

Summary of some of the landmark articles:

- **The significance of unruptured intracranial saccular aneurysms: Weibers et al Mayo clinic. 1987**
 1. 131 patients with 161 aneurysms were followed up until death, rupture or clipping (mean follow up interval 8.3 years). None of 102 aneurysms < 10mm bled while 15/51 patients with aneurysms > 10 mm bled 14 /15 died. The incidence of aneurysms in autopsy studies (0.2-9%) average **5%. SAH 10/100000 per year**
 2. The average size at which aneurysm ruptured was 21.3 mm while the average size of ruptured aneurysms in the same institution was 7.5 mm (rupture results in decrease in the **size** of filling compartment of the aneurysm)
 3. Saccular aneurysms develop with increasing age and stabilise after short period of time. If the initial stabilised size is < 10 mm the risk of rupture is minimal and these lesions probably do not require treatment
- **ISHUA** study (international study of UIA) is the largest Multicenter study. It has two arms, prospective and retrospective. This is a landmark study that has influenced the thinking about the natural history of UIA
- Retrospective arm which looked at the natural history of UIA. In this arm **1449** patients divided into 2 groups: Group 1-had no prior history of SAH and Group 2- had history of SAH from other aneurysm. The annual risk of haemorrhage for group 1 was 0.05% for aneurysms <10mm, 1% for those larger than 10mm and 6% for giant aneurysms (>25mm). In the second group the risk was 0.5% for those <10mm and 1% for those >10mm. In this study in addition to **size, location (higher risk for posterior circulation aneurysms) and past history of SAH for those less than 10 mm** were significant factors determining the risk of rupture of unruptured aneurysms
- In the prospective component the morbidity and mortality related to treatment were evaluated.

The **strengths** of this study include its **Multicenter** design which minimizes referral and treatment bias and its **size** which provides strong statistical power. The **most significant criticism** is related to the possibility of **selection bias** (all patients were selected for observation or surgery after consultation with a neurosurgeon, this may have created a subgroup of patients with less risk of rupture by removing the patients with high risk from the group ‘those who had surgery’. Removal of these high risk patients may have skewed downward the risk of rupture. The **retrospective nature** of this study might have introduced unrecognised selection bias and another concern is the **inclusion of patients with intracavernous aneurysms in the study population** (although investigators after excluding intracavernous aneurysms from the analysis concluded that the risk of haemorrhage was 0.066% for small and 1.38% for large aneurysms). **Weir et al** demonstrated that the rupture rate of 0.05%-0.066% is in conflict with the prevalence rate of UIA and the incidence of aneurysmal SAH (30000 SAH per year in North America). Using the figures provided by ISHUA study, one would expect that the prevalence of UIA in USA will be **16%** for those older than 30 years, which is not supported by the prevalence of UIA from MRI/MRA studies.

- **Unruptured intracranial aneurysms: natural history, clinical outcome and risks of surgical and endovascular treatment: Weibers et al (Mayo clinic) 2003.**
1. Data from the **prospective arm of ISUIA study**: 4060 patients. **Group1** –no history of SAH (**1692**) and **group 2** had clipping of ruptured aneurysm (**1917**) and coiling (**451**). Average follow up 4.1 years (5 years or more in 50%). The aims of this study were to assess the natural history of unruptured aneurysms and to assess the risk of surgical or endovascular intervention.
 2. The 5 year cumulative rupture rates for (ICA,ACA,A-com and MCA) were < 7mm (0), 7-12 mm (2.6%), 13-24 mm (14.5% and >25mm (40%).
 3. The 5 year cumulative rupture rates for (posterior circulation and p-com aneurysms) were <7mm (2.5%), 7-12mm (14.5%), 13-24mm (18.5%) and >25 mm 50%.
 4. This data indicates that aneurysm **size** and **location** are significant factors in determining the risk of future rupture
 5. The **total mortality and morbidity** in the surgical group was 12% in group1 and 10% in group 2. Factors associated with increased risk were age>50, large size, posterior circulation aneurysms and CVD.
 6. The total mortality morbidity rates for endovascular treated patients were 9.1% (group1) and 9.5 % (group 2). The M and M were less dependent on age in this group
 7. The risk of surgical or endovascular treatment equalled or exceeded the 5 year cumulative rate of rupture
 8. The lowest risk natural history group were asymptomatic patients with aneurysm < 7mm in the anterior circulation. The lowest surgical risk patients were < 50 years with aneurysm < 24 mm in the anterior circulation (5-6% at 1 year).

Natural history of unruptured intracranial aneurysms: probability and risk factors for aneurysm rupture: Juvula et al 2000

1. Long term cohort study included 142 patients with 181 aneurysms followed up to death or rupture (average follow up 19.7 years). 131 patients had SAH from another aneurysm.
 2. The annual incidence of rupture was 1.3%. **Size** of aneurysm, **smoking** and **age** (**The** younger the patient the higher the risk. Annual risk of 1.9 for those <30 years)) were significant factors determining the risk of rupture.
 3. History of SAH from other aneurysm, HTN and multiplicity and family history of aneurysm were not associated with increased risk of rupture
- The risk of rupture of UIA may be affected by the following factors:
 - 1.Size:** ISHUA study 0.05-0.066%-0.5% for those < 10mm, 1% for those >10mm and 6% for giant aneurysms.

- 2.Location** : higher risk of rupture for basilar bifurcation, p-com and A-com aneurysms
- 3.Multiplicity**: 15-20% of aneurysms are multiple. The risk of rupture is higher if the aneurysm is part of multiple aneurysms. The Japanese data 6.5% for multiple aneurysms Vs 1.9% for single lesions.
- 4.History** of SAH from another aneurysm (ISUA-0.05% VS. 0.5% for aneurysms < 10 mm.
- 5.Smoking**: strong association between smoking and aneurysmal rupture (Juvula et al
- 6.Aneurysm growth: controversial data in literature regarding whether growth of aneurysm on serial imaging increases the risk of rupture
- 7.Symptomatic aneurysms: headaches, cranial nerve palsies are symptoms of aneurysms other than SAH. Some studies suggested increased risk of haemorrhage from these aneurysms, others did not find a relation between symptomatic aneurysms and the risk of rupture
- 8.Age; most literature supports the concept of increasing age being associated with increased risk of rupture except in the very elderly.
- 9.Hypertension: most data are unclear about whether hypertension increases the risk of haemorrhage from UIA.
10. Gender: women may have an increased risk of rupture, but the data are inconclusive.

International subarachnoid aneurysm trial (ISAT): 2002 (The Lancet)

- Prospective randomised Multicenter trial to assess the safety and efficacy of coiling in comparison with surgery 2143 patients judged to be suitable for both treatments. 1070 had surgery and 1073 had coiling. Trial commenced in 1994. The outcome assessed at 2 months and 1 year using Rankin score. Poor outcome =RS 3-6(dependent or dead)
- 97.3%** of patients had **anterior** circulation aneurysms. **93% were small** < 10 mm in size and the majority of patients were **grade 1 and 2** (88%), grade3 6% and 4-5 (4%). Patients with MCA. Posterior circulation aneurysms are underrepresented in this trial
- - The trial was terminated prematurely by the steering committee because interim analysis showed that the poor outcome at 1 year (RS=3-6) was 30.6% in the surgical group vs. 23.7% in the coiling group. (6.9%reduction in the absolute and 22.6% reduction in the relative risk of poor outcome in the coiling group)
 - Strength:
 1. Prospective randomised Multicenter trial
 2. Large number of recruited patients.
 - Criticism :
 1. The percentage of patients recruited for the trial from different centres ranged between 1-44% of patients admitted with SAH (this may not represent the total group of patients with SAH)

2. There was small but significant ($p < 0.0001$) delay between the randomisation and the procedure between the two groups (1.7 days for clipping comparing with 1.1 days for coiling).

The natural history of unruptured AVM: Weibers et al Mayo clinic 1988:

- Retrospective study **166** patients with average F/U of **8 years**. The annual risk of rupture **2.2%** with mortality **29%** and morbidity of **23%**. The size of the AVM and the presence of HTN were of no value in predicting rupture
- Weibers et al in another paper 1996-65% of patients with AVM presents with intracranial haemorrhage. ICH is the most common type followed by SAH

The natural history of symptomatic AVM: 24 YEAR f/u. Ondra et al. Finland

- **166** patients with AVM followed prospectively for **24 years**. The annual bleeding rate was **4%**. **1% mortality** per year and **2.3 combined annual** mortality and morbidity.

Factors associated with increased risk of haemorrhage are:

- A. History of previous haemorrhage
- B. Presence of aneurysms (7% per year for feeding vessel aneurysms and 9.5% for intranidal aneurysms)
- C. Size (higher risk of haemorrhage for AVMs with small nidus (higher arterial pressure within the nidus of small AVMs.
- D. Impaired venous drainage (deep venous drainage and single draining vein)
- E. Age (2% in the first 10 years, 4% second 10 years, 7% per year > 60years)-controversial
- F. Male sex-controversial
- G. Pregnancy (controversial)
- H. HTN-controversial.

Angiographic features associated with high risk of haemorrhage include deep venous drainage, periventricular location, single draining vein, stenotic venous drainage.

International cooperative study on EC-IC bypass.

- Prospective randomised Multicenter study comparing surgery (STA-MCA) bypass with best medical treatment for ischemic symptoms in patients with distal ICA (distal to C2 vertebra) and MCA stenosis.
- 1495 patients were recruited (1977-1982). Patients were assessed every 6 months with average follow up of 55.8 months. 92% had follow up angiograms. The results were published in 1985.
- After careful analysis of the primary events of fatal and nonfatal strokes, it was clearly demonstrated that STA-MCA bypass did not reduce the rate of stroke in comparison with best medical treatment despite patency rate of the graft in 96% of cases.
- Criticism:
 1. Patients did not have objective assessment of cerebral blood flow (xenon CT, SPECT and PET) and despite the presence of stenosis of distal ICA and MCA the ischemic symptoms could still be due to embolisation from the heart or

stenotic vessels and obviously bypass surgery will not prevent stroke due to emboli.

2. The bypass which was used is low flow bypass which can augment, but not replace the blood flow in major vessels.
 - Most vascular surgeons agree that there is still a place for bypass surgery in selected group of patients with ischemic symptoms secondary to haemodynamic compromise.

STICH study (Lancet 2005 Jan 29, 365 (94570): 387-97).

Prospective randomised Multicenter study comparing surgery with medical treatment for supratentorial ICH. There was no overall benefit from early surgery compared to initial conservative treatment.

Criticism: Selection bias: patient were randomised only if the treating surgeon was unsure which treatment is best which means a young man with ICH and GCS of 8-13 will go for surgery and not be randomised and 80 year old with low GCS and basal ganglia haemorrhage will be treated medically and not be randomised or patient with GCS of 13 and small ICH will be observed and not randomised etc...

Prospective randomised Multicenter study recruited 1033 patients from 83 centres. 503 patients had early surgery and 530 had initial medical treatment (140 deteriorated and had surgery within 72 hours). The outcome was assessed at 6 months using questionnaire (eight point GOS). A favourable outcome 26% in the surgical group compared with 24% in the medical group. Overall there was no significant difference between the 2 groups. In patients who presented with coma the outcome was poor in both groups. Surgery increased the relative risk of poor outcome by 8% in this group. The results of the 10 published randomised trials including this trial showed no overall advantage of early surgery in patients with ICH.