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## **IMPACT OF ARUBA TRIAL ON CURRENT PRACTICE: INTERVENTIONAL TREATMENT AND STROKE RATES IN UNRUPTURED BRAIN ARTERIOVENOUS MALFORMATIONS IN THE POST-ARUBA ERA**

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### **Abstract**

Brain AVMs are the abnormal connection between veins and arteries of the brain, that can lead to headaches, seizures, and hemorrhages. The choice of treatment for bAVMs depends on several factors, such as the size and location of the malformations, the severity of symptoms, and the risk of hemorrhage. The ARUBA was a clinical trial that aimed to determine the best treatment approach for unruptured AVMs. Its results showed that conservative management was associated with a significantly lower risk of death or stroke compared to intervention, leading to a shift in the practice of neurosurgeons. In this review, trends in the post-ARUBA rates of stroke and interventions for unruptured bAVMs are discussed.

A noticeable decrease in the number of interventions for unruptured bAVMs has been seen post-ARUBA. This reduction has been particularly evident in minimally invasive procedures such as endovascular embolization and stereotactic radiosurgery. However, microsurgery, which is considered the gold standard for small-sized bAVMs, has remained consistent in terms of the number of procedures performed for ARUBA-eligible patients.

**Keywords:** ARUBA trial, brain arteriovenous malformations, endovascular embolization, microsurgery, stereotactic radiosurgery.

### **Резюме**

## **ВЛИЯНИЕ ARUBA НА ТЕКУЩУЮ ПРАКТИКУ: ПОКАЗАТЕЛИ ИНТЕРВЕНЦИОННОГО ЛЕЧЕНИЯ И ЧАСТОТА ИНСУЛЬТОВ ПРИ НЕРАЗОРВАВШИХСЯ АРТЕРИОВЕНОЗНЫХ МАЛЬФОРМАЦИЯХ ГОЛОВНОГО МОЗГА В ЭПОХУ ПОСЛЕ ARUBA**

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АВМ головного мозга – это аномальное соединение между венами и артериями головного мозга, которое может привести к головным болям, судорогам и кровоизлияниям. Выбор лечения АВМ зависит от нескольких факторов, таких как размер и расположение пороков развития, тяжесть симптомов и риск кровотечения. ARUBA представляло собой клиническое исследование, целью которого было определить лучший подход к лечению неразорвавшихся АВМ. Его результаты показали, что консервативное лечение было связано со значительно меньшим риском смерти или инсульта по сравнению с оперативным вмешательством, что привело к изменениям в практике нейрохирургов. В обзоре обсуждаются тенденции частоты возникновения инсультов и вмешательств при неразорвавшихся артериовенозных мальформациях головного мозга после испытания ARUBA.

После ARUBA наблюдалось заметное снижение количества вмешательств по поводу неразорвавшихся АВМ. Это снижение было особенно очевидным при минимально инвазивных процедурах, таких как эндоваскулярная эмболизация и стереотаксическая радиохирургия. Тем не менее, микрохирургия, которая считается золотым стандартом для лечения АВМ небольшого размера, остается неизменной с точки зрения количества процедур, выполняемых пациентам, соответствующим критериям ARUBA.

**Ключевые слова:** исследование ARUBA, артериовенозные мальформации головного мозга, эндоваскулярная эмболизация, микрохирургия, стереотаксическая радиохирургия.

Түйіндеме

## ARUBA СЫНАҒЫНЫҢ ҚАЗІРГІ ТӘЖІРИБЕГЕ ӘСЕРІ: ARUBA-ДАН КЕЙІНГІ ДӘУІРДЕГІ МИДЫҢ ЖАРЫЛМАҒАН АРТЕРИОВЕНОЗДЫ АҚАУЛАРЫНДАҒЫ ИНТЕРВЕНЦИЯЛЫҚ ЕМДЕУ ЖӘНЕ ИНСУЛЬТ КӨРСЕТКІШТЕРІ

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Мидың артериовеналық мальформациялары – бас ауруларына, құрысуларға және қан кетулерге әкелуі мүмкін ми тамырлары мен артериялары арасындағы қалыптан тыс байланыс. АВМ үшін емдеуді таңдау ақаулардың мөлшері мен орналасуы, симптомдардың ауырлығы және қан кету қаупі сияқты бірнеше факторларға байланысты. ARUBA жарылмаған АВМ үшін ең жақсы емдеу әдісін анықтауға бағытталған клиникалық сынақ болып табылады. Оның нәтижелері консервативті басқарудың араласумен салыстырғанда өлім немесе инсульт қаупінің айтарлықтай төмен болуымен байланысты екенін көрсетті, бұл нейрохирургтердің тәжірибесіне өзгерістер енгізді. Бұл шолуда ARUBA-дан кейінгі инсульт жылдамдығының үрдістері және жарылмаған АВМ үшін хирургиялық араласулар талқыланады.

ARUBA -дан кейін жарылмаған АВМ үшін араласулар санының айтарлықтай төмендеуі байқалды. Бұл төмендеу әсіресе эндоваскулярлық эмболизация және стереотактикалық радиохирургия сияқты аз инвазивті процедураларда айқын болды. Дегенмен, шағын өлшемді АВМ үшін алтын стандарт болып саналатын микрохирургия ARUBA-ға жарамды пациенттер үшін орындалатын процедуралар саны бойынша тұрақты болып қалды.

**Түйін сөздер:** ARUBA сынауы, бас миының артериовеналық мальформациялары, эндоваскулярлы эмболизация, микрохирургия, стереотактикалық радиохирургия.

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### Introduction

Brain arteriovenous malformations (thereafter – bAVMs) are abnormal connections between arteries and veins that lack capillaries [8], which can result in serious complications, the most life-threatening of which is intracranial hemorrhage, the risk of which is higher in those with a history of previous hemorrhage [16]. The incidence rate of bAVMs ranges from 1.12 to 1.42 per 100 thousand person-years [1]. Treatment options for bAVMs are conservative medical management and surgical interventions, with the latter becoming more disputable after a Randomized trial of Unruptured Brain Arteriovenous malformations (thereafter – ARUBA), especially in cases with no signs of previous intracerebral hemorrhage [35].

ARUBA was a prospective, multicenter, non-blinded, randomized controlled trial with a parallel and open-label design study that aimed to compare the efficacy of different

treatment options for unruptured bAVMs, including medical management and interventional therapies such as microsurgery, endovascular embolization, and stereotactic radiosurgery (thereafter – SRS). The trial was started in 2007 and involved 39 clinical sites in nine countries [35].

The study's primary outcome was the length of time before the composite endpoint of symptomatic stroke or bAVMs associated mortality [35]. An interim analysis was conducted in 2013 with 223 patients and a mean follow-up of 33.3 months. The results showed that the risk of death or stroke was reached in 35 (30.7%) of the 114 patients in the interventional group compared with 11 (10.1%) of the 109 patients in the medical management group, thereby emphasizing the preference for “watchful waiting” approach over surgical interventions in patients with unruptured bAVMs [35]. In 2020, the findings of extended follow-up reinforced the initial results of the ARUBA trial and

supported the use of medical management for preventing stroke and death in patients with unruptured bAVMs [34].

The ARUBA trial has been the subject of various studies that explore its methodology, design, and patient selection criteria. Concerns have been raised about the trial's patient selection criteria, particularly for the inclusion of patients with low Spetzler-Martin grade bAVMs who underwent surgical treatment. Some have suggested that these patients may have been selectively chosen based on factors such as AVM location or surgeon experience, which could have biased the results [15, 33, 46, 47].

Another criticism raised regarding the increased hemorrhage observed in the treatment arm of the ARUBA trial is that inappropriate use of treatment approaches could have played a role. Specifically, the use of endovascular interventions when surgical or other modalities would have been more appropriate, and vice versa, may have contributed to the higher rate of hemorrhage [12]. In addition, it is worth noting that microsurgery alone or in combination with other treatment modalities was only performed in six patients in the ARUBA trial [35]. This is despite evidence suggesting that microsurgery may have the fewest complications for low-grade (I-II Spetzler-Martin) bAVMs [45]. Therefore, the limited use of this treatment approach in the trial raises concerns about its generalizability and applicability to the wider population of patients with unruptured bAVMs.

Notwithstanding the criticisms that have been raised about the ARUBA trial, its results had an impact on the management of unruptured bAVMs and led to modifications in treatment methodology worldwide. There has been a shift towards more conservative management of unruptured bAVMs, with greater emphasis on monitoring and follow-up rather than immediate intervention, which has resulted in changes in intervention and stroke rates in patients with unruptured bAVMs. This paper, therefore, aimed to provide an overview of the post-ARUBA rates of stroke and interventions in patients with unruptured bAVMs.

## Methods

### Literature search strategy

The review included papers published post-2014, following the initial release of interim findings from the ARUBA trial. The search focused on keywords including "ARUBA trial", "stroke rates", "brain arteriovenous malformations", "endovascular embolization", "microsurgery", and "stereotactic radiosurgery" within the PubMed/MEDLINE and Google Scholar databases. Grey literature sources such as conference proceedings, dissertations, and government reports were excluded from the study. The papers written in English were included in the study, and papers written in other than the English language or with English abstracts only were excluded from the analysis.

### Main Text

#### Impact of ARUBA trial on the stroke rate among patients with unruptured bAVMs

While the ARUBA trial has shown promising results in the medical management of unruptured bAVMs, the mortality and stroke rates related to bAVMs remain controversial. There are differing viewpoints and conflicting evidence regarding the effectiveness of the medical management of ARUBA-eligible bAVMs in reducing stroke

and mortality rates. A recent study of a National Inpatient Sample of 121,415 patients has revealed an increase in the incidence of ruptured bAVMs by more than two times, as well as the hospital mortality rates by 3-fold when comparing data for before and after 2014 [48]. The significance of ARUBA's impact on bAVM outcomes would be diminished if there were an observable difference in the hospitalization rates between patients with previously ruptured and those with unruptured aneurysms during the same period in the same hospital [48]. These findings are supported by another analysis done by Patel et al., which showed that the proportion of bAVMs ruptures increased significantly from 17.0% (2009-2013) to 23.3% in the post-ARUBA period (2014-2018) [38]. Scholars suggest that a reduction in treatments administered to unruptured AVMs after 2014 could potentially lead to increased incidences of AVM ruptures [31]. However, controversial findings were found in a study by *Wahood et al.*, that analyzed the same database and demonstrated a lower odd of hemorrhage during the post-ARUBA in all cases who underwent any type of intervention even though the rate of endovascular interventions has remained constant, and the number of open surgeries has decreased [48].

When comparing the pre- and post-ARUBA groups, it is important to note that a higher proportion of patients underwent therapeutic interventions after the ARUBA trial. Although this difference was not statistically significant, it is worth considering. Interestingly, patients who received interventional therapies had a lower rate of symptomatic stroke or death compared to those who were under medical management. This contradicts the findings of the ARUBA trial. Additionally, the interventional therapy group had a lower annual incidence of stroke or death. However, it is important to highlight that there was no significant difference in the long-term functional outcomes, as measured by the mRS score of  $\geq 2$ , after a 5-year follow-up between the medical treatment and intervention groups [20].

The impact of the ARUBA trial on stroke rate among patients with unruptured bAVMs is not unambiguous. Although most studies have indicated an increase in hemorrhage, it is important to consider patients' characteristics and indications for treatment, as well as the treatment method, when preventing bAVMs-associated stroke. Study results found that when comparing to patients in the interventional arm of the ARUBA trial, the study participants showed significantly lower rates of death and stroke, as well as low functional impairment scores, thereby highlighting that interventions for unruptured AVMs at comprehensive stroke centers are associated with a positive safety record [2].

#### Impact of ARUBA trial on the rates of interventions in patients with brain AVMs

Although the ARUBA trial suggests that conservative management may be a viable option for patients with unruptured bAVMs, the treatment approach should be based on the patient's characteristics, including the size, location, and symptoms of bAVM, as well as the patient's overall health and preferences, and AVM classification. The Spetzler-Martin grading scale [41], along with subsequent modifications [28], has been the primary algorithm for surgical management, including surgical resection, SRS,

embolization, or a combination thereof. The results of the ARUBA trial, which reported more events in the interventional therapy group compared to the medical therapy group, were in contrast with previous surgical series, suggesting that the risks of interventions for certain grades AVMs were higher than reported elsewhere [47].

Since the ARUBA trial, scholars have reported changes in several interventions for unruptured bAVMs. A study based on national registry data observed a decrease of 8.37% in any interventions for bAVMs during the post-ARUBA period [48]. A recent study has reported the occurrence of ruptured AVMs rose after 2014, possibly indicating a shift in approach towards conservative and non-interventional management strategies for patients with unruptured bAVMs [13]. However, there is a study with controversial results. The study by Sussman et al. concluded that the ARUBA trial had no significant impact on the volume, type, or treatment approach for bAVMs referred to Stanford Health Care and Stanford Children's Health. There were no notable changes observed in the case volume or the proportion of unruptured AVMs treated [43]. The difference in a study results demands further studies and analysis.

Endovascular embolization of bAVMs is a minimally invasive treatment option that has resulted in total obliteration rates of 88% with low complication rates, making it viable for deeply localized bAVMs [5] and leads to improvements in seizure dynamics of 65% or more in patients with bAVM associated epilepsy [4]. Apart from a minimally invasive approach, endovascular treatment is a valuable option for unruptured bAVMs, including flow-related or nidal aneurysms, and high-flow fistulae [3, 26] and the method is an appropriate treatment option for difficult-to-reach bAVMs, particularly hemorrhagic deep-seated AVMs that cannot be treated with microsurgery or SRS [36]. Moreover, minimally invasive procedures such as endovascular treatment and SRS can assist in resolving the issue of residual bAVMs, which are present in 4% of microsurgical treatment cases [6].

Although endovascular interventions have a wide range of applications in the treatment of ARUBA-eligible patients, there has been a notable decrease in their use in post ARUBA era. A study of the National Inpatient Sample has reported that the decline in post-ARUBA interventions was predominantly due to the reduction in endovascular interventions from 18.8% to 13.9% [38], and no change was observed in the frequency of open surgery or combinations of endovascular and surgical approaches [38]. The prospective cohort study by Chen and colleagues did not find significant evidence favoring embolization over conservative management in effectively preventing long-term hemorrhagic stroke or death in patients with bAVMs [10]. Thereby having a potential impact on the decrease in minimally invasive intervention rates.

A post-ARUBA decline in endovascular intervention has also been seen in a study by Birnbaum et al., however, the rate of microsurgery, compared to other methods, was reported to increase [7]. This could be because a microsurgical resection, often combined with other treatments, appears to be the preferred treatment modality for achieving the highest rate of immediate and complete removal of brain AVMs in low-grade (I-II) brain AVMs cases

[45]. The findings from both ARUBA-eligible individuals and unruptured grade I/II patients collectively suggest favorable outcomes, particularly when surgical intervention is employed. Functional results for ARUBA-eligible patients resembled those receiving medical management in the ARUBA trial. Based on these findings, Nerva et al. advocate for treatment in carefully chosen patients with low-grade AVMs [37].

Microsurgical resection is considered for low-grade (I-II) bAVMs that are small to moderate in size, located in accessible areas of the brain, and causing significant symptoms [11, 25]. Studies that included ARUBA-eligible patients who underwent microsurgical resection revealed better clinical outcomes in the surgery group than in the conservative therapy group [22, 49]. In response to ARUBA, the BARBADOS trial has been proposed to confirm the usefulness of microsurgery for patients with unruptured grade I or II brain AVMs [44]. Favorable outcomes of microsurgery in treating eligible bAVMs in ARUBA could be a contributing factor to the lack of change or increase in the number of microsurgeries compared to other modalities in the post-ARUBA era [7, 38].

The key to achieving good outcomes in the microsurgical treatment of bAVMs is to create a precise and useful surgical risk estimation system that can be applied prospectively (i.e., before surgery). The estimated risk should be generalizable to all bAVMs and defined by the category and what treatment modality the bAVM requires. The ideal estimation system would essentially have to be dichotomized between surgical and conservative groups. Additionally, microsurgery, as well as gamma knife surgery, are reported to have a lower risk of stroke or death in ARUBA-eligible patients [27]. Also, treating unruptured bAVMs is safe when approached through a collaborative approach, with surgical removal being the primary treatment option whenever possible [30]. In addition, another study has concluded that early surgical resection of AVMs for all surgically accessible AVMs is recommended to prevent stroke and related neurological deficits [32]. Long-term neurological outcomes were comparable between early and delayed resection of ruptured AVMs. Delayed resection may result in a higher rate of complete obliteration, but careful monitoring for the risk of re-rupture during the waiting period for resection is crucial [51].

The Italian Society of Neurosurgery is expressing concern regarding the potential health impact of the conclusions drawn in the ARUBA Study. Specifically, they are emphasizing the risks associated with partial treatments like endovascular therapy, which may increase the risk of bleeding in patients with AVMs. The study's findings highlight a high incidence of death or symptomatic stroke after treatment, underscoring the importance of a comprehensive, multidisciplinary approach to managing AVMs. It is crucial to achieve complete AVM exclusion to ensure the best possible outcomes for patients [9].

A collaborative, or, a multimodal approach to treatment may be superior to the intervention arm of the ARUBA trial and similar to the medical arm in terms of safety endpoints [40]. The consensus among experts on bAVM management is to create a multidisciplinary committee of neurosurgeons specializing in AVM resection, embolization, and radiotherapy to perform multimodal assessments and

create personalized treatment strategies [24]. Combined treatment of bAVMs involves a combination of endovascular embolization, followed by surgical removal or SRS. Furthermore, the combined treatment modality has shown promising results in reducing hemorrhage [17].

SRS has become an effective minimally invasive treatment approach in the management of bAVMs since its development by a team of neurosurgeons and physicists in Sweden 70 years ago [29]. SRS has been shown to achieve high rates of AVM obliteration with minimal radiation exposure and a low risk of hemorrhage. SRS, however, is limited to those with nidus size for radiation being less than 3 cm or a volume less than 12 cm<sup>3</sup>, and the assessment of the effectiveness of SRS requires a follow-up study of at least three years.

The recent real-world study extensively compared microsurgery and SRS for brain AVMs in terms of long-term outcomes. Microsurgery was found to be superior in preventing future hemorrhages or fatalities and achieving AVM obliteration. However, it is important to note that microsurgery carries the risk of potential neurofunctional decline [18].

Many studies have concluded that SRS is a better treatment option for unruptured bAVMs than conservative management. Studies of ARUBA-eligible patients treated with Gamma knife radiosurgery have shown better outcomes compared to the primary ARUBA outcomes of hemorrhage and death [39, 50]. A multicenter study of a 2 236 ARUBA-eligible patients cohort who underwent Gamma knife radiosurgery with an average follow-up of 7 years showed a hemorrhage rate of only 1.1% [42]. Other multicenter studies have also shown lower rates of hemorrhage in post-SRS patients compared to pre-SRS patients [14]. In addition, the NASSAU study, which included 1 351 patients with unruptured bAVMs, included patients who underwent SRS with an average follow-up duration of 6.5 years. Findings from this investigation suggest improved patient outcomes over an extended monitoring period post-SRS, leading to the suggestion that the conclusions drawn from the ARUBA trial could be refuted [23].

Recent studies on AVMs undergoing SRS have reported cumulative 5-year and 10-year bleeding rates of 7% and 10%, respectively, further demonstrating the relative safety of SRS [19]. However, one potential drawback of SRS is the risk of Radiation-Induced Changes (thereafter – RIC), which occur in approximately 1 in 3 patients with AVMs and 1 in 4 patients with neurologic symptoms. A risk factor for RIC is deep nidus location, but these negative outcomes were observed mainly in unruptured bAVMs and repeat SRS cases [21]. Although there are limitations and potential risks associated with SRS, studies have consistently shown that it is a better option than medical management for unruptured AVMs [39, 42].

As well as endovascular interventions in the treatment of unruptured bAVMs, SRS also has seen a post-ARUBA decrease. The frequency of inpatient SRS treatment has declined from 0.5% to 0.1% [38], and this decrease could be attributed to the reduction in the number of endovascular interventions, which are often performed before SRS to reduce the AVM volume and/or to eliminate the vascular

structures that bear an increased risk of intracranial bleeding, thereby making the bAVM more amenable to SRS.

### Conclusion

The ARUBA trial has had significant consequences for the management of unruptured bAVMs, prompting changes in treatment methodology and spurring further research into this complex condition. While there remain limitations to the trial, its findings have provided insights into the potential risks and benefits of different treatment approaches, shaping clinical practice. Minimally invasive procedures such as endovascular treatment and SRS have a wide range of applications in the treatment of ARUBA-eligible patients, but their use has decreased in the post-ARUBA era. Microsurgical resection appears to be the preferred treatment modality for achieving the highest rate of immediate and complete removal of low-grade (I-II) bAVMs, and no drastic decline has been observed in its frequency. Changes in interventions had implications for treatment outcomes. However, the impact of the ARUBA trial on stroke rate among patients with unruptured bAVMs is not clear-cut and needs to consider patients' characteristics. Overall, the trial's findings have prompted a re-evaluation of the approach to managing unruptured bAVMs and sparked further research to improve outcomes for patients.

### Conflict of Interest Statement

*The authors have no conflicts of interest to declare.*

### Ethics Statement.

*Ethical approval has not been obtained because the study involves synthesizing existing knowledge and does not involve collecting new data from human subjects. Furthermore, the literature review does not involve reviewing confidential or sensitive information, such as patient records or proprietary data.*

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