

# UPDATE ON ENDOVASCULAR TREATMENT OF ANEURYSMS

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## Cerebral Aneurysms

Brain aneurysms are sacs that form from an arterial wall, usually occurring at vessel branching points. The prevalence of unruptured brain aneurysm is estimated close to 2% in an analysis of brain MRI (Vernooij) whereas the event of subarachnoid hemorrhage is much less common (up to 10/100,000 persons).

In the United States, the incidence of subarachnoid hemorrhage is 7.2 to 9.0 per 100 000/year, which has not changed significantly over the last 30 years (Rincon 2013). Mortality after SAH has declined steadily from 50% in the 1966 Cooperative Study to 30% (1979-1983) and 20% (2004-2008) in the National Hospital Discharge Survey (Rincon 2013).

## Natural History of Unruptured Intracranial Aneurysm

There are several studies which have evaluated the rupture risk of UIAs, including the International Study of Unruptured Intracranial Aneurysm (ISUIA), the Unruptured Cerebral Aneurysm Study (UCAS) Japan study and the Finnish series by Juvela et al (Juvela).

### *ISUIA*

The ISUIA study included retrospective and prospective natural history study on patients with unruptured intracranial aneurysm(s). In phase 1 retrospective study, 1449 patients with 1937 unruptured aneurysms were selected for conservative management. Among patients with no history of SAH, the rupture risk was 0.05% per year for aneurysms <10 mm and ≈1% per year for larger aneurysms. Larger aneurysm size, location in the posterior circulation were predictors of rupture risk. Among those with a history of SAH from a different aneurysm, the rupture risk was 0.5% per year for those <10 mm and ≈0.7% per year for larger aneurysms.

The second phase of ISUIA was a prospective natural history study of 1692 patients with 2686 unruptured aneurysms. Aneurysm rupture rates were stratified by size (cut point of <7 mm to define the smallest group of aneurysms), history of SAH from a different aneurysm, and location. Five-year cumulative rupture rates for patients without a history of subarachnoid hemorrhage in the anterior circulation (internal carotid artery, anterior communicating or anterior cerebral artery, or middle cerebral artery) were 0%, 2.6%, 14.5%, and 40% for aneurysms less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater, respectively, compared with rates of 2.5%, 14.5%, 18.4%, and 50%, respectively, for the same size categories involving posterior circulation and posterior communicating artery aneurysms.

### *UCAS*

The Unruptured Cerebral Aneurysm Study (UCAS) was a Japanese prospective cohort study of 5720 patients with 6697 unruptured cerebral aneurysms. The risk of rupture was 0.95%/year. Predictors of rupture were size, location, and the presence of a daughter sac. As compared with aneurysms that were 3 to 4 mm in the largest dimension, aneurysms that were 5 to 6 mm were not associated with a significantly increased risk of rupture, but the risk of rupture was increased for aneurysms that were 7 mm or larger.

### *Finish study*

Juvela et al (Stroke 2013) studied 142 patients with unruptured aneurysms for 3064 person years. Most patients in this series originally presented with a ruptured aneurysm to which the followed aneurysms were incidental. They found an annual rate of aneurysm rupture in the incidental aneurysms of 1.1%. Given the presentation of prior SAH, multiplicity of aneurysms, and limitation to the Finnish population, these results may not be applicable to unruptured aneurysms generally.

## *Endovascular Therapy of Intracranial Aneurysms*

The spectrum of endovascular treatment options for intracranial aneurysms has evolved dramatically over the past three decades. From the introduction of the Guglielmi Detachable Coil in 1990, to balloon assisted coil remodeling (Moret), stent assisted coiling, and flow diversion (Nelson), these technologies have increased the number of aneurysms that can be treated via endovascular methods with improved safety and efficacy.

The ATENA trial was the first prospective multicenter study to evaluate clinical outcome and risks of endovascular coiling treatment (37% with balloon remodeling, 8% with stent assist) in 649 patients with 1100 unruptured aneurysms (Pierot). Morbidity and mortality was 1.7% and 1.4% at one month, respectively.

Endovascular flow diversion has made the greatest impact on aneurysm treatment since coiling. A flow diverter is an endoluminal stent like construct designed to reconstruct the diseased parent artery across from where the aneurysm lies (Fiorella 2009). Several large series of flow diversion have shown remarkable results for treatment of large, giant, difficult to treat aneurysms which are prone to recurrence (Raymond 2003) with conventional endovascular coil technology (Intrepid, PUFIS PITA Becske).

### **FIAT**

The Flow Diversion in the treatment of Intracranial Aneurysm Trial (FIAT) study was a randomized trial comparing angiographic and clinical outcomes with a Flow-Diverter (FD) or best standard option (observation, coiling, stenting, or clipping) for patients with difficult to treat aneurysms. The trial was stopped early due to safety concerns. Twelve (16%) of 75 patients who were allocated to or received flow diversion were dead (n = 8) or dependent (n = 4) at 3 months or more, crossing a predetermined safety boundary. Death or dependency occurred in 5 (13%) of 38 patients randomly allocated and treated by flow diversion and in 5 (12.8%) of 39 patients allocated to standard treatment. Primary efficacy outcome, defined as angiographic occlusion at 3-12 months combined with independent clinical outcome, was below expectations of the trial hypothesis: 16 (42%) of 38 patients randomly allocated to flow diversion failed to reach the primary outcome, as compared with 14 (36%) of 39 patients allocated to standard treatment. In the FIAT study, flow diversion was not as safe and effective as initially hypothesized, particularly for patients with posterior circulation aneurysms. More randomized trials are necessary to determine the role of flow diversion in the management of patients with intracranial aneurysms.

Despite the widespread array of endovascular treatment options, the question of whether one should observe or treat an unruptured, asymptomatic aneurysm, remains unanswered by clinical trial. The Trial on Endovascular Aneurysm Management (TEAM) was a prospective randomized trial comparing coiling and conservative management in patients with unruptured aneurysm with the goal of studying safety and efficacy of endovascular treatment of intracranial aneurysm to prevent subarachnoid hemorrhage. The trial was stopped in 2009 due to poor recruitment at 80 patients (Raymond 2011).

In the absence of prospective trials comparing treatment versus conservative therapy for unruptured aneurysms, guides for patient selection such as the Unruptured Intracranial Aneurysm Treatment Score (UIATS) have been proposed as have models such as the PHASES scale to help predict the risk of future hemorrhage. (Etminan 2015) (Greving JP 2014)

### **Subarachnoid hemorrhage**

A ruptured aneurysm can carry significant morbidity and mortality to the patient. The risk of rerupture after subarachnoid hemorrhage is highest in the first day (4%), and then 1 to 2 percent each day in the first month (Kassell). Aneurysm rerupture is associated with a mortality of approximately 67% (Winn 1977). Ruptured aneurysms therefore need to be treated early to prevent rerupture.

Two trials demonstrated improved clinical outcomes from endovascular coiling compared to neurosurgical clipping. There was decreased death or dependence at one year with coiling compared to neurosurgical clipping in patients with subarachnoid hemorrhage. (Molyneux 2002) (McDougall, Spetzler et al. 2012)

### **ISAT**

The International Subarachnoid Aneurysm Trial (ISAT) was a landmark international, multicenter randomized clinical trial evaluating patients with ruptured aneurysms in whom the treating physician felt the patient could be treated with either endovascular coiling or neurosurgical clipping. The trial intended to enroll 2500 patients; after an interim planned analysis of 2143 patients, the trial was stopped by the steering committee. There were 24% of patients allocated endovascular treatment dependent or dead at 1 year compared to 31% allocated neurosurgical treatment (190/801, 23.7% vs. 243/793, 30.6%, p=0.0019) (Molyneux 2002).

At long term follow-up, mortality was lower with coiling compared to clipping at 5 and 10 years in the ISAT study. A recent follow up of ISAT patients reported that although rates of increased dependency alone did not differ between groups, the probability of death or dependency was greater in the neurosurgical group than in the endovascular group. Despite the small increased risk of recurrent SAH in the endovascular group the probability

of disability-free survival was greater in the endovascular than in the neurosurgical group at 10 years (OR 1.34, 95% CI 1.07–1.67). (Molyneux, Birks 2015)

### BRAT

The Barrow Ruptured Aneurysm Trial was a randomized trial of patients with subarachnoid hemorrhage treated with alternating clip vs coil strategy. There were 500 eligible patients enrolled prospectively in alternating method to clipping (n=238) or coiling (n=233). Cross over was permitted, but primary outcome was based on the initial treatment assigned as an intent to treat analysis. At one year, poor outcome (mRS > 2) was higher in the clip vs coil group (33.7% vs 23%, OR 1.68, 95% CI 1.08–2.61; p = 0.02).

The 6 year results of the BRAT study showed no significant difference in poor outcome as defined by mRS > 2 for coiled vs clipped patients (57/162, 35% vs 72/174, 41%, p=0.24). The outcomes for posterior circulation favored coiling. The retreatment rate was lower for clipping vs coiling (4.6% vs 16%, p<0.0001) (Spetzler). The drawback of the study was that it was underpowered to evaluate clinical outcome and the analysis of anterior vs posterior circulation outcomes was posthoc. (Spetzler, McDougall et al. 2015)

### FUTURE RESEARCH

There are several ongoing trials (Table 1).

#### CURES

The Canadian UnRuptured Endovascular Versus Surgery Trial (CURES) trial is a randomized trial comparing the results of surgical clipping versus endovascular treatment of unruptured aneurysms (UIAs). There is a composite primary end-point of either: failure to accomplish aneurysm obliteration with the initial treatment modality, a major saccular aneurysm remnant or recurrence, or intracranial hemorrhage following treatment at one year. The international study will address which strategy leads to the best overall clinical outcomes in terms of mortality, morbidity, and clinical efficacy.

#### ISATII

ISAT II is a pragmatic, multicenter, randomized trial comparing clinical outcomes for non-ISAT patients with subarachnoid hemorrhage allocated to coiling or clipping. The primary end-point is the incidence of poor clinical outcome (defined as mRS >2) at one year, similar to ISAT. Secondary end-points presence of a major recurrence at one year. The goal recruitment is 1,896 patients (862 each arm plus 10% losses) to demonstrate a significant difference between coiling and clipping, hypothesizing 23% and 30% poor clinical outcome rates, for coiling and clipping, respectively. The trial should involve at least 50 international centers, and will take approximately 12 years to complete.

	Patient population	Randomization	Primary Outcome	Enrollment
CURES	Unruptured aneurysm	Coil vs Clip	Failure to close aneurysm, Recurrent aneurysm, ICH at 1 year	Goal 260, Current 136 (Aug 2016)
ISAT II	Ruptured aneurysm	Coil vs Clip	Poor clinical outcome 1 year	Goal 1896, Current 89 (Aug 2016)

## REFERENCES

- Connolly ES, Rabinstein AA, Carhuapoma JR et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. *Stroke* 2012;43:1711-1737.
- Darsaut TE, Jack AS, Kerr RS, Raymond J. International subarachnoid aneurysm trial – ISAT Part II: Study protocol for a randomized controlled trial. *Trials*. 2013; 14: 156.
- Darsaut TE, Findlay, Raymond. CURES trial. The design of the Canadian UnRuptured Endovascular versus Surgery (CURES) trial. *Can J Neurol Sci*. 2011;38(2):236-41.
- Guglielmi G, Viñuela F, Sepetka I, Macellari V. Electrothrombosis of saccular aneurysms via endovascular approach: part 1: electrochemical basis, technique, and experimental results. *J Neurosurg*. 1991;75:1–7.
- Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms. A long-term follow-up study. *Stroke* 2013;44(9):2414-21.
- Kassell NF, Torner JC. Aneurysm rebleeding: a preliminary report from the Cooperative Aneurysm Study. *Neurosurgery* 1983;13:479-81.
- Macdonald RL. Editorial: Clip or coil? Six years of follow-up in BRAT. *J Neurosurg* 2015;123(3):605-7.
- McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, et al.: The Barrow Ruptured Aneurysm Trial. *J Neurosurg* 2012;116:135–144.
- Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D. The pipeline embolization device for the intracranial treatment of aneurysms trial. *Am J Neuroradiol* 2011;32(1):34-40.
- Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002;360: 1267–1274.
- Molyneux AJ, Kerr RS, Birks J, Ramzi N, Yarnold J, Sneade M, Rischmiller J for the ISAT collaborators. Risk of recurrent subarachnoid hemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol* 2009; 8: 427–33
- Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet* 2015;385(9969):691-7.
- Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Mozzafarian D, Benjamin EJ, Go AS, Arnett DK et al. Heart Disease and Stroke Statistics. 2015 Update. *Circulation*
- Nguyen TN, Masoud H, Tarlov N, Holsapple J, Chin LS, Norbash AM. Expanding Endovascular Therapy of Very Small Ruptured Aneurysms with the 1.5-mm Coil. *Interv Neurol*. 2015; 4(1-2):59-63.
- Pierot L, Spelle L, Vitry F et al. ATENA investigators. Immediate clinical outcome of patients harboring unruptured intracranial aneurysms treated by endovascular approach: results of the ATENA study. *Stroke* 2008;39:2497-2504.
- Raymond J, Darsaut TE, Molyneux AJ; TEAM collaborative Group. A trial on unruptured intracranial aneurysms (the TEAM trial): results, lessons from a failure and the necessity for clinical care trials. *Trials* 2011;12:64.
- Raymond J, Gentric JC, Darsaut TE, Iancu D, Chagnon M, Weill A, Roy D. Flow diversion in the treatment of aneurysms: a randomized care trial and registry. *J Neurosurgery* 2016 November.

Rincon F, Rosenwasser R, Dumont A. The epidemiology of nontraumatic subarachnoid hemorrhage in the United States. *Neurosurgery* 2013;73:217-223.

Sandercock P; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005;366:809–817.

Spetzler RF, McDougall CG, Zabramski JM, Albuquerque FC, Hills NK, Russin JJ, Partovi S, Nakaji P, Wallace RC. The Barrow Ruptured Aneurysm Trial: 6-year results. *J Neurosurg.* 2015 Sep;123(3):609-17.

Thompson BG, Brown RD, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES, et al. Guidelines for the management of patients with unruptured intracranial aneurysms. A guideline for healthcare professionals from the American Heart Association / American Stroke Association. *Stroke* 2015;46

UCAS study investigators.

Vernooij MW, M. Arfan Ikram, M.D., Hervé L. Tanghe, M.D., Arnaud J.P.E. Vincent, M.D., Albert Hofman, M.D., Gabriel P. Krestin, M.D., Wiro J. Niessen, Ph.D., Monique M.B. Breteler, M.D., and Aad van der Lugt, M.D. Incidental Findings on Brain MRI in the General Population. *N Engl J Med* 2007; 357:1821-1828.

Wiebers DO, Whisnant JP, Huston J, 3rd, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003;12;362(9378):103–10

Winn HR, Richardson Ae, Jane JA. The long term prognosis in untreated cerebral aneurysms: I. The incidence of late hemorrhage in cerebral aneurysm: a 10-year evaluation of 364 patients. *Ann Neurol* 1977;1:358-370