Neuroradiology (2020) 62:411–416
https://doi.org/10.1007/s00234-020-02365-4

EDITORIAL

What neurointerventionists think about the treatment of unruptured brain arteriovenous malformations: the complexity of moving towards evidence-based treatment

Mayank Goyal[1,2] · Johanna M Ospel[1,3] · Nima Kashani[1,2] · Adnan H Siddiqui[4] · Ricardo Hanel[5] · Mohammed Almekhlafi[1,2] · René Chapot[6]

Published online: 23 January 2020

Pial arteriovenous malformations of the brain (brain AVMs) are a rare condition. Since most brain AVMs become apparent only if they are symptomatic or as incidental findings when brain imaging is performed for a different reason, determining the prevalence of unruptured brain AVMs is difficult, and estimates range from 100 to 600/100,000 [1].

Treatment complication rates for unruptured brain AVMs have been extensively reported in the literature (although mostly in retrospective series) and the risk factors for treatment complications are reasonably well-understood, with the Spetzler-Martin grading system classifying unruptured brain AVMs according to their surgical complication risk [2]. Risk factors for endovascular and radiosurgical complications are also well-studied [3–5]. When looking at an unruptured brain AVM, experienced operators can usually quite accurately assess the complexity of a surgical, radiosurgical, and or endovascular treatment and estimate the likelihood of complications and complete cure. However, the natural history of brain AVMs remains unclear [6]. This is complicated by the fact that brain AVMs are highly variable in their size and location, feeding and draining vessels. In conjunction with patient features (age, functional status, etc.), it seems difficult to predict the natural history of an unruptured brain AVM in a given patient. The principal measure of natural history is derived from a single pre-interventional cohort of 160 patients from Finland which reflected an annual risk of 3–4%. The ARUBA trial reported a spontaneous rupture rate of 2.2% per year without treatment [7], but this estimate is likely to be biased because several subtypes of brain AVMs (e.g., multifocal or vein of Galen AVMs) and lesions that were deemed "untreatable" by the local team were excluded from the trial. Our knowledge about factors that increase bleeding risk of these lesions is sparse. There is limited evidence that deep venous drainage may increase the risk of hemorrhage, but these data were derived from very small case series and with regard to other risk factors, we are relying primarily on assumptions [8, 9]. Given the lack of knowledge about the natural history, it is almost impossible to weigh the treatment risks against the risk of rupture and subsequent bleeding. ARUBA showed that for patients with unruptured brain AVMs, natural history was superior to intervention when measuring stroke and death over a 3-year follow-up. [7]. The trial, however, was criticized for its slow enrolment, failure to standardize the treatment arm, lack of subgroup analysis, and overrepresentation of certain treatment modalities. We recently conducted a multinational web-based survey (ESCAPE ALICE: EndovaSCular TreAtment Preference Evaluation at the Advanced Live Interventional Course of Essen). We obtained responses of 248 physicians from 48 countries (Figs. 1 and 2). In the first part of the survey, physicians were asked to provide their demographic baseline characteristics (age, sex,

✉ Mayank Goyal
mgoyal@ucalgary.ca

1 Department of Clinical Neurosciences, University of Calgary, Calgary, CA, USA

2 Department of Diagnostic Imaging, University of Calgary, Calgary, CA, USA

3 Division of Neuroradiology, Clinic of Radiology and Nuclear Medicine, University Hospital Basel, University of Basel, Basel, Switzerland

4 Department of Neurosurgery, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, USA

5 Baptist Neurological Institute, Baptist Health System, Jacksonville, USA

6 Department of Interventional Neuroradiology, Alfred Krupp Krankenhaus, Essen, Germany

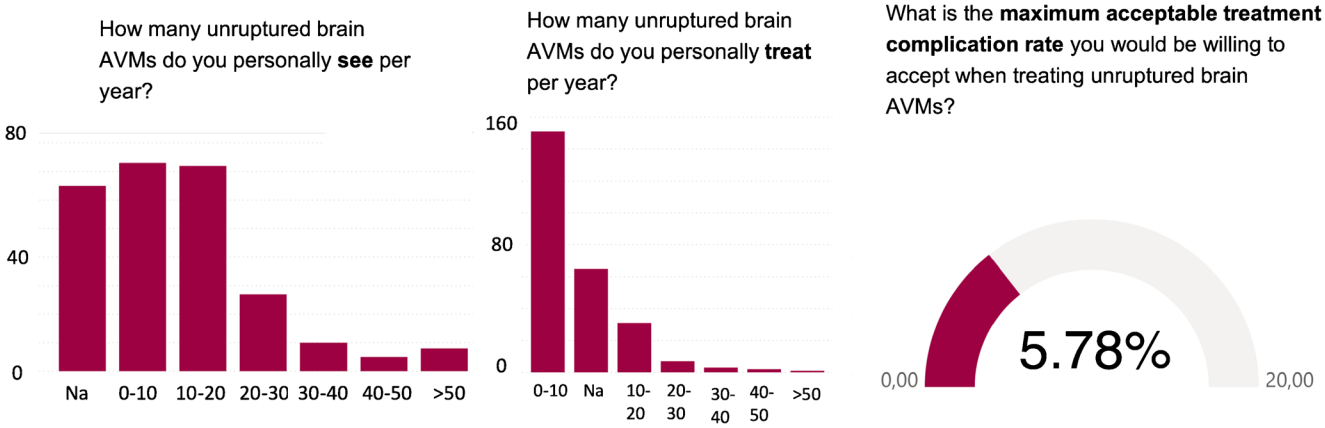

Fig. 1 Participants of the Endovascular Treatment Preference Evaluation at the Advanced Neurointerventional Live Course Essen (ESCAPE ALICE) participants

city/country of practice, specialty, career stage, etc.). The second part included specific questions about the ARUBA trial and its limitations as well as questions regarding the design of a future AVM trial to overcome these limitations. Response data were collected from November 4 to November 28, 2019. Most physicians were neurointerventionalists ($n = 193$, 77.8%) between 31 and 50 years old ($n = 186$, 75.0%) and senior staff/division head ($n = 202$, 81.5%). When asked what the major limitations of ARUBA were, insufficient experience and non-enrollment of low-risk patients were considered the most important (Table 1), in spite of the fact that all participating sites in ARUBA had to have a case volume of at least 10 brain AVMs per year and documented academic interest in clinical brain arteriovenous malformation research. Moreover, 136 of 223 (61%) of ARUBA patients had a Martin-Spetzler grade of 1 or 2 [7]. Of course, it is important to note that the survey participants were neurointerventionists and, as such, might be biased towards treatment of these lesions.

Another limitation that has not been adequately addressed in the survey is the fact that ARUBA was initially set up as a

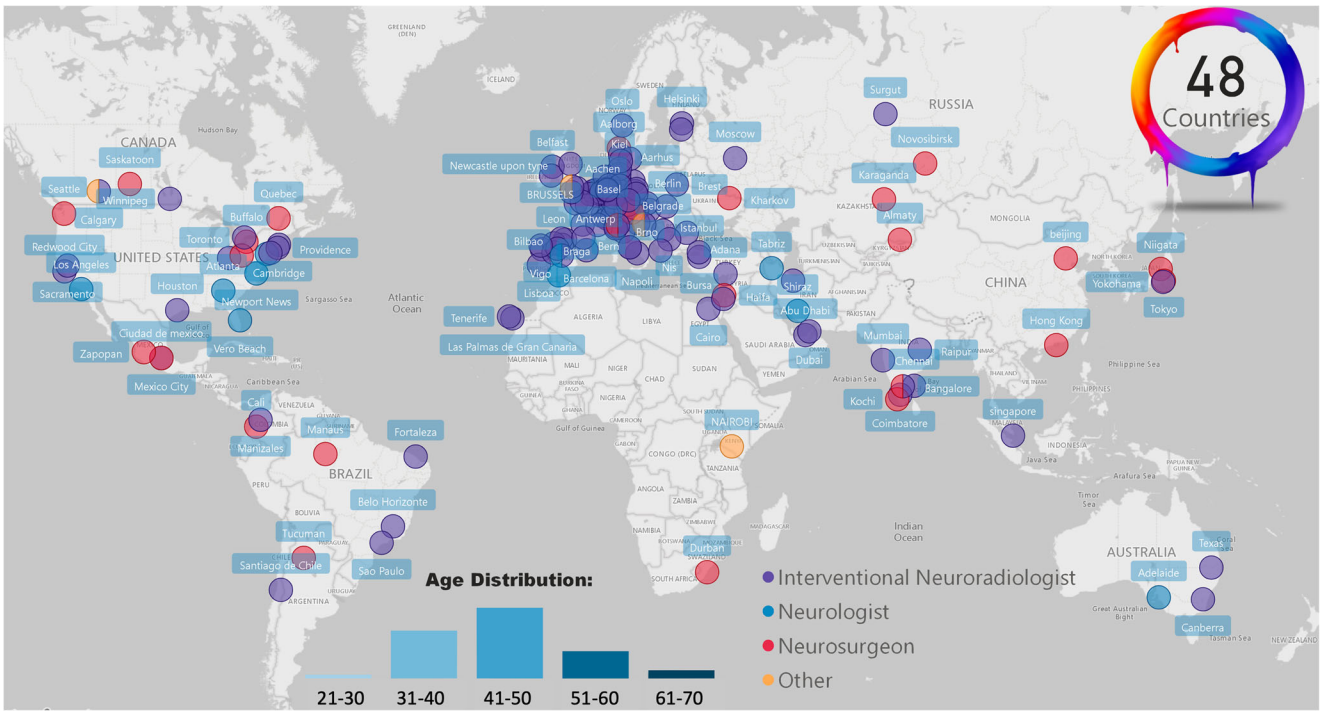

Fig. 2 Personal AVM caseload (left, AVMs seen per year; middle, AVMs treated per year) and maximum acceptable treatment complication risk (right) reported by the ESCAPE ALICE participants. The majority of physicians sees 0–20 unruptured brain AVMs annually and treats 0–10 of these lesions per year like the ARUBA investigators. The maximum complication rate physicians were willing to accept for treatment of unruptured brain AVMs was on average 5.78%

Table 1 Results from a survey among 248 neurointerventionalists. "What do you think were the most important problems of the ARUBA trial? Please order the following limitations according to their importance from 1 (most important) to 6 (least important)"

Order of importance	Problem
1	Sites were not experienced enough
2	Low risk patients were not enrolled
3	Unruptured brain AVMs are such a heterogeneous condition that no trial can ever capture all the nuances
4	No criteria for selecting highly skilled operators
5	Since the trial, there have been so many new and better technologies developed that the results are no longer valid
6	Complications (what was considered a complication) were not well-defined

Note: Median ranks are shown for each of the statement. Answer options were derived from personal communication and the literature [10–13]

multidisciplinary trial (presence of a multidisciplinary AVM treatment team was a pre-condition for participating sites [7]), but neurosurgery, which plays an important role in AVM management, was underrepresented as a specialty. This is an issue of trial execution, not trial design and something that future trialists will have to work hard to mitigate. One also has to consider that since ARUBA was conducted, progress has been made in endovascular treatment approaches, so that "endovascular cure" is now considered the treatment goal. New embolic agents and alternative access routes such as the transvenous approach have reportedly higher cure rates without an increase in complications in small studies [14]. On the other hand, the growing number of centers offering treatment for unruptured brain AVMs may have led to a dilution of experience, with most patients getting treated in low-volume centers by insufficiently skilled operators rather than in high-volume centers by highly specialized operators. This is particularly true for endovascular treatment, since the establishment of thrombectomy as a standard of care has led to an exponential increase in hospitals offering neurovascular services. These centers usually do not confine themselves to endovascular stroke treatment and offer a comprehensive neurovascular service for non-emergent conditions as well, oftentimes without having a multidisciplinary team and the necessary skillsets. In theory, patient preferences should also be considered in treatment decision-making. However, the information level and power distribution between patient and physician are highly unequal, and most patients will leave the decision whether and how to treat largely up to their doctor. The ARUBA trial, despite its limitations, is currently the best available evidence for the natural history and treatment outcomes of unruptured brain AVMs. One would assume that its results have led to a decrease in treatment rates. But unruptured brain AVMs continue to be treated, despite the rather discouraging outcomes of the ARUBA treatment arm [15]. Many operators use the alleged methodological flaws of the trial as a justification to treat (we are better/select our patients better/use better devices/use different modalities than the operators in the trial). This subjective opinion is possibly biased by overestimation of personal skills as well as heterogeneity in treatment approaches, but without strong clinical evidence in support. Unfortunately, there is nothing to indicate that the level of evidence will get any better in the near future. In our survey, 85% of the physicians stated that they do not understand the factors which determine the risk of rupture in unruptured brain AVMs (Fig. 3), and 90% stated that they think there is a need for an unruptured brain AVM trial in intermediate-risk patients that compares interventional treatment with conservative management, while only 39% considered a trial comparing different treatment modalities necessary. When asked which patients should be enrolled in such a trial, most physicians (57%) stated that all patients with unruptured brain AVMs should be enrolled (Fig. 3).

Assuming that the survey results are representative of the level of equipoise among operators, designing and executing another randomized controlled trial that can overcome the limitations of ARUBA will be very challenging, if not impossible. One approach for an ARUBA-like trial would be to treat only those patients in whom treatment complication rates are low to intermediate (since including patients with high treatment risks could affect the results of the entire trial). Some might argue that only patients with intermediate risk should be enrolled, since there is no clinical equipoise for those with low treatment complication risk. Others may feel that all patients, irrespective of the complication risks, should be enrolled since such a trial design would be most comprehensive and yield the most genuine and generalizable results. The advantages and disadvantages for each of these trial designs are summarized in Table 2.

There are numerous other questions to be answered when planning such a trial, for example, which sites should be chosen? If only specialized academic centers with a high level of expertise and high case volume are selected, the trial is more likely to show treatment benefit, but less likely to represent clinical reality, while the opposite would be true for a trial that applies less restrictive criteria for the enrolling centers. It is also important to note that in our survey with participation from 48 countries, the majority of respondents treat only a

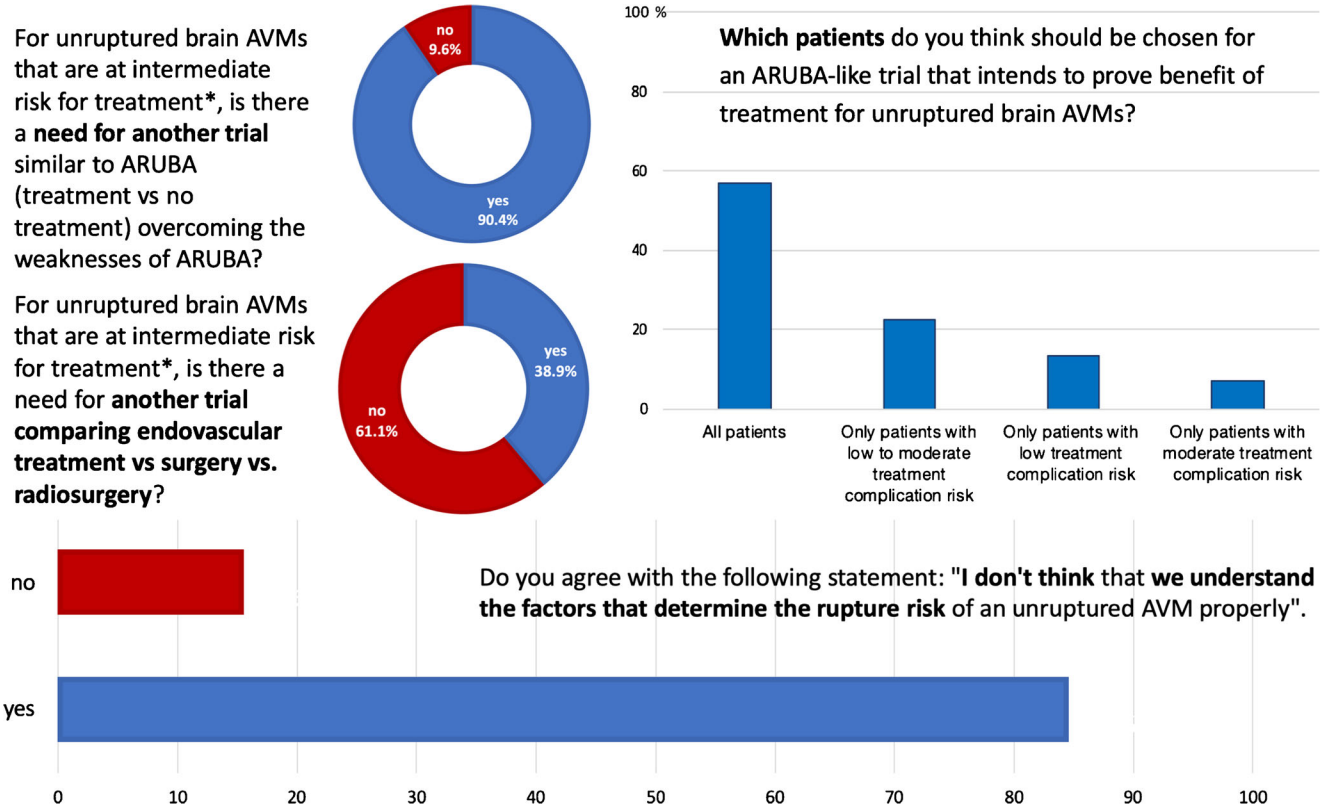

Fig. 3 Key results from the ESCAPE ALICE survey. Doughnut charts (top left) show the perceived need for another trial in unruptured brain AVMs. The vertical bar chart (top right) shows which patients should be enrolled in such a trial and the horizontal bar chart (bottom) illustrates how many participants think that we do/do not understand the factors that determine the rupture risk of an unruptured brain AVM

small number of patients per year. Given the rarity of the condition, an unruptured brain AVM trial would probably run over several years. For instance, TOBAS (ClinicalTrials.gov: NCT02098252), an ongoing trial which is designed to generate additional evidence for the efficacy of conservative management vs. interventional therapy of unruptured brain AVMs, started enrolment in 2014 and is expected to continue for many years [16]. How should advances in treatment technology and newly developed treatment strategies be incorporated into such a lengthy trial? Should patients be randomized into a control arm and an intervention arm, or should those patients within the intervention arm also be randomized to different treatment modalities? Zarin et al. recently wrote about the harms resulting from uninformative trials (trials that are not meaningful for patients, clinicians, scientists, or policymakers) [17]. From a researcher's and sponsor's perspective, such trials are a waste of time, resources, and effort. From a patient's perspective, enrolment in trials which are foreseeable to be uninformative is a violation of trust. Zarin et al. list several key requirements for a trial to be informative—among them are (1) a study design that is able to provide meaningful evidence related to the research question and (2) feasibility, i.e., a realistic plan for recruitment of a sufficient number of participants. Meeting these two requirements will be challenging for an unruptured brain AVM trial: the plethora and heterogeneity of treatment options will likely dilute and/or obscure treatment effect, and rarity of the condition will make patient recruitment difficult and result in long enrolment periods and possibly an insufficient sample size. The low incidence of AVMs and increasing number of physicians offering endovascular treatment also raise the question how to define the appropriate minimum level of expertise/technical skills needed for endovascular treatment of AVMs.

In light of these concerns, is it realistic and reasonable to attempt another randomized trial for unruptured brain AVMs?

In our opinion, there are two possible approaches to this problem:

1. Acknowledging that an informative randomized controlled trial is not feasible: due to the numerous problems mentioned above, it is likely that we are unable to successfully achieve clear evidence for the superiority of interventional treatment or conservative management in unruptured brain AVMs. In such a case, we should at the very least try to maintain high-quality registries and regulatory bodies should ensure that all patients get

Table 2 Possible trial designs and target populations for an unruptured AVM trial

Target population	Advantages	Disadvantages
All patients	Many potential trial candidates and high enrolment rates Comprehensive results Better generalizability of the results	Showing treatment benefit might be challenging due to high complication rate Lack of clinical equipoise may exclude patients perceived to be easy to treat
Patients with *low to intermediate treatment risk* only	Showing treatment benefit might be easier due to lower complication rates	Selective patient population and lack of generalizability There would be a risk of "cherry-picking" towards those with intermediate procedural risk
Patients with *low treatment risk* only	This group would yield the highest chance of showing treatment benefit	Only few potential trial candidates and slow enrolment Highly selective patient population and lack of generalizability
Patients with *intermediate treatment risk* only	This group would have the highest equipoise	Only few potential trial candidates and slow enrolment Highly selective patient population and lack of generalizability Significant chance of control arm doing better if procedural complication rate higher than expected.

enrolled in these registries. However, maintaining high-quality registries is difficult and requires substantial resources that may not be available in all geographies. What's more, results from registries generally do not impact guidelines and levels of evidence.

2. Conducting a trial focused on the "low-hanging-fruit" [18] in order to minimize the risk of an uninformative trial. This would mean to randomize only patients at low risk of treatment complications and would require a strategy for operators to identify these patients. The selection criteria could be based on registry data. Some operators might feel the lack of clinical equipoise in low-risk patients and thus, it might become difficult to convince physicians to enroll patients. We believe, however, that this is the only way to generate level 1A evidence for treatment of unruptured brain AVMs, similar to the approach that has been taken in endovascular stroke treatment: although many physicians thought it unethical to randomize patients with large vessel occlusions, doing so ensured a positive result of the thrombectomy trials [19], which in the long run led to guideline changes, increased the interest of researchers, policymakers, and industry and thereby accelerated technology, technical development, and access and organization of acute stroke care. A similar attempt in unruptured brain AVM patients may be the way to begin the journey towards evidence-based medicine. Such a trial would, of course, have to ensure that all the limitations of ARUBA are adequately addressed and the leadership team would have to secure adequate engagement and participation from all relevant specialties. Ensuring sufficient operator skills in particular will be difficult, but it is absolutely necessary. To avoid this, a minimal amount of procedures performed per operator and year should be defined. Unlike stroke, endovascular treatment of brain AVMs is an elective procedure and there is enough time to transfer patients to specialized centers which meet these requirements, so that all patients receive the best possible treatment. Such a trial will also have to address the heterogeneity in treatment modalities including apportionment of multimodal approaches.

The importance of generating high-quality evidence cannot be minimized. When ignoring this, we will either assault patients with unnecessary high-risk procedures or deny them brain and life-saving therapies. It behooves us to design pragmatic approaches and have the will to follow through to complete such a trial in a reasonable time frame to address the need for clinical evidence.

Acknowledgments The authors are most grateful to all survey participants.

Funding information NA

Compliance with ethical standard

Conflict of interest MG consults for Medtronic, Stryker, Microvention, Mentice, GE Healthcare, and holds a licensing agreement with GE Healthcare regarding systems of acute stroke diagnosis. The remaining authors have nothing to disclose.

Ethical approval NA

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Berman MF, Sciacca RR, Pile-Spellman J, Stapf C, Connolly ES Jr, Mohr JP, Young WL (2000) The epidemiology of brain

arteriovenous malformations. Neurosurgery 47(2):389–396; discussion 397. https://doi.org/10.1097/00006123-200008000-00023
2. Spetzler RF, Martin NA (1986) A proposed grading system for arteriovenous malformations. J Neurosurg 65(4):476–483. https://doi.org/10.3171/jns.1986.65.4.0476
3. Hartmann A, Pile-Spellman J, Stapf C, Sciacca RR, Faulstich A, Mohr JP, Schumacher HC, Mast H (2002) Risk of endovascular treatment of brain arteriovenous malformations. Stroke 33(7):1816–1820. https://doi.org/10.1161/01.str.0000020123.80940.b2
4. Kano H, Flickinger JC, Tonetti D, Hsu A, Yang HC, Flannery TJ, Niranjan A, Lunsford LD (2017) Estimating the risks of adverse radiation effects after gamma knife radiosurgery for Arteriovenous malformations. Stroke 48(1):84–90. https://doi.org/10.1161/STROKEAHA.116.014825
5. Dumont TM, Kan P, Snyder KV, Hopkins LN, Siddiqui AH, Levy EI (2015) A proposed grading system for endovascular treatment of cerebral arteriovenous malformations: Buffalo score. Surg Neurol Int 6:3. https://doi.org/10.4103/2152-7806.148847
6. Petridis AK, Fischer I, Cornelius JF, Kamp MA, Ringel F, Tortora A, Steiger HJ (2016) Demographic distribution of hospital admissions for brain arteriovenous malformations in Germany–estimation of the natural course with the big-data approach. Acta Neurochir 158(4):791–796. https://doi.org/10.1007/s00701-016-2727-2
7. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, Al-Shahi Salman R, Vicaut E, Young WL, Houdart E, Cordonnier C, Stefani MA, Hartmann A, von Kummer R, Biondi A, Berkefeld J, Klijn CJ, Harkness K, Libman R, Barreau X, Moskowitz AJ, International Ai (2014) Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet 383(9917):614–621. https://doi.org/10.1016/S0140-6736(13)62302-8
8. Alexander MD, Cooke DL, Nelson J, Guo DE, Dowd CF, Higashida RT, Halbach VV, Lawton MT, Kim H, Hetts SW (2015) Association between venous Angioarchitectural features of sporadic brain Arteriovenous malformations and intracranial hemorrhage. AJNR Am J Neuroradiol 36(5):949–952. https://doi.org/10.3174/ajnr.A4224
9. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw AV, Connolly ES, Pile-Spellman J, Mohr JP (2006) Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology 66(9):1350–1355. https://doi.org/10.1212/01.wnl.0000210524.68507.87
10. Cognard C (2015) A randomized trial of unruptured brain arteriovenous malformations study: what impact on clinical care and therapeutic decision? AJNR Am J Neuroradiol 36(4):619–622. https://doi.org/10.3174/ajnr.A4294
11. Elhammady MS, Heros RC (2017) Editorial: the ARUBA study: where do we go from here? J Neurosurg 126(2):481–485. https://doi.org/10.3171/2015.7.JNS151408
12. Magro E, Gentric JC, Darsaut TE, Ziegler D, Msi, Bojanowski MW, Raymond J (2017) Responses to ARUBA: a systematic review and critical analysis for the design of future arteriovenous malformation trials. J Neurosurg 126(2):486–494. https://doi.org/10.3171/2015.6.JNS15619
13. Pierot L, Fiehler J, Cognard C, Soderman M, Spelle L (2014) Will a randomized trial of unruptured brain arteriovenous malformations change our clinical practice? AJNR Am J Neuroradiol 35(3):416–417. https://doi.org/10.3174/ajnr.A3867
14. Chen CJ, Norat P, Ding D, Mendes GAC, Tvrdik P, Park MS, Kalani MY (2018) Transvenous embolization of brain arteriovenous malformations: a review of techniques, indications, and outcomes. Neurosurg Focus 45(1):E13. https://doi.org/10.3171/2018.3.FOCUS18113
15. Reynolds AS, Chen ML, Merkler AE, Chatterjee A, Diaz I, Navi BB, Kamel H (2019) Effect of a randomized trial of Unruptured brain Arteriovenous malformation on interventional treatment rates for Unruptured Arteriovenous malformations. Cerebrovasc Dis 47(5–6):299–302. https://doi.org/10.1159/000502314
16. Magro E, Gentric JC, Batista AL, Kotowski M, Chaalala C, Roberge D, Weill A, Stapf C, Roy D, Bojanowski MW, Darsaut TE, Klink R, Raymond J (2018) The treatment of brain AVMs study (TOBAS): an all-inclusive framework to integrate clinical care and research. J Neurosurg 128(6):1823–1829. https://doi.org/10.3171/2017.2.JNS162751
17. Zarin DA, Goodman SN, Kimmelman J (2019) Harms from uninformative clinical trials. JAMA. https://doi.org/10.1001/jama.2019.9892
18. Goyal M, Simonsen CZ, Fisher M (2018) Future trials on endovascular stroke treatment: the not-so-easy-to-pluck fruits. Neuroradiology 60(2):123–126. https://doi.org/10.1007/s00234-017-1966-0
19. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millan M, Davis SM, Roy D, Thornton J, Roman LS, Ribo M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG, collaborators H (2016) Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 387 (10029):1723–1731. doi:https://doi.org/10.1016/S0140-6736(16)00163-X