Life after ARUBA: Management of Unruptured Brain Arteriovenous Malformations (AVMs)

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No Disclosures
Brain AVMs

- Incidence ~1 in 100,000 person-years
- 38-68% of new cases are first-ever hemorrhages
- Rate of hemorrhage 2-4% per year
- Increased risk of hemorrhage: initial hemorrhage, deep venous drainage, deep and infratentorial locations, associated arterial aneurysms, nidus size (venous stenosis, smoking, HTN, pregnancy in some studies)
- Hemorrhage has a 1-year case fatality rate of 10-30%
- Hemorrhage produces neuro deficit in 20-30%
Hemorrhage

CT

CTA

Courtesy Dr. Linda Bagley
Time Resolved MRA

Courtesy Dr. Linda Bagley
## Overall AVM rupture rates and risk factors for rupture across all series

<table>
<thead>
<tr>
<th>Factor</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>annual hemorrhage rate (%)</strong></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>3.0 (2.7–3.4)</td>
</tr>
<tr>
<td>unruptured AVM</td>
<td>2.2 (1.7–2.7)</td>
</tr>
<tr>
<td>ruptured AVM</td>
<td>4.5 (3.7–5.5)</td>
</tr>
<tr>
<td><strong>increased risk for rupture (HR)</strong></td>
<td></td>
</tr>
<tr>
<td>prior hemorrhage</td>
<td>3.2 (2.1–4.3)</td>
</tr>
<tr>
<td>deep location</td>
<td>2.4 (1.4–3.4)</td>
</tr>
<tr>
<td>exclusively deep venous drainage</td>
<td>2.4 (1.1–3.8)</td>
</tr>
<tr>
<td>associated aneurysm</td>
<td>1.8 (1.6–2.0)</td>
</tr>
<tr>
<td><strong>little to no effect on rupture risk (HR)</strong></td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td>1.4 (0.6–2.1)</td>
</tr>
<tr>
<td>size &lt;3 cm</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>older age</td>
<td>1.0 (0.4–1.6)</td>
</tr>
</tbody>
</table>

Spetzler-Martin Grading System: I-V Scale

CNS Location  | Size | Venous Drainage
---           | ---  | ---
Non-eloquent  | Small (<3 cm) | Superficial 0
Eloquent      | Medium (3-6 cm) | Deep 1
              | Large (>6 cm)  |
Spetzler-Ponce 3-tier system

- Class A: SM grades I-II
- Class B: SM grade III
- Class C: SM grades IV-V

- Risk of permanent adverse outcome with surgical resection of unruptured Class A AVMs
  \[ = 1 - 8\% \]

Spetzler, Ponce *JNS* 2011;114:842-9
Consequences of Hemorrhage

- Mortality: 6-29%
- Permanent morbidity: 16-35%
- Combined M&M: 41-85%

Crawford et al JNNP 1986;49:1-10
DaCosta et al Stroke 2009;40:100-105
Hernesniemi et al Neurosurg 2008;63:823-31
AVMs - Treatment

- Microsurgery
Treatment cont’d

- Embolization
Treatment cont’d

• Stereotactic Radiosurgery
ARUBA

• A Randomised trial of Unruptured Brain Arteriovenous malformations

• www.thelancet.com Published online November 20, 2013
  http://dx.doi.org/10.1016/S0140-6736(13)62302-8

• The Lancet, Volume 383, Issue 9917, Pages 614 - 621, 15 February 2014
Trial Design

• Prospective randomized non-blinded trial
• Adults ≥ 18 yo
• 39 clinical sites in 9 countries
• Randomized to medical mgmt vs intervention (surgery, embolization or SRS, or combinations)
• Primary outcome is time to composite endpoint of death (any cause) or symptomatic stroke
• Secondary outcome is clinical impairment at 5 years (mRS ≥ 2)
• Intention to treat analysis
Exclusions

- Prior hemorrhage
- Prior treatment
- AVM that is ‘unsuitable for eradication’ by the local center
Outcomes assessment

• Clinical outcome: independent neurologist
• Radiographic outcome: independent international adjudicators
• Clinical outcome scales:
  – mRS
  – NIHSS
  – EuroQOL
  – SF-36
Patients

- Mean age 45; women 40%
- Presentations: headache, seizure, focal deficit
- Asymptomatic 40%
- No SM grade 5 AVMs
- 32% gr 3-4 (Int grp); 45% gr 3-4 (Med grp)
- Posterior fossa AVMs rare (6% Int grp, 5% Med)
- Eloquent location 47%
Findings

• Randomization Apr 2007 – Apr 2013
• Stopped early because of superiority of medical mgmt group
• Outcomes available for 223 patients with mean F/U 33.3 months (114 intervention, 109 medical mgmt)
• Primary endpoint reached by 10.1% in medical group vs. 30.7% in intervention group
Findings cont’d

• Risk of death or stroke lower in medical mgmt group: hazard ratio 0.27.

• Higher no. of strokes (45 vs. 12, p<0.0001) and neuro deficits unrelated to stroke (14 vs. 1, p=0.0008) in intervention vs. medical group

• The trial is continuing to monitor these patients for an additional 5 years
Findings cont’d

• 13% of screened patients were randomized (higher than prior stroke trials)

• Better functional outcome in medical group:
  – Risk of death and disability (mRS≥2) 15.1% in medical vs. 46.2% in intervention group, RR 0.33

• Medical mgmt: 2.2% risk of hemorrhage/yr

• Primary outcomes in different countries similar

• 98% data complete; only 3% lost to F/U

• Risk of intervention is higher than previously suspected

• Outcomes of patients treated outside the trial unknown
Intervention

• Neurosurgery alone: n = 5
• Embolization alone: n = 30
• “Radiotherapy” alone: n = 31
• Embo + NS: n = 12
• Embo + SRS: n = 15
• Embo+NS+SRS: n = 1
ARUBA

- Underutilization of surgical resection:
  - 16% of cases included surgery
  - 4% - surgery alone
  - SRS – 26% (2-3 year latency)
  - Embolization in 40%
  - Embolization alone in 26% (was experienced surgical expertise even available in these centers??)

The results are primarily a demonstration of the complications of embolization in a subset of patients with bAVMs thought to be suitable for randomization
Microsurgery for SM grade 1-2 AVMs

- Grade 1 – 96% good outcomes
- Grade 2 – 90%
Crossovers

• 7 patients in medical grp → intervention
• 3 in intervention grp had an event prior to tx (included in medical grp for as-treated analysis)
• Median time from randomization to intervention was 76 days
• At time of analysis 53 pts had ongoing tx plans, and 20 had not yet started tx
• 3% discontinued participation in trial (5tx, 2med)
The Case Against A Randomized Trial of Unruptured Brain Arteriovenous Malformations: Misinterpretation of a Flawed Study

Nicholas C. Bambakidis, MD; Kevin M. Cockroft, MD; Joshua A. Hirsch, MD; E. Sander Connolly, MD; Sepideh Amin-Hanjani, MD; Philip M. Meyers, MD; Robert M. Friedlander, MD

Stroke 2014;45:2808-10 (Online July 31, 2014) Doi:10.1161/STROKEAHA.114.006519
Weaknesses

• Nonblinded; slow recruitment of patients
• Selection bias – 726 eligible pts, 323 refused to enroll, 177 pts managed outside the randomization process – no registry
• No standardization of the treatment arm – only 5 pts were treated with surgery, and 76 pts in tx arm had SM gr 1-2 AVMs. Literature supports surgery with 96% cure, SRS 38%, embo 13%
• No details of SRS and embo pts – 30 pts were treated with embo alone (rarely curative)
• >10% were SM gr4; >25% were SM gr3
Major Weaknesses

• Treatment arm is below standard of care
• 33 months follow up is too short
• Even the proposed 5 year follow up is too short for a lesion with lifelong risk of stroke and death
• Neither ARUBA nor the Scottish study was powered to examine the effects of the individual treatment options
What Have We Learned?

• ARUBA confirms that partial AVM treatment is a doomed strategy (all risk, little benefit)

• Conservative mgmt:
  – 10% risk of stroke or death OVER 33
  – 15% risk of disability MONTHS

• SM Grade 3 AVMs are heterogeneous – should individualize treatment

• SM Grades 4&5 – conservative mgmt unless progressive neuro decline or repeated bleeds
Patients treated outside the trial at UCSF

- ARUBA-eligible patients
- Prospective bAVM registry
- 74 pts: 61 treated, 13 observed
- 43/61 (70%) had resection w/ or w/o embolization (only 18% resection in ARUBA)
- 9/61 treated pts had CVA or died
- 1/13 observed pts died of AVM bleed
- No difference between groups in rates of stroke, death or clinical impairment

UCSF Trial

• 14.8% rate of stroke or death with tx
• ARUBA: 30.7% risk with tx
• Impairment: UCSF 13.8% vs. ARUBA 46.2%
• SRS pts had highest rate of stroke or death (26.7%) and impairment (20%)
• Surgery pts had only 11.6% rate of stroke or death and 14.6% rate of impairment
The Scottish Intracranial Vascular Malformation Study (SIVMS)

- Population-based cohort study of 204 pts >16 yo
- Prospective follow up for 12 years
- Compared primary outcome of death or sustained morbidity of any cause (OHS≥2)
- Secondary outcome of symptomatic stroke or death due to bAVM, associated aneurysm or intervention

Al-Shahi Salman et al: *JAMA* 2014 Apr;311(16):1661-9
Scottish trial results

- Patients who had intervention (103/204) were younger, more likely to have presented with a seizure, and less likely to have a large bAVM.
- Rate of progression to the primary outcome was lower in conservative mgmt pts over the first 4 years (HR 0.59), but not thereafter.
- Rate of progression to secondary outcome was lower in conservative group over 12 yr f/u (HR 0.37).
Figure 2. Progression to the Primary Outcome During 12 Years of Prospective Follow-up

Log-rank (Mantel-Cox) $\chi^2 = 0.01; P = .91$

<table>
<thead>
<tr>
<th>No. at risk (No. of events in preceding year)</th>
<th>Intervention</th>
<th>Conservative management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>103</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>72 (30)</td>
<td>90 (8)</td>
</tr>
<tr>
<td></td>
<td>60 (6)</td>
<td>71 (18)</td>
</tr>
<tr>
<td></td>
<td>53 (1)</td>
<td>56 (7)</td>
</tr>
<tr>
<td></td>
<td>45 (2)</td>
<td>44 (3)</td>
</tr>
<tr>
<td></td>
<td>39 (2)</td>
<td>35 (3)</td>
</tr>
<tr>
<td></td>
<td>34 (4)</td>
<td>28 (1)</td>
</tr>
<tr>
<td></td>
<td>31 (2)</td>
<td>23 (3)</td>
</tr>
<tr>
<td></td>
<td>27 (0)</td>
<td>21 (1)</td>
</tr>
<tr>
<td></td>
<td>23 (1)</td>
<td>18 (3)</td>
</tr>
<tr>
<td></td>
<td>19 (0)</td>
<td>11 (2)</td>
</tr>
<tr>
<td></td>
<td>16 (0)</td>
<td>9 (0)</td>
</tr>
<tr>
<td></td>
<td>7 (0)</td>
<td>6 (0)</td>
</tr>
</tbody>
</table>

The primary outcome (number of events reported) occurred due to
Hand injuries during the study period for 2 years.

Bars indicate
95% confidence intervals for cumulative incidence.

JAMA  April 23/30, 2014  Volume 311, Number 16
Figure 3. Progression to the Secondary Outcome During 12 Years of Prospective Follow-up

Log-rank (Mantel-Cox) $\chi^2 = 15.45; P < .001$

<table>
<thead>
<tr>
<th>Prospective Follow-up Time, y</th>
<th>Intervention</th>
<th>Conservative management</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>103</td>
<td>101</td>
</tr>
<tr>
<td>1</td>
<td>73 (28)</td>
<td>96 (1)</td>
</tr>
<tr>
<td>2</td>
<td>64 (6)</td>
<td>86 (6)</td>
</tr>
<tr>
<td>3</td>
<td>57 (1)</td>
<td>73 (3)</td>
</tr>
<tr>
<td>4</td>
<td>50 (1)</td>
<td>61 (1)</td>
</tr>
<tr>
<td>5</td>
<td>45 (1)</td>
<td>53 (1)</td>
</tr>
<tr>
<td>6</td>
<td>41 (0)</td>
<td>42 (0)</td>
</tr>
<tr>
<td>7</td>
<td>37 (1)</td>
<td>36 (1)</td>
</tr>
<tr>
<td>8</td>
<td>34 (0)</td>
<td>33 (0)</td>
</tr>
<tr>
<td>9</td>
<td>30 (0)</td>
<td>28 (1)</td>
</tr>
<tr>
<td>10</td>
<td>22 (0)</td>
<td>21 (0)</td>
</tr>
<tr>
<td>11</td>
<td>18 (0)</td>
<td>15 (0)</td>
</tr>
<tr>
<td>12</td>
<td>8 (0)</td>
<td>11 (0)</td>
</tr>
</tbody>
</table>
Scottish trial results

• Selection bias for intervention?
  – Perhaps these AVMs had higher risk features and thus a more dangerous natural history (higher rate of hemorrhage in treated group); only 1 death was attributed to intervention
Morgan’s Series (Sydney)  
1989-2013

- Prospectively collected database of ubAVMs
- Included surgical and non-surgical cases
- Sensitivity analysis to include patients who did not have surgery – to see how they might have influenced the predicted outcome from surgery for all cases of similar S-P class ubAVMs if they had undergone surgery and had a poor outcome
- Goal – to improve the generalizability of the reported risk of surgery

Bervini et al JNS Aug 2014
Grade III Subtypes

- Type 1: S1E1V1
- Type 2: S2E1V0
- Type 3: S2E0V1
- Type 4: S3E0V0

- Conclusion: Size matters

Pandey et al (Steinberg): JNS 2012 Jun;116(6):1279-88
Supplementary Grading Scale (Lawton)

- Age
- Hemorrhagic presentation
- Diffuseness
- Deep perforating artery supply


- SM grade 1-2 AVMs (n=296): morbidity 0.7%
- SM grade 3-4 (n=65; noneloquent): 17%
- SM grade 3-5 (n=168; eloquent): 21%

### TABLE 4. Risk of Adverse Outcome Due to Surgery by Spetzler-Martin Grade

<table>
<thead>
<tr>
<th>SM Grade</th>
<th>Operated</th>
<th>Adverse Outcome, No. (%)</th>
<th>95% CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98</td>
<td>1 (1)</td>
<td>0-6</td>
</tr>
<tr>
<td>2</td>
<td>198</td>
<td>1 (0.5)</td>
<td>0-3</td>
</tr>
<tr>
<td>3</td>
<td>169</td>
<td>24 (14)</td>
<td>10-20</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>17 (31)</td>
<td>21-45</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>5 (50)</td>
<td>24-76</td>
</tr>
<tr>
<td>Total</td>
<td>529</td>
<td>48 (9)</td>
<td>7-12</td>
</tr>
</tbody>
</table>

*SM, Spetzler-Martin; CI, confidence interval. P < .001.*

Davidson, Morgan: **Neurosurgery** 2010 Mar;66(3):498-504
So what do we do NOW with....

- Unruptured posterior fossa AVMs – risk of a bleed is higher, and risk of death or serious morbidity is higher with a bleed
- Young patients with SM gr 1-2 AVMs?
- Unruptured but symptomatic AVMs (intractable headaches, repeated seizures)?
19 yo boy fell off his bike, intoxicated
16 yo girl with incapacitating headaches
44 yo woman with headaches
ARUBA:
A Prospective Randomized Clinical Trial

• The gold standard in Medicine
• It must now be part of every AVM discussion
• Answers a specific question at a specific time point
• One short-term study may not be the final word

• So please use good clinical judgment and stay tuned...