endovascular treatment as a first option. In contrast, in a small eloquent uBAVM, radiosurgery is the best option. This recommendation is supported by published reports [4, 13, 38]. In selected cases, endovascular treatment may be considered.

Everyone agreed that in small non-eloquent uBAVMs a treatment has always to be suggested.

- Is large size a contraindication to treatment?

Large-size uBAVMs were considered by 84% of the panel a reason to withhold treatment. From a surgical point of view, grade IV and V malformations are generally considered not treatable [26, 36] because the surgical risk is very high. Reducing the malformation size with repeated endovascular sessions did not prove to reduce the bleeding risk and, on the contrary, seemed to increase the risk of complications [6, 19, 22].

In accordance with the fact that bigger malformations seem to have a higher risk of bleeding and are more likely to be symptomatic, a staged radiosurgery treatment can be suggested as investigational therapy to downgrade the malformation size [2, 25, 27, 34]. Staged radiosurgery can be followed by surgery or endovascular treatment if not completely effective.

- Are deep feeders a contraindication to treatment?

Lawton first found that deep feeder supply was associated with a worse outcome [8], but in a subsequent paper [17], this association was less evident. Today's surgical instruments, such as non-stick bipolar, are more effective in favoring coagulation. If there are few single deep feeders, they can be selectively embolized prior to surgery, although endovascular panelists do not consider selective embolization a low-risk procedure.

Deep feeders are considered a surgical problem when they involve several lenticulo-striatal vessels [29], but they are not a contraindication for radiosurgery.

- Are deep-seated malformations a contraindication to treatment?

In most of the cases they are a problem for surgery but not for radiosurgery or endovascular treatment.

- Is diffuseness a contraindication to treatment?

Diffuseness is a problem for all of the three disciplines [8, 17, 38]. Defining the diffuseness is not easy. Most of the panel agreed that MRI in conjunction with angiography can help to identify the sparseness of the nidus. Superficial pial vessel recruitment in some cases can be misinterpreted as diffuseness when evaluated only on angiographic projections and has to be distinguished from true diffuseness.

- Should a new randomized trial be proposed or a Registry can be better?

There was an agreement that practical experience has to be translated in numbers to provide a more solid scientific basis to overcome the ARUBA impasse. In accordance with the methodologist, the panel agreed that even though another

randomized trial can have disadvantages, it is very difficult to accomplish and, as happened with the ARUBA Study, can fail on the patient's recruitment. Moreover, randomization requires a high level of uncertainty, and in many high-volume centers this may not be an option. A prospective Multicenter International Registry can be more easily conducted and will provide more reliable results on uBAVM treatment. A registry is a valuable option for assessing treatment effectiveness for a number of reasons, including the enrollment of a homogeneous inception cohort (e.g., at the time of diagnosis), the inclusion of patients from different sources, the adoption of pre-planned outcome measures, the minimization of drop-outs, the standardization of baseline variables (including prognostic predictors), and the allowance for sufficient follow-up for the outcomes to be measured.

At the end of the day, the panel made the following statements and general recommendations on behalf of the European Societies of Neurosurgery, Interventional Therapy and Radiosurgery:

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- Brain arteriovenous malformation (AVM) is a complex disease associated with potentially severe natural history.
 - The results of a randomized trial (ARUBA) cannot be applied equally for all unruptured brain arteriovenous malformation (uBAVM) and for all treatment modalities.
 - Considering the multiple treatment modalities available, patients with uBAVMs should be evaluated by an interdisciplinary neurovascular team consisting of neurosurgeons, neurointerventionalists, radiosurgeons, and neurologists *experienced* in the diagnosis and treatment of brain AVM.
 - Balancing the risk of hemorrhage and the associated restrictions of everyday activities related to untreated unruptured AVMs against the risk of treatment, there are sufficient indications to treat unruptured AVMs grade 1 and 2 (Spetzler–Martin).
 - There may be indications for treating patients with higher grades, based on a case to case consensus decision of the experienced team.
 - If treatment is indicated, the primary strategy should be defined by the multidisciplinary team prior to the beginning of the treatment and should aim at complete eradication of the uBAVM.
 - The main factors to be taken into account for the management are:
 - Treatment-related severe complication rate of <5% for grade 1 and 2 (Spetzler–Martin) malformations
 - Life expectancy justifying acceptance of the risk associated with the selected treatment modality (*Severe treatment-related complications are defined as those resulting in unprecedented permanent disability (mRS 2–6) at 12 months*)
 - After having considered the pros and cons of a randomized trial vs. a registry, the panel proposed a prospective European Multidisciplinary Registry.
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Acknowledgments We gratefully acknowledge the financial support by B. Braun that offered an unrestricted educational grant.

Compliance with ethical standards

Conflicts of interest None.

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