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LITERATURE REVIEW

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# Interventional outcomes for patients eligible for entry into the ARUBA clinical trial: a systematic review and meta-analysis

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**OBJECTIVE** A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) suggested that medical management afforded outcomes superior to those following intervention for unruptured arteriovenous malformations (AVMs), but its findings have been controversial. Subsequent studies of AVMs that would have met the eligibility requirements of ARUBA have supported intervention for the management of some cases. The present meta-analysis was conducted with the object of summarizing interventional outcomes for ARUBA-eligible patients reported in the literature.

**METHODS** A systematic literature search (PubMed, Web of Science, Google Scholar) for AVM intervention studies that used inclusion criteria identical to those of ARUBA (age ≥ 18 years, no history of AVM hemorrhage, no prior intervention) was performed. The primary outcome was death or symptomatic stroke. Secondary outcomes included AVM obliteration, hemorrhage, death, and poor outcome (modified Rankin Scale score ≥ 2 at final follow-up). Bias assessment was performed with the Newcastle-Ottawa Scale, and the results were synthesized as pooled proportions.

**RESULTS** Of the 343 articles identified through database searches, 13 studies met the inclusion criteria, yielding an overall study cohort of 1909 patients. The primary outcome occurred in 11.2% of patients (pooled = 11%, 95% CI 8%–13%). The rates of AVM obliteration, hemorrhage, poor outcome, and death were 72.7% (pooled = 78%, 95% CI 70%–85%), 8.4% (pooled = 8%, 95% CI 6%–11%), 9.9% (pooled = 10%, 95% CI 7%–13%), and 3.5% (pooled = 2%, 95% CI 1%–4%), respectively. Annualized primary outcome and hemorrhage risks were 1.85 (pooled = 2.05, 95% CI 1.31–2.94) and 1.34 (pooled = 1.41, 95% CI 0.83–2.13) per 100 patient-years, respectively.

**CONCLUSIONS** Intervention for unruptured AVMs affords acceptable outcomes for appropriately selected patients. The risk of hemorrhage following intervention compared favorably to the natural history of unruptured AVMs. The included studies were retrospective and varied in treatment and AVM characteristics, thereby limiting the generalizability of their data. Future studies from prospective registries may clarify patient, nidus, and intervention selection criteria that will refine the challenging management of patients with unruptured AVMs.

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**KEYWORDS** ARUBA; arteriovenous malformation; embolization; hemorrhage; intervention; radiosurgery; stroke; vascular disorders

Brain arteriovenous malformations (AVMs) are rare, anomalous cerebrovascular connections between dysplastic arteries and veins that converge at a nidus. Hemorrhage is the foremost cause of morbidity and death from these lesions, and its risk in untreated unruptured AVMs is approximately 1%–3% per year.[1–7] Since the relatively young age at diagnosis begets a substantial cumulative lifetime risk of intracranial hemorrhage in many patients, the impetus for AVM treatment is to prevent future hemorrhage by obliteration of the nidus.[8] In 2014, A Randomized Trial of Unruptured Brain AVMs (ARUBA) reported at the interim analysis (mean follow-

**ABBREVIATIONS** AVM = arteriovenous malformation; mRS = modified Rankin Scale; SM = Spetzler-Martin; SRS = stereotactic radiosurgery.

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up 33 months) that patients with unruptured AVMs were afforded superior outcomes from medical management compared to those from any intervention, and these conclusions were echoed by the final follow-up in 2020 (mean duration 50 months).[9,10]

ARUBA incited controversy within the cerebrovascular community, and the trial has been criticized for its relatively limited follow-up duration, selection of treatment approaches, inadequate obliteration rates, and excess rates of the primary outcome (death or symptomatic stroke) and hemorrhage in the intervention arm.[11–14] Consequently, studies describing the outcomes of various interventions for unruptured AVM have been put forth to rebut the findings of ARUBA.[7,13,15–25] However, an up-to-date statistical compilation of studies of ARUBA-eligible patients ("ARUBA-eligible studies") is absent from the literature.[26] Therefore, the aims of this systematic review and meta-analysis were to 1) summarize interventional outcomes for ARUBA-eligible patients who had been treated outside the clinical trial setting and 2) indirectly compare pooled posttreatment outcomes of ARUBA-eligible patients with those of ARUBA and natural history studies.

## Methods

### Literature Search

This systematic review of the literature and meta-analysis were performed according to the guidelines set forth by the PRISMA statement. The literature search was performed in PubMed, Web of Science, and Google Scholar using the search term ("A Randomized Trial of Unruptured Brain Arteriovenous Malformations" OR ("ARUBA Trial") OR "ARUBA-eligible") on August 4, 2020. Overlapping publications in the search results from the different databases were removed. The inclusion (patients with an age ≥ 18 years and an unruptured brain AVM) and exclusion (prior AVM hemorrhage or intervention) criteria of this review paralleled those of ARUBA. Case reports and case series with fewer than 5 patients, studies published in languages other than English, and publications without any of the outcomes reported in ARUBA were excluded from our analysis.

### Literature Review and Data Extraction

No registered protocol was used for this review. Articles were initially screened by title and abstract. The remaining articles were screened with full-text review to determine eligibility for inclusion. Each full-text review was performed by two authors, and any disagreement between the authors was adjudicated by a third author. The references of these studies were further reviewed for additional studies that qualified for inclusion in the review. Data extracted from the included studies composed the same variables collected in ARUBA to allow comparisons between the meta-analysis and the trial results.

Baseline patient data included age, sex, clinical presentation (seizures, headache, focal neurological deficit, other, and asymptomatic), and pretreatment modified Rankin Scale (mRS) score. AVM data included Spetzler-Martin (SM) grade, maximum diameter, location (laterality, lobar, infratentorial, eloquent), presence of AVM-associated arterial aneurysms, and venous drainage pattern (exclusively superficial or deep component).[27] AVM interventions were classified as surgery, stereotactic radiosurgery (SRS), embolization, or combination therapy. Definitions of SRS protocols and eloquent areas from the individual studies are included in Supplemental Table 1. The primary outcome was death from any cause or symptomatic stroke (identical to the primary outcome of ARUBA). Secondary outcomes included major interventional complications, AVM obliteration, hemorrhagic stroke, ischemic stroke, any stroke, death, and poor outcome. Major complications included any immediate or delayed posttreatment event that resulted in neurological deterioration compared to baseline function. Poor outcome was defined as an mRS score ≥ 2 at the final follow-up. The follow-up duration was also recorded.

### Statistical Analysis

Statistical analyses were performed using Stata software (version 16, StataCorp LLC). Means and associated standard deviations were calculated for continuous variables. For the variables without reported means and associated standard deviations, corresponding medians and ranges were recorded, if available. For variables with frequency counts, absolute counts were extracted to calculate proportions. Weighted pooled means and associated 95% confidence intervals were computed for continuous variables using the random-effects model with the DerSimonian-Laird method. For studies that did not report a mean or standard deviation, these values were estimated from the median, range, and sample size using the methods described by Hozo et al.[28] Weighted pooled proportions and associated 95% confidence intervals were computed for count variables using the random-effects model with the DerSimonian-Laird method after the Freeman-Tukey double arcsine transformation. The exact binomial method was used to compute 95% confidence intervals of proportions for individual studies. Annualized rates of the primary outcome, hemorrhage, and death were calculated by dividing the number of events by patient-years of follow-up. These rates were also pooled using the random-effects model with the DerSimonian-Laird method. Study heterogeneity was assessed using Cochran's Q and $I^2$ test statistics. Heterogeneity was considered to be significant when both the Q value was within the 10% level of significance ($p < 0.10$) and the $I^2$ value exceeded 50%. The quality of studies was assessed using the Newcastle-Ottawa Scale.

## Results

### ARUBA-Eligible Patient and AVM Characteristics

Of the 343 articles identified through database searches, 13 articles met the inclusion criteria and were included in the final analysis (Fig. 1, Supplemental Table 2 for study quality assessment).[7,13,15–25] One study initially appeared to meet inclusion criteria, but it was excluded because the cohort included patients with baseline mRS scores ≥ 2, an ARUBA exclusion criterion.[29] Table 1 summarizes the crude and pooled estimates of baseline patient characteristics. Among the 1909 ARUBA-eligible patients included in our analysis, 48.1% (pooled = 49%, 95% CI 45%–52%) were female and the mean age was 40.7 years

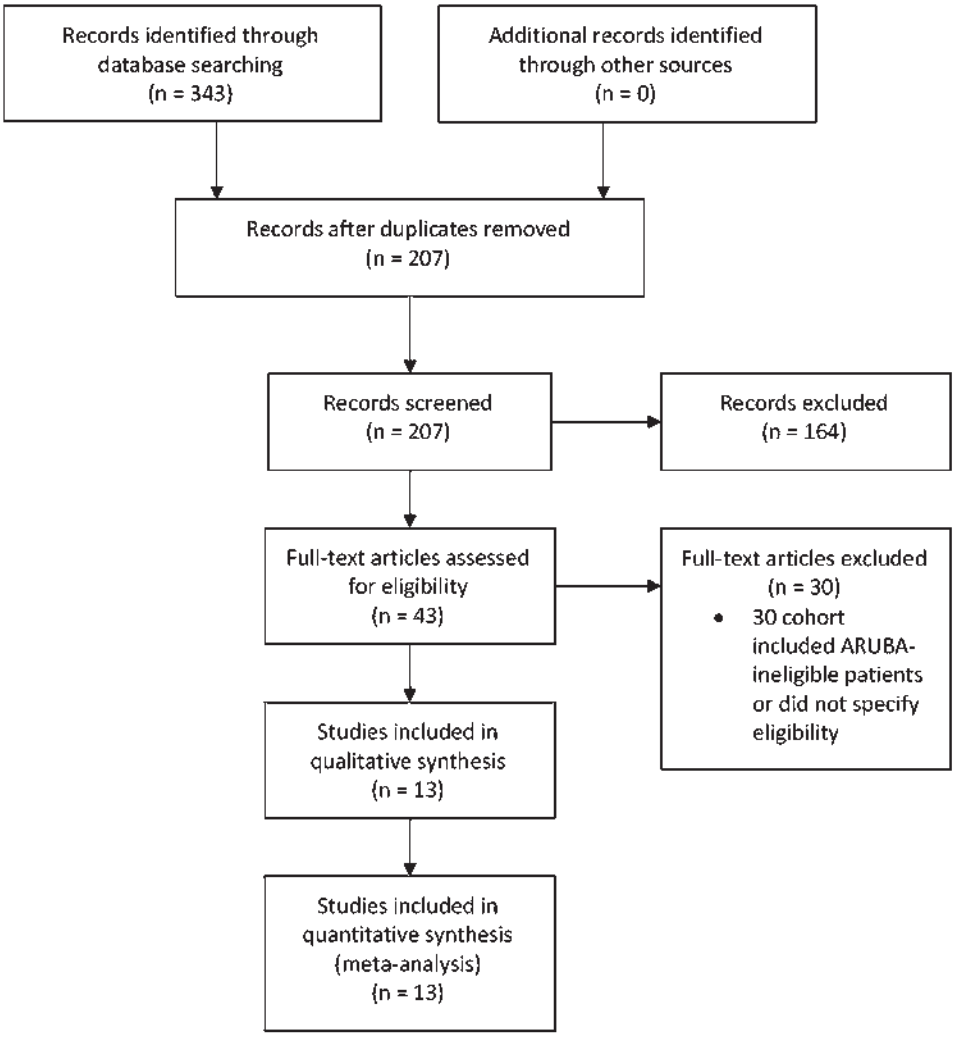


**FIG. 1.** PRISMA flow diagram.

(pooled = 41.1 years, 95% CI 40.2–42.1 years). The clinical presentations were seizures, headache, focal neurological deficit, other symptoms, and asymptomatic in 33.2% (pooled = 38%, 95% CI 31%–46%), 30.8% (pooled = 31%, 95% CI 21%–42%), 11.9% (pooled = 10%, 95% CI 4%–17%), 10.9% (pooled = 9%, 95% CI 2%–21%), and 31.8% (pooled = 24%, 95% CI 12%–39%), respectively. The baseline mRS scores were 0 and 1 in 54.4% (pooled = 52%, 95% CI 39%–64%) and 45.5% (pooled = 48%, 95% CI 35%–60%), respectively.

Table 2 summarizes the crude and pooled estimates of baseline AVM characteristics. The SM grades were I, II, III, IV, and V AVMs in 28.9% (pooled = 16%, 95% CI 12%–21%), 36.8% (pooled = 37%, 95% CI 34%–39%), 37.6% (pooled = 34%, 95% CI 29%–39%), 9.9% (pooled = 10%, 95% CI 8%–13%), and 0.5% (pooled = 0%, 95% CI 0%–1%), respectively. The mean maximum AVM diameter was 2.6 cm (pooled = 2.7 cm, 95% CI 2.2–3.3 cm), and maximum diameter was < 3 cm in 52.5% of cases (pooled = 51%, 95% CI 45%–58%). AVMs localized to the left side, eloquent brain regions, lobar parenchyma, and the infratentorial compartment in 53.9% (pooled = 54%, 95% CI 50%–58%), 62.4% (pooled = 61%, 95% CI 54%–67%), 69.1% (pooled = 81%, 95% CI 66%–93%), and 11.4% (pooled = 8%, 95% CI 4%–13%) of the patients, respectively. The incidences of AVM-associated arterial aneurysms, exclusively superficial venous drainage, and any component of deep venous drainage were 13.1% (pooled = 14%, 95% CI 10%–19%), 56.9% (pooled = 64%, 95% CI 54%–73%), and 43.1% (pooled = 36%, 95% CI 27%–46%), respectively.

### ARUBA-Eligible Interventions and Posttreatment Outcomes

Table 3 summarizes the crude and pooled estimates of interventions and posttreatment outcomes. The interventional approaches were surgery with or without embolization, SRS with or without embolization, combined surgery and SRS with or without embolization, and embolization alone in 18.8% (pooled = 30%, 95% CI 10%–57%), 78.5% (pooled = 63%, 95% CI 36%–87%), 0.5% (pooled = 0%, 95% CI 0%–1%), and 2.1% (pooled = 1%, 95% CI

**TABLE 1. Crude and pooled estimates of baseline ARUBA-eligible patient characteristics**

| Authors & Year | No. of Patients | No. of Centers | Mean Age in Years (SD) | No. of Females | Clinical Presentation (no. of patients) | | | | | Baseline mRS Score (no. of patients) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Seizure | Headache | Focal Neurological Deficit | Other | Asymptomatic | 0 | 1 |
| Pulli et al., 2019[13] | 142 | 1 | 39.7 (16.3) | 75 | 41 | — | — | 58 | 43 | 103 | 39 |
| Kim et al., 2019[15] | 264 | 1 | 40.7 (12) | 98 | 66 | 80 | 44 | 29 | 92 | — | — |
| Tonetti et al., 2018[16] | 233 | 1 | 41.7 | 129 | 99 | 96 | 23 | 5 | 23 | — | — |
| Maruyama et al., 2018[17] | 75 | 1 | 40.8 (13.9) | 31 | 19 | 0 | 1 | 0 | 69 | 45 | 30 |
| Link et al., 2018[7] | 86 | 1 | 43.6 (14.6) | 41 | 35 | 44 | — | 44 | 9 | — | — |
| Lang et al., 2018[18] | 105 | 1 | 43 (1.3) | 62 | 35 | 57 | 45 | — | — | — | — |
| Singfer et al., 2017[19] | 61 | 1 | 38 (11) | 29 | 25 | 19 | 5 | — | 9 | 16 | 45 |
| Schramm et al., 2017[20] | 104 | 2 | 38.4 | 48 | 65 | — | — | — | — | — | — |
| Javadpour et al., 2016[21] | 34 | 1 | 39 (13) | 18 | 23 | 7 | 1 | 0 | 5 | — | — |
| Ding et al., 2016[22] | 509 | 7 | 39.7 (13.7) | 238 | 103 | 86 | 36 | 10 | 252 | — | — |
| Nerva et al., 2015[23] | 61 | 1 | 40 (15) | 29 | 24 | 27 | 12 | 0 | 12 | 29 | 32 |
| Rutledge et al., 2014[24] | 61 | 1 | 41 | 27 | 28 | 19 | 0 | 14 | 0 | 33 | 27* |
| Pollock et al., 2013[25] | 174 | 1 | 42.5 (33–50)† | 94 | 70 | 77 | — | — | 27 | 86 | 88 |
| Pooled estimate‡ | — | — | 41.1 (40.2–42.1) | 49% (45%–52%) | 38% (31%–46%) | 31% (21%–42%) | 10% (4%–17%) | 9% (2%–21%) | 24% (12%–39%) | 52% (39%–64%) | 48% (35%–60%) |
| Crude estimate | 1909 | — | 40.7 | 919/1909 (48.1%) | 633/1909 (33.2%) | 512/1663 (30.8%) | 167/1403 (11.9%) | 160/1465 (10.9%) | 541/1700 (31.8%) | 312/574 (54.4%) | 261/574 (45.5%) |

* mRS data missing for 1 patient.
† Median (range).
‡ Pooled means and proportions with corresponding 95% confidence intervals.

**TABLE 2. Crude and pooled estimates of baseline ARUBA-eligible AVM characteristics**

| Authors & Year | SM Grade (no. of patients) | | | | | Mean Max AVM Diameter in cm (SD) | No. w/ Max AVM Diameter <3 cm | AVM Location (no. of patients) | | | | No. w/ Associated Arterial Aneurysm | Venous Drainage (no. of patients) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | | | Lt Side | Lobar | Infratentorial | Eloquent Region | | Superficial Only | Any Deep |
| Pulli et al., 2019[13] | 33 | 55 | 40 | 14 | 0 | 2.55 (1.2) | — | 79 | 121 | 11 | 76 | 14 | 91 | 51 |
| Kim et al., 2019[15] | 52 | 87 | 87 | 38 | 0 | 3.6 (1.6) | — | — | 238 | 8 | 121 | 53 | 199 | 65 |
| Tonetti et al., 2018[16] | 12 | 92 | 109 | 19 | 0 | — | 134 | 125 | — | 17 | 169 | 22 | 146 | 87 |
| Maruyama et al., 2018[17] | 19 | 32 | 19 | 4 | 1 | — | 24 | — | 67 | 5 | 32 | — | 49 | 26 |
| Link et al., 2018[7] | 16 | 35 | 29 | 6 | 0 | 2.7 (1.2) | 52 | 44 | — | 6 | 59 | 15 | 63 | 23 |
| Lang et al., 2018[18] | 15 | 31 | 35 | 23 | 1 | — | 55 | — | 71 | 16 | 74 | — | 65 | 40 |
| Singfer et al., 2017[19] | 11 | 20 | 21 | 8 | 1 | — | 26 | — | 52 | — | 31 | — | 41 | 20 |
| Schramm et al., 2017[20] | 21 | 42 | 29 | 12 | 0 | — | 50 | — | — | — | 54 | — | 69 | 35 |
| Javadpour et al., 2016[21] | 8 | 16 | 8 | 2 | 0 | — | 23 | 19 | 31 | 3 | 19 | — | 26 | 8 |
| Ding et al., 2016[22] | 49 | 183 | 245 | 32 | 0 | 2 (0.9) | — | — | 226 | 108 | 352 | 50 | 159 | 350 |
| Nerva et al., 2015[23] | 6 | 25 | 20 | 7 | 3 | 2.9 (1.8) | — | — | 54 | 4 | 42 | 15 | 36 | 25 |
| Rutledge et al., 2014[24] | 9 | 21 | 21 | 7 | 3 | 3.4 | 25 | — | 47 | 1 | 37 | — | 42 | 19 |
| Pollock et al., 2013[25] | 85 (I & II)* | — | 55 | 34 (IV & V)* | — | 2.7 (2.1–3.5)† | 101 | — | — | — | 126 | — | 100 | 74 |
| Pooled estimate‡ | 16% (12%–21%) | 37% (34%–39%) | 34% (29%–39%) | 10% (8%–13%) | 0% (0%–1%) | 2.7 (2.2–3.3) | 51% (45%–58%) | 54% (50%–58%) | 81% (66%–93%) | 8% (4%–13%) | 61% (54%–67%) | 14% (10%–19%) | 64% (54%–73%) | 36% (27%–46%) |
| Crude estimate | 502/1735 (28.9%) | 639/1735 (36.8%) | 718/1909 (37.6%) | 172/1735 (9.9%) | 9/1735 (0.5%) | 2.6 | 490/933 (52.5%) | 267/495 (53.9%) | 907/1312 (69.1%) | 179/1570 (11.4%) | 1192/1909 (62.4%) | 169/1295 (13.1%) | 1086/1909 (56.9%) | 823/1909 (43.1%) |

* Excluded from crude estimates.
† Median (range).
‡ Pooled means and proportions with corresponding 95% confidence intervals.

**TABLE 3. Crude and pooled estimates of ARUBA-eligible interventions and posttreatment outcomes**

| | Intervention (no. of patients) | | | | | | No. of Patients | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors & Year | Surgery ± Embol | SRS ± Embol | Embol Alone | Surgery + SRS ± Embol | Mean FU in mos (SD) | No. w/ Major Complication | AVM Obliteration | Primary Outcome | Hemorrhagic Stroke | Ischemic Stroke | Any Stroke | Death | Poor Outcome |
| Pulli et al., 2019[13] | 34 | 99 | 7 | 2 | 61 (42) | 9 | 81 | 13 | — | — | — | 3 | 13 |
| Kim et al., 2019[15] | 0 | 264 | 0 | 0 | 55.5 (39.9) | 38 | 164 | 37 | 28 | 9 | 37 | 1 | — |
| Tonetti et al., 2018[16] | 0 | 233 | 0 | 0 | 100.8 | — | 168 | 32 | 26 | — | — | 22 | — |
| Maruyama et al., 2018[17] | 14 | 61 | 0 | 0 | 64.2 (40.4) | — | 57 | 9 | 9 | — | — | 1 | 5 |
| Link et al., 2018[7] | 56 | 22 | 8 | 0 | — | 3 | 81 | 7 | 5 | 2 | 7 | 1 | 3 |
| Lang et al., 2018[18] | 42 | 58 | 0 | 5 | 43 | 26 | 71 | 8 | 5 | 1 | 6 | 4 | — |
| Singfer et al., 2017[19] | 1 | 34 | 25 | 1 | 60 (29–91)* | — | 44 | 12 | 9 | 3 | 12 | 5 | 14 |
| Schramm et al., 2017[20] | 104 | 0 | 0 | 0 | — | 8 | 103 | — | — | — | — | 0 | 10 |
| Javadpour et al., 2016[21] | 34 | 0 | 0 | 0 | 69 (6–126)* | 5 | 34 | 0 | 0 | 0 | 0 | 0 | 2 |
| Ding et al., 2016[22] | 0 | 509 | 0 | 0 | 86.2 (62.3) | 57 | 382 | — | 32 | — | 32 | 22 | — |
| Nerva et al., 2015[23] | 31 | 30 | 0 | 0 | 25.2 | 20 | 44 | — | — | — | — | 0 | 8 |
| Rutledge et al., 2014[24] | 43 | 15 | 1 | 2 | 21 | — | 43 | 9 | — | — | — | 3 | 8 |
| Pollock et al., 2013[25] | 0 | 174 | 0 | 0 | 64* | — | 115 | 20 | 15 | 0 | 15 | 4 | 16 |
| Pooled estimate† | 30% (10%–57%) | 63% (36%–87%) | 1% (0%–4%) | 0% (0%–1%) | 62 (51.7–73.4) | 13% (8%–18%) | 78% (70%–85%) | 11% (8%–13%) | 8% (6%–11%) | 1% (0%–4%) | 8% (5%–12%) | 2% (1%–4%) | 10% (7%–13%) |
| Crude estimate | 359/1909 (18.8%) | 1499/1909 (78.5%) | 41/1909 (2.1%) | 10/1909 (0.5%) | 70.9 | 166/1305 (12.7%) | 1387/1909 (72.7%) | 138/1235 (11.2%) | 129/1541 (8.4%) | 15/724 (2.1%) | 94/1233 (7.6%) | 66/1909 (3.5%) | 79/798 (9.9%) |

Embol = embolization; FU = follow-up.
* Median (range).
† Pooled means and proportions with corresponding 95% confidence intervals.

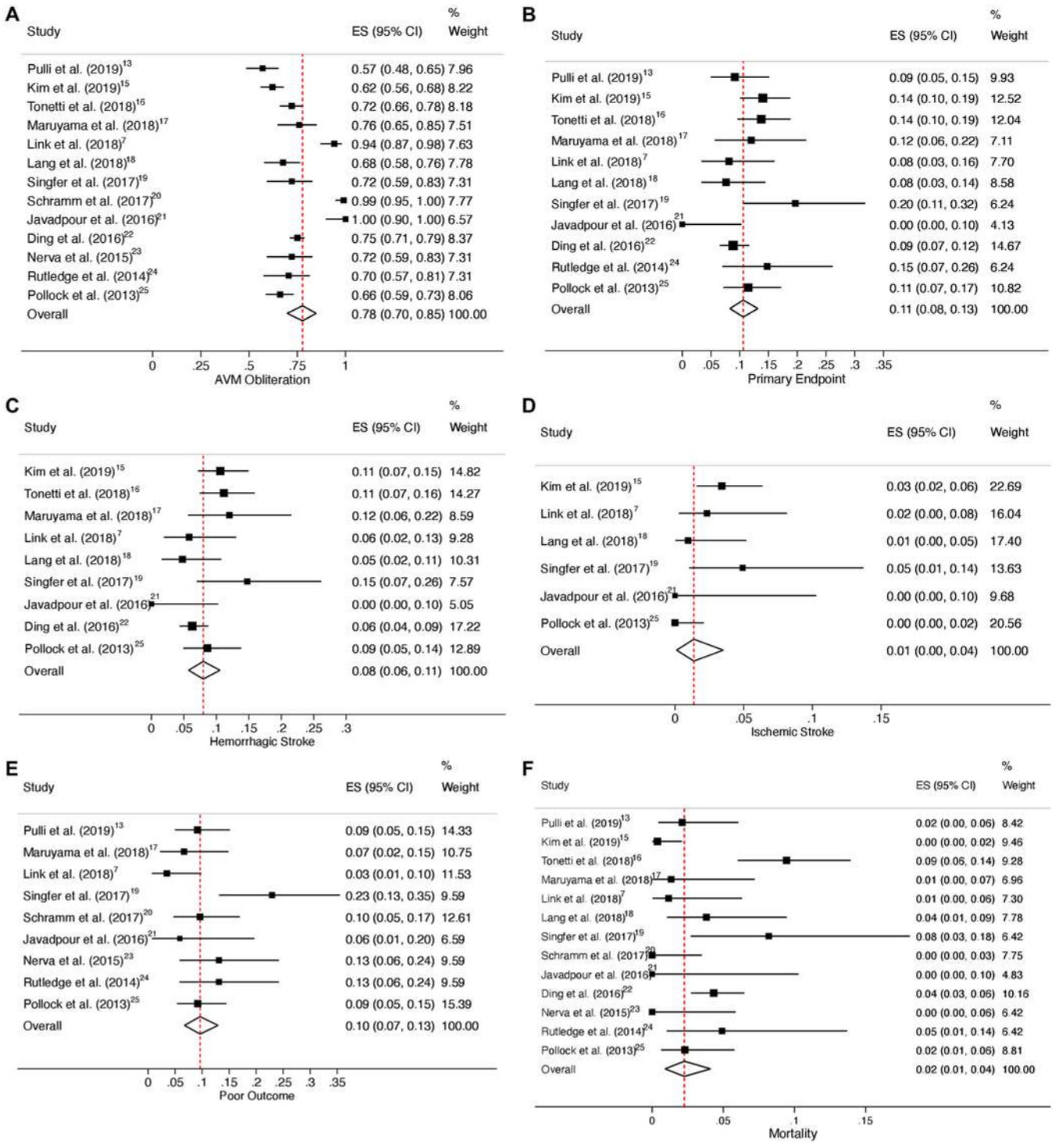


**FIG. 2.** Pooled rate estimates for AVM obliteration (**A**), primary outcome (**B**), hemorrhage (**C**), ischemic stroke (**D**), poor outcome (**E**), and death (**F**) after intervention for ARUBA-eligible patients. ES = effect size. Figure is available in color online only.

0%–4%), respectively. The major complication rate was 12.7% (pooled = 13%, 95% CI 8%–18%). Mean follow-up duration was 70.9 months (pooled = 62 months, 95% CI 51.7–73.4 months). AVM obliteration was achieved in 72.7% of patients (pooled = 78%, 95% CI 70%–85%; Fig. 2A), and the primary outcome occurred in 11.2% of patients (pooled = 11%, 95% CI 8%–13%; Fig. 2B). Rates of hemorrhagic stroke, ischemic stroke, poor outcome, and mortality were 8.4% (pooled = 8%, 95% CI 6%–11%; Fig. 2C), 2.1% (pooled = 1%, 95% CI 0%–4%; Fig. 2D), 9.9% (pooled = 10%, 95% CI 7%–13%; Fig. 2E), and 3.5% (pooled = 2%, 95% CI 1%–4%; Fig. 2F), respectively.

**TABLE 4. Crude and pooled estimates of annualized interventional outcome rates in ARUBA-eligible patients**

| Authors & Year | Annualized Rate (per 100 patient-yrs) | | |
|---|---|---|---|
| | Primary Outcome | Hemorrhage | Death |
| Pulli et al., 2019[13] | 1.80 | 1.8* | 0.42 |
| Kim et al., 2019[15] | 3.03 | 2.29† | 0.08 |
| Tonetti et al., 2018[16] | 1.63 | 1.33 | 1.12 |
| Maruyama et al., 2018[17] | 2.24 | 2.24 | 0.25 |
| Link et al., 2018[7] | — | — | — |
| Lang et al., 2018[18] | 2.13 | 1.33 | 1.06 |
| Singfer et al., 2017[19] | 3.93 | 2.95 | 1.64 |
| Schramm et al., 2017[20] | — | — | 0‡ |
| Javadpour et al., 2016[21] | 0 | 0 | 0 |
| Ding et al., 2016[22] | 1.23 | 0.88 | 0.60 |
| Nerva et al., 2015[23] | — | — | 0 |
| Rutledge et al., 2014[24] | 8.43 | — | 2.81 |
| Pollock et al., 2013[25] | — | 2§ | — |
| Pooled estimate (95% CI) | 2.05 (1.31–2.94) | 1.41 (0.83–2.13) | 0.50 (0.20–0.91) |
| Crude estimate | 1.85 | 1.34 | 0.67 |

* Includes hemorrhagic and ischemic stroke; excluded from pooled and crude estimates.
† For the first 3 years, 3.2 hemorrhages per 100 patient-years.
‡ Excluded from pooled and crude estimates because of a lack of follow-up duration data.
§ Two hemorrhages per 100 patient-years for the first 5 years, declining to 0.2 hemorrhages per 100 patient-years thereafter. Excluded from pooled and crude estimates because of a lack of follow-up duration data.

Table 4 summarizes the crude and pooled estimates of annualized interventional outcome rates. Annualized rates for the primary outcome, hemorrhage, and death were 1.85 (pooled = 2.05, 95% CI 1.31–2.94; Supplemental Fig. 1A), 1.34 (pooled = 1.41, 95% CI 0.83–2.13; Supplemental Fig. 1B), and 0.67 (pooled = 0.50, 95% CI 0.20–0.91; Supplemental Fig. 1C) per 100 patient-years, respectively. The pooled annualized posttreatment primary outcome rate of ARUBA-eligible patients was lower than the primary outcome rates of both the medical management and interventional arms of ARUBA (Fig. 3A and C). The pooled annualized posttreatment hemorrhage rate of ARUBA-eligible patients was also lower than the hemorrhage rates of both the ARUBA medical management and interventional arms, and it was similar to unruptured AVM hemorrhage rates reported by natural history studies (Fig. 3B and D).[30,31] The pooled annualized posttreatment mortality rate was similar to the mortality rates of both the ARUBA medical management and interventional arms (Fig. 3E).[30,31] Head-to-head comparisons of baseline data and outcomes among ARUBA, natural history studies, and the present analysis can be found in Supplemental Table 3.

### Outcomes After SRS or Surgery With or Without Embolization for ARUBA-Eligible Patients

Table 5 summarizes the crude and pooled estimates of outcomes for ARUBA-eligible patients treated with SRS with or without embolization and those treated with surgery with or without embolization. SRS with or without embolization was performed in 1180 ARUBA-eligible patients. The major complication rate was 12.3% (pooled = 12%, 95% CI 10%–15%). Mean follow-up duration was 81.5 months (pooled = 70.8 months, 95 CI 40.7–100.9 months). AVM obliteration was achieved in 70.3% of patients (pooled = 69%, 95% CI 63%–75%), and the primary outcome occurred in 13.3% of patients (pooled = 12%, 95% CI 9%–15%). Rates of hemorrhagic stroke, ischemic stroke, poor outcome, and death were 8.6% (pooled = 9%, 95% CI 6%–12%), 2.1% (pooled = 1%, 95% CI 0%–3%), 9.2% (pooled = 9%, 95% CI 5%–15%), and 4.2% (pooled = 3%, 95% CI 1%–8%), respectively. Estimated annualized rates for the primary outcome, hemorrhage, and death were 1.67 (pooled = 1.85, 95% CI 1.03–2.90), 1.26 (pooled = 1.40, 95% CI 0.74–2.26), and 0.66 (pooled = 0.53, 95% CI 0.13–1.18) per 100 patient-years, respectively.

Surgery with or without embolization was performed in 138 ARUBA-eligible patients. The major complication rate was 9.4% (pooled = 9%, 95% CI 5%–15%). Mean follow-up duration was 69 months (pooled = 69 months, 95% CI 58.9–79.1 months). AVM obliteration was achieved in 99.3% of patients (pooled = 100%, 95% CI 97%–100%), and the primary outcome occurred in 0% of patients (pooled = 0%, 95% CI 0%–10%). Rates of hemorrhagic stroke, ischemic stroke, and death were each 0% (pooled = 0%, 95% CI 0%–10%), and poor outcome occurred in 8.7% of patients (pooled = 8%, 95% CI 4%–14%). Estimated annualized rates for the primary outcome, hemorrhage, and death were each 0 (pooled = 0, 95% CI 0–1.93).

## Discussion

### Results in the Context of ARUBA

The findings of ARUBA cast doubts on the benefit of intervention for unruptured AVMs.[9,10] However, the trial has also drawn many criticisms for the methodology of its intervention arm. Accordingly, misgivings about the generalizability of ARUBA's conclusions have spurred multiple independent studies that have sought to refute the conclusions of ARUBA by reporting real-world results of intervention for unruptured AVMs. In the current systematic review and meta-analysis, we consolidated the results of studies of ARUBA-eligible patients to allow for plausible comparisons with the findings of ARUBA and natural history studies of unruptured AVMs. Although patient demographics and baseline mRS score distributions of the pooled data were similar to those of ARUBA, distributions of clinical presentations were different. Specifically, ARUBA had more asymptomatic patients (45% and 39% in ARUBA medical management and interventional arms, respectively, vs 24%, 95% CI 12%–39% in this meta-analysis) and more patients with headaches (55% and 48% in ARUBA medical management and interventional arms, respectively, vs 31%, 95% CI 21%–42% in meta-analysis). Our study had more eloquent AVMs (61%, 95% CI 54%–67% in meta-analysis vs 47% in each ARUBA medical management and interventional arm) and left-sided AVMs (54%, 95% CI 50%–58% in meta-analysis vs 46% and 43% in ARUBA medical management and interventional arms,

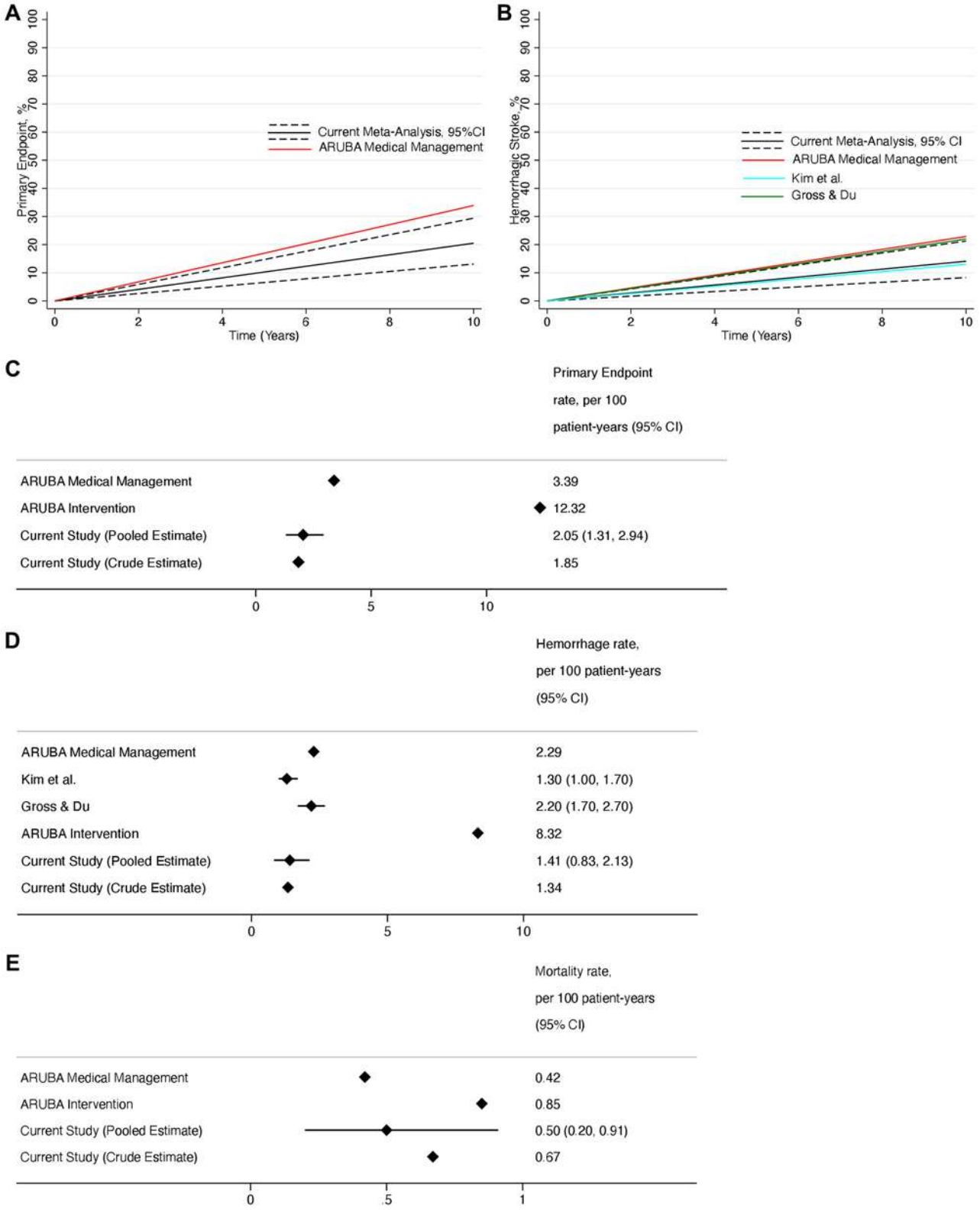


**FIG. 3. A:** Comparison of pooled annualized primary outcome rate of current meta-analysis versus annualized primary endpoint rate of ARUBA medical management arm. **B:** Comparison of pooled annualized hemorrhage rate of current meta-analysis to annualized hemorrhage rates of ARUBA medical management arm and natural history studies. **C:** Comparisons of pooled annualized primary outcome rate of current meta-analysis to annualized primary outcome rates of ARUBA medical management and interventional arms. **D:** Comparison of pooled annualized hemorrhage rate of current meta-analysis to annualized hemorrhage rate of ARUBA medical management arm, ARUBA interventional arm, and natural history studies. **E:** Comparison of pooled annualized mortality rate of current meta-analysis to annualized mortality rates of ARUBA medical management and interventional arms. Figure is available in color online only.

**TABLE 5. Crude and pooled estimates of outcomes for ARUBA-eligible patients after SRS or surgery with or without embolization**

| Authors & Year | No. of Patients | Mean FU in mos (SD) | No. of Patients | | | | | | | | Annualized Rate (per 100 patient-yrs) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Major Complication | AVM Obliteration | Primary Outcome | Hemorrhagic Stroke | Ischemic Stroke | Any Stroke | Death | Poor Outcome | Primary Outcome | Hemorrhage | Death |
| SRS ± Embol | | | | | | | | | | | | | |
| Kim et al., 2019[15] | 264 | 55.5 (39.9) | 38 | 164 | 37 | 28 | 9 | 37 | 1 | — | 3.03 | 2.29* | 0.08 |
| Tonetti et al., 2018[16] | 233 | 100.8 | — | 168 | 32 | 26 | — | — | 22 | — | 1.63 | 1.33 | 1.12 |
| Ding et al., 2016[22] | 509 | 86.2 (62.3) | 57 | 382 | — | 32 | — | 32 | 22 | — | 1.23 | 0.88 | 0.60 |
| Pollock et al., 2013[25] | 174 | 64† | — | 115 | 20 | 15 | 0 | 15 | 4 | 16 | — | 2‡ | — |
| Pooled estimates§ | — | 70.8 (40.7–100.9) | 12% (10%–15%) | 69% (63%–75%) | 12% (9%–15%) | 9% (6%–12%) | 1% (0%–3%) | 9% (5%–15%) | 3% (1%–8%) | 9% (5%–15%) | 1.85 (1.03–2.90) | 1.40 (0.74–2.26) | 0.53 (0.13–1.18) |
| Crude estimates | 1180 | 81.5 | 95/773 (12.3%) | 829/1180 (70.3%) | 89/671 (13.3%) | 101/1180 (8.6%) | 9/438 (2.1%) | 84/947 (8.9%) | 49/1180 (4.2%) | 16/174 (9.2%) | 1.67 | 1.26 | 0.66 |
| Surgery ± Embol | | | | | | | | | | | | | |
| Schramm et al., 2017[20] | 104 | — | 8 | 103 | — | — | — | — | 0 | 10 | — | — | 0¶ |
| Javadpour et al., 2016[21] | 34 | 69 (6–126)† | 5 | 34 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Pooled estimates§ | — | 69.0 (58.9–79.1) | 9% (5%–15%) | 100% (97%–100%) | 0% (0%–10%) | 0% (0%–10%) | 0% (0%–10%) | 0% (0%–10%) | 0% (0%–10%) | 8% (4%–14%) | 0 (0–1.93) | 0 (0–1.93) | 0 (0–1.93) |
| Crude estimates | 138 | 69 | 13/138 (9.4%) | 137/138 (99.3%) | 0 | 0 | 0 | 0 | 0 | 12/138 (8.7%) | 0 | 0 | 0 |

* For the first 3 years, 3.2 hemorrhages per 100 patient-years.
† Median (range).
‡ Two hemorrhages per 100 patient-years for the first 5 years, declining to 0.2 hemorrhages per 100 patient-years thereafter. Excluded from pooled and crude estimates given a lack of follow-up duration data.
§ Pooled means and proportions with corresponding 95% confidence intervals.
¶ Excluded from pooled and crude estimates given a lack of follow-up duration data.

respectively), but the remaining AVM characteristics were similar between the baseline data sets.

### Intervention Modalities

Intervention profiles were drastically different between our meta-analysis and ARUBA, particularly with regard to the use of embolization monotherapy (1%, 95% CI 0%–4% in meta-analysis vs 26% of ARUBA as-treated cohort). We believe this discrepancy could have contributed to ARUBA's modest obliteration rate of 44%, which was lower than the 78% (95% CI 70%–85%) obliteration rate of ARUBA-eligible patients in our study. Embolization is generally regarded as an adjunctive rather than a definitive AVM therapy in the United States.[32] Curative embolization can incur relatively high complication rates, and this was demonstrated by ARUBA, wherein embolization monotherapy afforded equal rates (50%) of obliteration and the primary outcome (i.e., death or symptomatic stroke).[10] The risk of the primary outcome in ARUBA patients who had undergone embolization monotherapy was much higher than the risk of permanent neurological deficit or death (6.6%) reported in a meta-analysis of AVM embolization outcomes.[33] Therefore, this subset of ARUBA patients was exposed to an elevated upfront risk of complications without a reasonable likelihood of subsequent obliteration.

### AVM Outcomes

The obliteration rate of SRS monotherapy in ARUBA (18%) was alarmingly lower than the pooled obliteration rate of SRS studies with ARUBA-eligible patients (69%, 95% CI 63%–75%). This broad gap between SRS outcomes could be attributed to multiple potential factors, including the shorter follow-up duration of ARUBA, lower utilization of catheter angiography to confirm obliteration in ARUBA-eligible studies, and selection differences in nidus characteristics, SRS dose, and SRS technique. In addition to the lower overall and treatment-specific obliteration rates in ARUBA, the primary outcome rate of the trial's intervention arm (35%) was higher than that of our meta-analysis (11%, 95% CI 8%–13%). The ARUBA intervention arm also had higher annualized primary outcome (12.32 vs 2.05, 95% CI 1.31–2.94 per 100 patient-years) and hemorrhage (8.32 vs 1.41, 95% CI 0.83–2.13 per 100 patient-years) rates as well as a higher probability of a poor outcome (38% vs 10%, 95% CI 7%–13%). Thus, intervention for ARUBA-eligible patients concomitantly provided lower adverse outcome and higher success rates than the ARUBA intervention arm.

Our meta-analysis also demonstrated outcomes similar or better than those of the ARUBA medical management arm. The overall primary outcome (11%, 95% CI 8%–13% in meta-analysis vs 14% in ARUBA medical management) and hemorrhage (8%, 95% CI 6%–11% in meta-analysis vs 10% in ARUBA medical management) rates were comparable, but ARUBA-eligible patients had lower poor outcome rates (10%, 95% CI 7%–13% vs 18%) and lower annualized rates of the primary outcome (2.05, 95% CI 1.31–2.94 vs 3.39 per 100 patient-years) and hemorrhage (1.41, 95% CI 0.83–2.13 vs 2.29 per 100 patient-years) than patients in the ARUBA medical management arm. Additionally, the annualized hemorrhage risk of ARUBA-eligible patients in our meta-analysis was similar to those reported in the natural history studies by Kim et al. (1.30, 95% CI 1.00–1.70) and Gross and Du (2.20, 95% CI 1.70–2.70).[30,31] However, we acknowledge that pooled and annualized rates in the present meta-analysis did not distinguish periprocedural stroke or death from subsequent AVM-associated hemorrhage secondary to a lack of obliteration. The upfront risk of AVM intervention is expected to be higher and the risk of postobliteration hemorrhage is expected to be lower than the calculated annualized risk.[13] Thus, we would expect the annualized hemorrhage rates of treated versus untreated unruptured AVMs to diverge over longer follow-up periods. However, the granularity of the study-level data did not permit such analysis.

These findings indicate that intervention may be considered for unruptured AVMs in appropriately selected patients. Younger patients, those with few medical comorbidities, symptomatic cases, SM grade I–II lesions, and lesions in noneloquent locations may be candidates for intervention.[7,17,20,21] Patients with AVMs in deep or eloquent locations, as well as those with significant comorbidities, may benefit from SRS or embolization.[7,17,18,20,21] The presence of favorable and unfavorable factors for intervention must be weighed against each other in multidisciplinary consultation to create an individualized plan for each case.

### Study Limitations

The limitations of the current study should be recognized. Since this was a study-level meta-analysis, examination of individual patient data and generation of Kaplan-Meier plots for comparison with the ARUBA results were precluded. A lack of individual patient data from both the pooled studies and ARUBA also prohibited any direct comparisons of outcomes. In the absence of granular patient-level data, we were unable to provide time-dependent analyses of outcomes, so we instead extrapolated annualized and overall event rates for comparisons. Furthermore, there was significant heterogeneity among the included studies with respect to intervention modalities and AVM characteristics, including SM grade. Indeed, both ARUBA and the studies analyzed herein demonstrated the need for more granular reporting of AVM outcomes based on intervention modality and nidal characteristics, as these are significant determinants of patient outcome. Given the retrospective nature of the included studies, risks of bias were ranked as high for all bias categories.

The limited number of studies and heterogeneous reporting did not allow for rigorous subgroup analyses by individual and combined interventional modalities. For example, only 2 studies reported sufficient data to compare primary outcome rates by SM grade (9% for grades I–II vs 14.9% for grades III–IV; Supplemental Table 4). Differences in baseline patient and AVM characteristics between our meta-analysis and ARUBA may contribute to the differences in outcomes. Although patients in each of the studies included in our review met the eligibility criteria for ARUBA, it is unclear whether these patients would have been deemed to have equipoise for either intervention or medical management in the trial itself. We were unable to eliminate publication bias from the analyses since centers with favorable results were likely more inclined to

publish their results with the intent of reporting outcomes superior to those of ARUBA. Ongoing trials and observational studies, including the Treatment of Brain AVMs (TOBAS) study and Multicenter AVM Research Study (MARS), could clarify the role of intervention in the contemporary management of unruptured AVMs.[34,35]

## Conclusions

ARUBA-eligible patients who had undergone intervention had lower rates of adverse outcomes and higher rates of obliteration than patients in the ARUBA intervention arm. The annual hemorrhage risk of ARUBA-eligible patients following intervention compared favorably with those of the ARUBA medical management arm and natural history studies. Thus, this meta-analysis indicates that intervention can afford a reasonable risk-to-benefit profile for appropriately selected patients with unruptured AVMs. Future studies from prospective registries are necessary to refine the patient, nidus, and intervention selection criteria that will optimize the long-term outcomes of patients with unruptured AVM.

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## References

1. Can A, Gross BA, Du R. The natural history of cerebral arteriovenous malformations. *Handb Clin Neurol*. 2017;143:15-24.
2. Hanakita S, Shin M, Koga T, Igaki H, Saito N. Risk reduction of cerebral stroke after stereotactic radiosurgery for small unruptured brain arteriovenous malformations. *Stroke*. 2016;47(5):1247-1252.
3. Pabaney AH, Reinard KA, Massie LW, Naidu PK, Mohan YS, Marin H, Malik GM. Management of perisylvian arteriovenous malformations: a retrospective institutional case series and review of the literature. *Neurosurg Focus*. 2014;37(3):E13.
4. Corniola MV, Meling TR, Bijlenga P, Bernava G, Machi P, Schaller K. Posterior fossa arteriovenous malformations: experience with 14 patients and a systematic review of the literature. *J Neurol Surg A Cent Eur Neurosurg*. 2020;81(2):170-176.
5. Chen CJ, Ding D, Wang TR, Buell TJ, Ilyas A, Ironside N, et al. Microsurgery versus stereotactic radiosurgery for brain arteriovenous malformations: a matched cohort study. *Neurosurgery*. 2019;84(3):696-708.
6. Cenzato M, Tartara F, D'Aliberti G, Bortolotti C, Cardinale F, Ligarotti G, et al. Unruptured versus ruptured AVMs: outcome analysis from a multicentric consecutive series of 545 surgically treated cases. *World Neurosurg*. 2018;110:e374-e382.
7. Link TW, Winston G, Schwarz JT, Lin N, Patsalides A, Gobin P, et al. Treatment of unruptured brain arteriovenous malformations: a single-center experience of 86 patients and a critique of the A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) trial. *World Neurosurg*. 2018;120:e1156-e1162.
8. Chen CJ, Ding D, Derdeyn CP, Lanzino G, Friedlander RM, Southerland AM, et al. Brain arteriovenous malformations: a review of natural history, pathobiology, and interventions. *Neurology*. 2020;95(20):917-927.
9. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet*. 2014;383(9917):614-621.
10. Mohr JP, Overbey JR, Hartmann A, Kummer RV, Al-Shahi Salman R, Kim H, et al. Medical management with interventional therapy versus medical management alone for unruptured brain arteriovenous malformations (ARUBA): final follow-up of a multicentre, non-blinded, randomised controlled trial. *Lancet Neurol*. 2020;19(7):573-581.
11. Feghali J, Huang J. Updates in arteriovenous malformation management: the post-ARUBA era. *Stroke Vasc Neurol*. 2019;5(1):34-39.
12. Magro E, Gentric JC, Darsaut TE, Ziegler D, Bojanowski MW, Raymond J. Responses to ARUBA: a systematic review and critical analysis for the design of future arteriovenous malformation trials. *J Neurosurg*. 2017;126(2):486-494.
13. Pulli B, Chapman PH, Ogilvy CS, Patel AB, Stapleton CJ, Leslie-Maszwi TM, et al. Multimodal cerebral arteriovenous malformation treatment: a 12-year experience and comparison of key outcomes to ARUBA. *J Neurosurg*. 2020;133(6):1792-1801.
14. Starke RM, Sheehan JP, Ding D, Liu KC, Kondziolka D, Crowley RW, et al. Conservative management or intervention for unruptured brain arteriovenous malformations. *World Neurosurg*. 2014;82(5):e668-e669.
15. Kim BS, Yeon JY, Kim JS, Hong SC, Shin HJ, Lee JI. Gamma Knife radiosurgery for ARUBA-eligible patients with unruptured brain arteriovenous malformations. *J Korean Med Sci*. 2019;34(36):e232.
16. Tonetti DA, Gross BA, Atcheson KM, Jankowitz BT, Kano H, Monaco EA, et al. The benefit of radiosurgery for ARUBA-eligible arteriovenous malformations: a practical analysis over an appropriate follow-up period. *J Neurosurg*. 2018;128(6):1850-1854.
17. Maruyama D, Satow T, Kataoka H, Mori H, Hamano E, Orita Y, et al. Multimodal interventional treatment and outcomes for unruptured arteriovenous malformations. *Acta Neurochir Suppl (Wien)*. 2018;129:115-120.
18. Lang M, Moore NZ, Rasmussen PA, Bain MD. Treatment outcomes of A Randomized Trial of Unruptured Brain Arteriovenous Malformation-eligible unruptured brain arteriovenous malformation patients. *Neurosurgery*. 2018;83(3):548-555.
19. Singfer U, Hemelsoet D, Vanlangenhove P, Martens F, Verbeke L, Van Roost D, Defreyne L. Unruptured brain arteriovenous malformations: primary ONYX embolization in ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-eligible patients. *Stroke*. 2017;48(12):3393-3396.
20. Schramm J, Schaller K, Esche J, Boström A. Microsurgery for cerebral arteriovenous malformations: subgroup outcomes in a consecutive series of 288 cases. *J Neurosurg*. 2017;126(4):1056-1063.
21. Javadpour M, Al-Mahfoudh R, Mitchell PS, Kirollos R. Outcome of microsurgical excision of unruptured brain arteriovenous malformations in ARUBA-eligible patients. *Br J Neurosurg*. 2016;30(6):619-622.
22. Ding D, Starke RM, Kano H, Mathieu D, Huang P, Kondziolka D, et al. Radiosurgery for cerebral arteriovenous malformations in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)-eligible patients: a multicenter study. *Stroke*. 2016;47(2):342-349.
23. Nerva JD, Mantovani A, Barber J, et al. Treatment outcomes of unruptured arteriovenous malformations with a subgroup analysis of ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-eligible patients. *Neurosurgery*. 2015;76(5):563-570.
24. Rutledge WC, Abla AA, Nelson J, Halbach VV, Kim H, Law-

ton MT. Treatment and outcomes of ARUBA-eligible patients with unruptured brain arteriovenous malformations at a single institution. *Neurosurg Focus*. 2014;37(3):E8.
25. Pollock BE, Link MJ, Brown RD. The risk of stroke or clinical impairment after stereotactic radiosurgery for ARUBA-eligible patients. *Stroke*. 2013;44(2):437-441.
26. Hong CS, Peterson EC, Ding D, Sur S, Hasan D, Dumont AS, et al. Intervention for A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)–eligible patients: an evidence-based review. *Clin Neurol Neurosurg*. 2016;150:133-138.
27. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65(4):476-483.
28. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
29. Wong J, Slomovic A, Ibrahim G, Radovanovic I, Tymianski M. Microsurgery for ARUBA Trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformation)-eligible unruptured brain arteriovenous malformations. *Stroke*. 2017;48(1):136-144.
30. Kim H, Al-Shahi Salman R, McCulloch CE, Stapf C, Young WL. Untreated brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors. *Neurology*. 2014;83(7):590-597.
31. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: a meta-analysis. *J Neurosurg*. 2013;118(2):437-443.
32. Derdeyn CP, Zipfel GJ, Albuquerque FC, Cooke DL, Feldmann E, Sheehan JP, Torner JC. Management of brain arteriovenous malformations: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48(8):e200-e224.
33. van Beijnum J, van der Worp HB, Buis DR, Al-Shahi Salman R, Kappelle LJ, Rinkel GJ, et al. Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. *JAMA*. 2011;306(18):2011-2019.
34. Darsaut TE, Magro E, Gentric JC, Batista AL, Chaalala C, Roberge D, et al. Treatment of Brain AVMs (TOBAS): study protocol for a pragmatic randomized controlled trial. *Trials*. 2015;16:497.
35. Kim H, Al-Shahi Salman Rustam, Flemming Kelly D, et al. Abstract: Long-term outcomes in unruptured brain arteriovenous malformation patients: the Multicenter Arteriovenous Malformation Research Study (MARS). *Stroke*. 2019;50(suppl 1):ATP585.

## Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

## Author Contributions

Conception and design: Ding, Chen. Acquisition of data: Snyder, Farzad, Ironside. Analysis and interpretation of data: all authors. Drafting the article: Ding, Snyder, Ironside. Critically revising the article: all authors. Reviewed submitted version of manuscript: Ding, Snyder, Chen, Ironside, Kellogg, Southerland, Park, Sheehan. Approved the final version of the manuscript on behalf of all authors: Ding. Statistical analysis: Chen. Study supervision: Ding.

## Supplemental Information

### Online-Only Content

Supplemental material is available with the online version of the article.

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