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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mohr JP, Parides MK, Stapf C, et al for the international ARUBA investigators. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet* 2013; published online Nov 20. http://dx.doi.org/10.1016/S0140-6736(13)62302-8.

A Randomized trial of Unruptured Brain AVMs (ARUBA)
Supplementary web material

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Enrollment Criteria

Inclusion Criteria

1. Patient must have unruptured BAVM diagnosed by MRI/MRA, CTA and/or angiogram
2. Patient is 18 years of age or older
3. Patient has signed Informed Consent and Release of Medical Information and Health Insurance Portability and Accountability Act (HIPPA, US-only) Forms

Exclusion Criteria

1. Patient has BAVM presenting with evidence of recent or prior hemorrhage
2. Patient has received prior BAVM therapy (endovascular, surgical, radiotherapy)
3. Patient has BAVM deemed untreatable by local team, or has concomitant vascular or brain disease that interferes with/or contraindicates any interventional therapy type (stenosis/occlusion of neck artery)
4. Patient has baseline Rankin of ≥2
5. Patient has concomitant disease/ life expectancy to less than 10 years
6. Patient has thrombocytopenia (<100,000/μL)
7. Patient has uncorrectable coagulopathy (INR>1.5)
8. Patient is pregnant or lactating
9. Patient has known allergy against iodine contrast agents
10. Patient has known multiple-foci BAVMs
11. Patient has any form of arteriovenous or spinal fistulas
12. Patient has a diagnosed Vein of Galen type malformation
13. Patient has a diagnosed cavernous malformation
14. Patient has a diagnosed dural arteriovenous fistula
15. Patient has a diagnosed developmental venous anomaly
16. Patient has a diagnosed neurocutaneous syndrome such as cerebro-retinal angiomatosis (von Hippel-Lindau), encephalo-trigeminal syndrome (Sturge-Weber), or Wyburn-Mason syndrome
17. Patient has diagnosed BAVMs in context of moya-moya-type changes
18. Patient has diagnosed hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber)

Supplementary Table S1
Synopsis of baseline characteristics of ARUBA patients and those diagnosed with an unruptured bAVM in two large population-based cohorts.

	ARUBA (N=223)	**Scotland** [1] **(N=114)**	**Finland** [2] **(N=187)**	**P**
Demographics				
Age (years)	44 (±12)	47 (±14)	36 (±15)	<0·0001
Female gender	93 (41%)	48 (42%)	80 (43%)	0·98
Clinical Presentation				
Seizure	95 (43%)	58 (51%)	n.a.	0·15
Asymptomatic	94 (42%)	44 (39%)	n.a.	0·53
Modified Rankin Score				
mRS 0	107 (48%)	14 (12%)	n.a.	<0·0001
mRS 1	116 (53%)	71 (63%)	n.a.	0·07
bAVM Morphology				
† bAVM size <3cm	138 (62%)	47 (41%)	41 (22%)*	<0·0001
Lobar AVM location, any	203 (91%)	n.a.	137 (73%)	<0·0001
Infratentorial AVM location	12 (5%)	n.a.	10 (5%)	0·98
‡ Eloquent AVM location	105 (47%)	58 (51%)	n.a.	0·51
Spetzler-Martin grade 1	65 (29%)	21 (18%)	13 (7%)	<0·0001
Spetzler-Martin grade 2	71 (32%)	27 (24%)	15 (27%)	<0·0001
Spetzler-Martin grade 3	63 (28%)	19 (17%)	61 (33%)	0·0097
Spetzler-Martin grade 4	23 (10%)	11 (10%)	46 (25%)	<0·0001
Spetzler-Martin grade 5	0	1 (1%)	14 (8%)	<0·0106
Concurrent Arterial Aneurysms				
§ Associated aneurysm, any	36 (16%)	23 (20%)	24 (13%)	0·24
Unrelated aneurysm, any	11 (5%)	11 (10%)	n.a.	0·10
Venous Drainage Pattern				
Superficial only	147 (66%)	66 (58%)	102 (55%)	0·06
Any deep	75 (34%)	48 (42%)	82 (44%)	0·08

Data are mean (SD) or number (%); n.a. = not available in published source; *Dataset available for bAVM size <25mm only

Table 4a Secondary analysis of primary endpoint event rates by Spetzler Martin grade and treatment allocation (by randomization assignment)

Spetzler–Martin grade*	Interventional Therapy (IT) (n=114)		Medical Management (MM) (n=109)		P
	N patients	N patients with events	N patients	N patients with events	
I	32	2 (6·3%)	33	4 (12·1%)	0·42
II	44	15 (34·1%)	27	2 (7·4%)	0·0105
III	28	16 (57·1%)	34	3 (8·8%)	<0·0001
IV	8	2 (25%)	15	2 (13·3%)	0·48

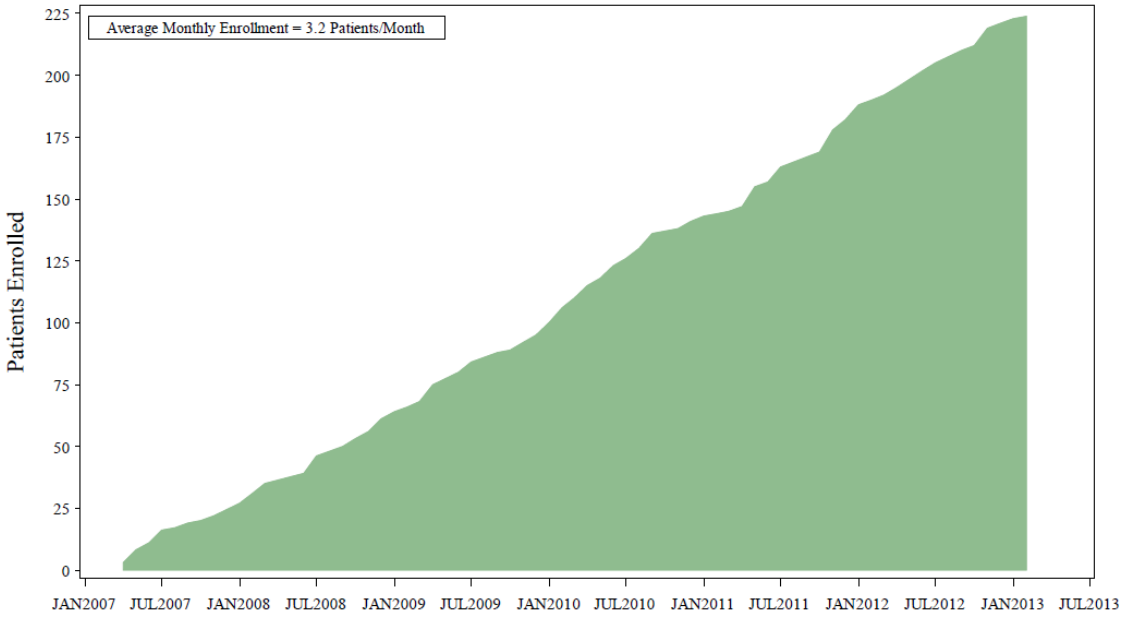
Table 4b Secondary analysis of primary endpoint event rates by Spetzler Martin grade and treatment allocation (as treated)

Spetzler– Martin grade*	Interventional Therapy (IT) (n=98)		Medical Management (MM) (n=125)		P
	N patients	N patients with events	N patients	N patients with events	
I	28	4 (14·3%)	37	2 (5·4%)	0·22
II	37	16 (43·3%)	34	1 (2·9%)	<0·0001
III	28	16 (57·1%)	34	3 (8·8%)	<0·0001
IV	5	0 (0%)	18	4 (22·2%)	0·25

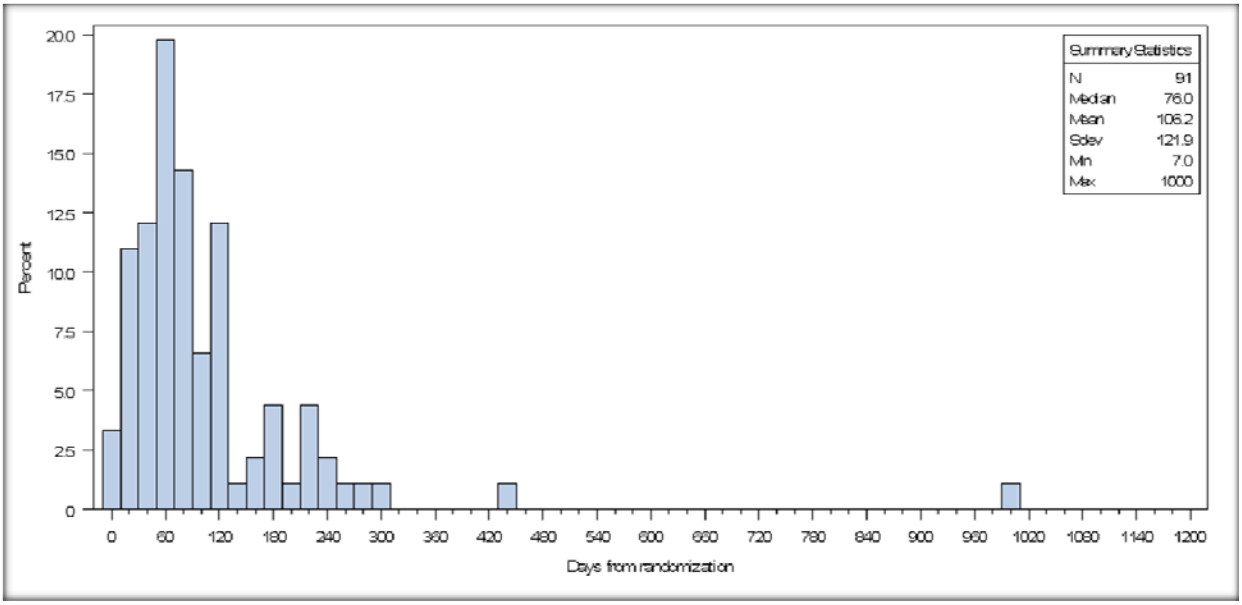
Data are number of patients (%).

* Baseline SM not available for 2 patients as they did not have diagnostic angiography at enrolment

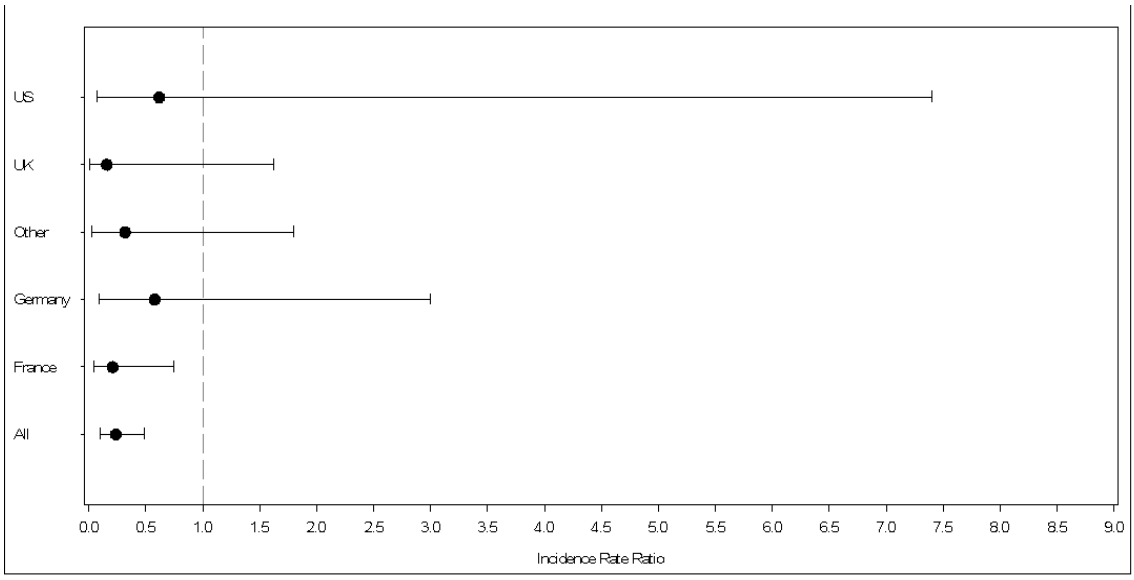
Supplementary Figure S1
Aggregate Subject enrollment between April 2007 and February 2013 when database was frozen for interim analysis



Supplementary Figure S2
Time to first interventional treatment event



Supplementary Figure S3
Incidence rate ratio of primary outcome events (death or stroke) by country.



Incident rate ratios are given with 95% confidence intervals.
Countries contributing less than 15 patients are listed among “other”.

Supplement References

[1] Wedderburn CJ, van Beijnum J, Bhattacharya JJ, Counsell CE, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP, Al-Shahi Salman R; SIVMS Collaborators. Outcome after interventional or conservative management of unruptured brain arteriovenous malformations: a prospective, population-based cohort study. Lancet Neurol. 2008;7:223-30.

[2] Laakso A, Dashti R, Seppänen J, Juvela S, Väärt K, Niemelä M, Sankila R, Hernesniemi JA. Long-term excess mortality in 623 patients with brain arteriovenous malformations. Neurosurgery. 2008;63:244-53.