

# Neurointerventional NEWS

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## Introduction

Michael Forsting, Editor

Dear Colleagues

This is the first Neurointerventional Newsletter of 2014.

This issue again deals with a lot of interesting aspects of intracranial aneurysm therapy.

You get the newest information about a subgroup of elderly patients; what is the current opinion about the good old stents and the new flow diverters; and what is state-of-the-art in aneurysms of the middle cerebral artery. And there are several papers dealing with unruptured aneurysms.

I really recommend not only reading our summaries and comments, but also trying to read the original papers. They will help you in finding the right decision for this large patient group.

I hope you will enjoy this issue and will be happy to receive feedback from many readers.

Sincerely

Michael Forsting, Essen, Germany

**Contributions to this issue:** Tommy Andersson, Alain Bonafé, Patrick Brouwer, James Byrne, Lucio Castellán, Andy Clifton, Michael Forsting, Zsolt Kulcsár, Jorge Olier, Rodrigo Rivera, István Szikora



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**Michael Forsting**  
Chairman of the Institute of Radiology and  
Neuroradiology at the University Clinics  
Essen, Germany



## Critical Review of Literature Intracranial Aneurysms

### Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies

Jacoba P Greving, Marieke J H Wermer, Robert D Brown Jr, Akio Morita, Seppo Juvola, Masahiro Yonekura, Toshihiro Ishibashi, James C Torner, Takeo Nakayama, Gabriël J E Rinkel, Ale Algra  
Lancet Neurol 2014; 13: 59–66

The decision as to whether to treat incidental intracranial saccular aneurysms is complicated by limitations in current knowledge of their natural history. The authors combined individual patient data from prospective cohort studies to determine predictors of aneurysm rupture and to construct a risk prediction chart to estimate five-year aneurysm rupture risk by risk factor status. They systematically reviewed and pooled analysis of individual patient data from 8382 participants in six prospective cohort studies with subarachnoid hemorrhage as outcome. They analyzed cumulative rupture rates with Kaplan-Meier curves and assessed

predictors with Cox proportional-hazard regression analysis.

Rupture occurred in 230 patients during 29166 person-years of follow-up. The mean observed one-year risk of aneurysm rupture was 1.4% (95% CI 1.1–1.6) and the five-year risk was 3.4% (2.9–4.0).

Predictors were age, hypertension, history of subarachnoid hemorrhage, aneurysm size, aneurysm location, and geographical region. In studying populations from North America and European countries, other than Finland, the estimated five-year absolute risk of aneurysm rupture ranged from 0.25% in individuals younger than 70

years without vascular risk factors with a small-sized (<7mm) internal carotid artery aneurysm, to more than 15% in patients aged 70 years or older with hypertension, a history of subarachnoid hemorrhage, and a giant-sized (>20mm) posterior circulation aneurysm. By comparison with populations from North America and European countries, other than Finland, Finnish people had a 3.6-times increased risk of aneurysm rupture and Japanese people a 2.8-times increased risk. The PHASES score is an easily applicable aid for prediction of the risk of rupture of incidental intracranial aneurysms.



## Personal comment

The authors did a great job. It is still not easy to give recommendations to patients with unruptured aneurysms. Many neurologists still rely on simple size criteria: larger than 7mm is bad, smaller than 7mm is a no-go for treatment. All physicians really involved in aneurysm treatment know from their experience that this is much too easy a view. The authors developed a practical risk score (PHASES) that predicts

a patient's risk of aneurysm rupture on the basis of a set of routinely assessed patient and aneurysm characteristics. They found that the largest amount of prognostic information was contained in six predictors: age, hypertension, history of subarachnoid hemorrhage, aneurysm size, aneurysm location, and geographical region. Sex, smoking status at time of aneurysm detection, and presence of multiple aneurysms had no important effect on the risk of rupture. Last but not least: PHASES

stands for: Population (American, European, Finnish), Hypertension, Age, Size of aneurysm, Earlier SAH from another aneurysm and Site of Aneurysm.

My opinion is that for a certain period – until we have more knowledge about unruptured aneurysms – this score will become a standard. Congratulations.

Michael Forsting, Essen, Germany

Funded by Netherlands Organisation for Health Research and Development

## Stent-Assisted Coiling versus Coiling Alone in Unruptured Intracranial Aneurysms in the Matrix and Platinum Science Trial: Safety, Efficacy, and Mid-Term Outcomes

Hetts SW, Turk A, English JD, Dowd CF, Mocco J, Prestigiacomo C, Nesbit G, Ge SG, Jin JN, Carroll K, Murayama Y, Gholkar A, Barnwell S, Lopes D, Johnston SC, McDougall C; on behalf of the Matrix and Platinum Science Trial Investigators AJNR Am J Neuroradiol. 2013 Nov 7. [Epub ahead of print]

This paper addresses an important topic in an area where currently we are short of objective data on which to base our practice. The authors used data collected as part of a multicentre randomized prospective trial (MAPS Trial\* (NCT00396981, www.clinicaltrials.gov) of polymer-modified coils and platinum bare metal coils to assess the safety and efficacy of stent assisted coiling (SAC) in a subset of treatments performed for unruptured aneurysms. SAC was used in 38% of treatments.

The data provided reasonably well matched cohorts of 137 SAC and 224 non-SAC treated patients from the trial cohort of 626 patients. The treatments were performed for solitary unruptured aneurysms and operators were at liberty to use a Neuroform™ Stent System (Stryker Neurovascular) in either one or two stage procedures, as necessary. Inevitably this policy resulted in variations in the use of SAC, with 25 centres using SAC for all or some treatments and 16 centres only performing non-SAC treatments. The study cohort included a relatively high proportion (9%) of excluded patients due to protocol violations or loss to follow-up. Case report forms were audited in 40% of all and 100% of SAC treated patient on completion of 12 months follow-up. The primary end point used in the main study was target aneurysm recurrence (TAR), which includes target aneurysm bleeding after treatment,

retreatment and death from an unknown cause during follow-up. But in this study the authors concentrated on patient and aneurysm characteristics, procedural details, safety, neurologic and angiographic outcomes. Stroke was not a separate end-point but mRS data was collected at 12 and 24 months. No comparison of coil type was made. The data are presented in a series of tables as comparisons of percentage rather than an event/patient number, which is a pity, and confidence intervals are only provided for multivariate analysis of ischemic stroke and aneurysm recurrence rates.

The study reports that periprocedural serious adverse events occurred during 6.6% SAC and 4.5% non-SAC treatments, which were not statistically different, despite SAC being used in more difficult aneurysm morphologies. At 12 months follow-up, the overall outcomes were the same except for ischemic stroke which was more common in the SAC group

## Personal comment

The authors justify their retrospective analysis on the grounds that higher quality data is obtained in prospective randomised trials. I think this is true and using these data is useful. We should remember that there has not been a randomised trial justifying endovascular interventions for unruptured aneurysms and it is salutary to

see that at one year the mRS was worse in 8-12% of patients and 2% had died. Since SAC was more often used in wide necked aneurysms and those with lower dome to neck ratios, the finding that the use of the stent was associated with lower rates of poor angiographic outcomes and statistically higher rates of improving occlusions rates on follow-up suggests that it provides better protection against recurrence. Disappointingly the rate of retreatment within one year was the same (8%) in both groups.

I found several interesting items in the data which point to how treatments for unruptured aneurysms are performed. For instance, over a third of patients treated with coils alone were given dual antiplatelets drugs (APD) and there was a 2.9% rate for hemorrhagic stroke in the SAC group at 12 months. The authors discuss this issue and saw the lack of a uniform APD regime as a limitation to the study. The higher incidence of baseline risk factors for ischemic stroke was identified as contributing to this complication as was APD non-compliance in the SAC group. The need to define for a safe standard APD regime for prophylaxis against ischemic stroke after SAC remains a challenge which data such as that provided in this paper can help to resolve.

James Byrne, Oxford, UK

\* Trial sponsored by Stryker Neurovascular



## New Generation of Flow Diverter (Surpass) for Unruptured Intracranial Aneurysms. A Prospective Single-Center Study in 37 Patients

J. de Vries, J. Boogaarts, A. van Norden, A.K. Wakhloo

Stroke June, 2013

This case series presents a cohort of patients treated with the relatively new Surpass™ Flow Diverter (Stryker Neurovascular). This device has a near constant, and relatively high, pore density after deployment, theoretically improving flow diversion compared with competitive devices.

In this paper a cohort of 37 patients, harboring 49 aneurysms, is presented after clinical and radiological analysis up to six months. Treatment was performed for aneurysms in both the anterior and posterior circulation and included 14 bifurcation aneurysms. Aneurysms were characterized as saccular (n=14, of which five were previously coiled), fusiform and dissecting (n=10, of which one was previously coiled), multiple with segmental disease (n=24), and blister aneurysm (n=1). In one case the treatment was performed to treat an ICA dissection, which presented with a major thromboembolic stroke. All patients were treated with the standard dual antiplatelet regimen.

Procedural complications described were clot formation, distal MCA guidewire perforation prior to device placement, and two ICA dissections, one of which led to an ICA occlusion.

Post procedural complications consisted of 1) transient hemiparesis with MR signs of thromboembolic events, 2) TIAs in a clopidogrel non-responder, 3) severe epistaxis responding well to clopidogrel cessation, 4) frontal parenchymal hemorrhage after Surpass Flow Diverter placement in the posterior cerebral artery and 5) mass effect due to aneurysm thrombosis necessitating surgical debulking. In the latter two cases the dual antiplatelets were discontinued for obvious reasons, which led to TIAs in the first case, resolving after restarting the clopidogrel, and device occlusion in the second case.

Other complications were: 6) a subarachnoid hemorrhage at three weeks after treatment that was only discovered at six weeks follow up when the patient

reported the event, 7) partial device apposition in the region of the aneurysm neck with TIA's after discontinuation of clopidogrel at three months. MRI showed occlusion of the ICA and continuing clopidogrel prevented further symptoms.

Clinical results at six months showed improvement of symptoms in seven patients, stable results in 29 patients and worsening of symptoms (from mRS 0 to 3) in one patient due to a post-procedural stroke. There were no mortalities observed, and one procedure-related permanent neurological deficit was reported.

Radiological analysis showed complete occlusion in six out of 10 bifurcation aneurysms at six months. The 31 aneurysms with complete neck coverage showed complete occlusion in 29 cases. Narrowing of the device (<10%) and intimal hyperplasia (four cases) were observed but proved clinically asymptomatic. The authors detected 56 covered side branches without any clinical sequelae.

The authors conclude that the device shows a safety profile, clinical- and angiographic outcome, that is comparable or better than the current devices on the market.

### Personal comment

*This paper transparently describes a well-documented cohort of patients treated with the novel Surpass Flow Diverter. The data in the paper is quite extensive and this short summary didn't cover the full extent of the paper.*

*The use of flow diverters has been accepted for certain indications, and if we consider Surpass to be 'yet another flow diverter' this cohort doesn't lead to new insights. From my personal Surpass experience I tend to agree with a lot of the results put forward by the authors. However, there are several issues that shouldn't go unnoticed and warrant further research before reaching the conclusions of the paper.*

*Based on their cohort the authors claim a safety profile that is better than the current devices on the market. However, the pre- and peri-procedural complications are not that much different from the ones encountered with SILK (Balt) and PED (Covidien). Albeit that the clinical results are not bad, there were a number of serious events that could easily have turned out to be devastating. Furthermore, the results are only for the six months follow-up, so long-term results need to be awaited.*

*The authors defend the use of flow diverters by quoting a high recurrence rate of coiling. Although I support the need for better therapies, this quote is not appropriate since recent studies show a retreatment rate of about 3-5.5%. Another point of debate can be the assumption that flow diverter treatment is as safe as coiling. This claim is a false one if we consider that a large number of the problems encountered with flow diverters can be attributed to dual antiplatelet use, which is not the case in simple coiling. The generalized complication rate of 3%, for both coiling and flow diverter use, is in my opinion an underestimation. Hence, I would like to stress that the safety of endovascular treatment should be compared to surgery based on the specific type of endovascular treatment.*

*As the authors rightfully recognize, the cohort consists of 19 patients with aneurysms below 6mm in maximal diameter. Smaller aneurysms are not often the target for therapy and, although the authors provide many reasons for their decision to treat, it limits the comparability of this cohort to the previously published data on similar devices.*

*Furthermore, comparability is also hampered by the choice to include multiple subsets of aneurysms. A partially thrombosed fusiform aneurysm is likely to respond differently to FD treatment than a blister aneurysm, a sidewall aneurysm or a mere dissection causing a stroke.*



*That the indications chosen may be a reflection of the current flow diverter use does not change the fact that we still don't know what we are analyzing.*

*Another fact to consider is that, during the cohort, the Surpass™ Flow Diverter changed to newer generations, which considerably improved navigation, deliverability and visibility. This 'device-evolution' is a well-known phenomenon in testing new devices and it renders randomized trials useless in this phase of development. Publications on*

*cohorts show us where we stand, but if we really want to get answers we have to rely on well-designed, prospective registries. From these we can notice a trend of what is going on for each separate subgroup of aneurysms. These trends will eventually lead us to a future well-designed randomized trial with the established devices.*

*De Vries and Wakhloo, the ingenious minds behind Surpass, did a very nice job in presenting the results of their first cohort and their initial results need to be*

*applauded. Nevertheless, as they undoubtedly endorse, we will have to focus our future research on the many basic questions regarding the poorly understood mechanisms of intra-aneurysmal thrombosis, response to dual-antiplatelets, distant parenchymal hemorrhages and long term aneurysm ruptures. We still have a long way to go...*

**Patrick A. Brouwer,  
Leiden/Rotterdam/The Hague,  
The Netherlands**

## Endovascular Treatment of Intracranial Aneurysms with Flow Diverters: A Meta-Analysis

Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF  
Stroke. 2013;44:442-447. Epub 2013 Jan 15

In this meta-analysis 29 articles were included embracing altogether 1654 aneurysms. The paper focused on the most important variables, namely aneurysm occlusion rates and treatment related morbidity and mortality, also according to aneurysm size.

Complete aneurysm occlusion rate at six months was 76%, with similar values for small, large and giant lesions. The procedure related morbidity-mortality rate was 9% (morbidity 5%, mortality 4%), with better safety results for small aneurysms. Early and late intra-parenchymal hemorrhage occurred in 3% of cases, and was not associated with aneurysm size. Subarachnoid hemorrhage from presumably delayed aneurysm ruptures occurred in 4% of the cases, and was associated with large and giant aneurysms. The total ischemic stroke rate was 6%, also with higher frequency in patients with larger aneurysms, and in aneurysms from the posterior circulation, implying the role of the perforators. The authors concluded flow diversion is feasible and effective, although not without negligible morbidity and mortality rates, especially in larger aneurysms

### Personal comment

*The first flow diverter device was implanted in the frames of a clinical study in 2007, and the first series about the performance of this technology was published in 2009.*

*Less than four years later we already have a meta-analysis of the published papers.*

*This shows the great impact of this technology in the field of endovascular aneurysm treatment.*

*Flow diverters opened up the possibility to cure very difficult to treat aneurysms or lesions considered previously as untreatable by reconstructing and reinforcing severely diseased parent arteries. Hence, no wonder that after the very encouraging and promising initial results they were close to being considered the panacea for aneurysms. This paper however has clearly put the finger on the tender spot of this new technology, namely aneurysm occlusion and morbidity-mortality rates.*

*The results show that at six months about one quarter of the aneurysms treated with flow diverters alone are still not completely occluded. This number is especially striking if we consider the 9% morbidity and mortality rate, meaning that every fourth patient has undergone such a risky treatment without being cured. Behind this increased morbidity and mortality rates we find two important factors: procedure related delayed ruptures and ischemic events.*

*According to the suggestion of this paper, delayed ruptures occurred in 4% of all aneurysms treated, which is definitively higher than previous estimates of 1-2%. How could we avoid delayed ruptures? Although the authors state that it is not known if intra-saccular coiling would reduce this risk, we do know from historical evidence that coiled aneurysm, with or without stent assistance, do not present this phenomenon. Why would then coiling not work in association with flow diverters - not to mention, that the other great advantage of additional coiling would be immediate occlusion.*

*On the other hand, the high incidence of ischemic events has taught us that more individualized and accurate antiplatelet therapy is needed. Further, technical improvement of delivery and deployment systems and, eventually, decreasing thrombogenicity of these devices is required. It is time now to acknowledge the results of this meta-analysis and draw the conclusions needed to increase the effectiveness and the safety of this great technology.*

**Zsolt Kulcsár, Zurich, Switzerland**



## Justification of Unruptured Intracranial Aneurysm Repair : A Single-Center Experience

Ishibashi T, Murayama Y, Saguchi T, Ebara M, Arakawa H, Irie K, Takao H, Abe T  
AJNR Am J Neuroradiol. 2013 Aug;34(8):1600-5. Epub 2013 Apr 11

Whether to treat UIAs depends on various factors, aneurysmal size being by far the strongest predictor of rupture.

T. Ishibashi and colleagues reported their single center experience with a total of 1110 UIAs prospectively enrolled. Patients were either treated (325) or managed conservatively (603). In the observation group the rupture rate was 3.5%, significantly related to the aneurysmal size ( $p=0.001$ ).

The authors recommended treatment of UIAs larger than 5mm, although this study

suffers from several limitations: selection bias (the decision to treat was made mainly by the patient), absence of randomization; and loss of follow-up (around 10%).

### Personal comment

*Whether these results can be directly translated in European countries remains controversial, as Japanese people have a 2.8 time increased rupture risk<sup>1</sup>.*

*The individual risk of rupture should incorporate not only the aneurysmal size, but also take into account the region of*

*origin of the patient, presence of hypertension, patient's age, previous history of SAH, and site of the aneurysm, with a higher risk assigned to aneurysms arising from the anterior cerebral arteries, posterior communicating arteries, or the posterior circulation vessels.*

Alain Bonafé, Montpellier, France

1. Greving JP, Wermer MJ, Brown RD Jr et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014 ;13:59-66.

## Endovascular treatment of unruptured intracranial aneurysms and circulating endothelial cells

Vendrell JF, Cezar R, Kuster N, Lobotesis K, Costalat V, Machi P, Bonafe A, Vendrell JP  
Eur J Radiol. 2013 Apr;82(4):671-9

The authors of this paper made a tremendous effort to track down causes of clinically silent thromboembolic complications of endovascular aneurysm treatment. They hypothesized that such complications may result from microembolization of Circulating Endothelial Cells (CEC) mechanically detached from the arterial wall during catheter and device manipulation and carried out by the blood flow towards the cerebral capillary bed. Using a highly elaborated technique, they counted the number of circulating CEC-s and CEC clusters.

In 15 cases of unruptured aneurysms the number of CEC-s and CEC clusters were counted in samples taken from the Femoral Artery (FA) immediately after puncture, from the ICA immediately after introducing a 6F long sheath into its lumen (ICA1) and after completion of the procedure (ICA2), and from a Peripheral Vein before (PV1) and after (PV2) the procedure. Venous blood samples of 10 healthy individuals were used as controls. None of the patients had either angiographically visible embolization or clinical complications but 13 silent new ischemic foci were found on Diffusion Weighted MRI (DWI) in nine out of the 15 cases. Cell count demonstrated higher number of CEC-s in FA as compared to normal venous samples or PV1, and higher count in ICA1 as compared to FA or ICA2. More CEC-s were found in PV2 than in PV1

samples. Clusters of CE-s were not found in normal subjects and PV1 samples. Clusters of <5 cells were identified in ICA1 and PV2 samples, and clusters of >5 cells were seen in ICA1 samples. The authors concluded that arterial puncture and catheter manipulation results of detachment of CEC-s from the arterial wall resulted in free flowing endothelial cells and even cell clusters in the arterial circulation. While single CEC-s or clusters of <5 cells are unlikely to cause embolization due to their size, larger cluster may do so. That would explain the increase of CEC-s and <5 cells clusters in PV2 samples and the absence of clusters of >5 cells – those are the ones that got caught in the cerebral capillary bed. There was no correlation between cell counts and new DWI lesions

### Personal comment

*While this is a great work giving a completely new insight to the potential effect of endovascular manipulation, some of the conclusions must be handled carefully. We agree with the authors, that the major weakness of the work is the lack of correlation between the cell counts and the incidence of DWI lesions. Although they describe an extremely meticulous (maybe even too meticulous) method of avoiding iatrogenic embolization, there is absolutely*

*no guarantee of completely avoiding small air bubbles carried by device surfaces or generated by syringe change, etc. The authors mention that they consistently prepare their patients with clopidogrel, just in case a stent becomes necessary for the treatment of the unruptured aneurysm. It is unclear if they actually used stent + coil technique in this series and if there were any correlation between this and silent DWI lesion. Similarly, there is no mention of potential relationship of any other procedural details or aneurysm configuration and the number of new lesions. We are convinced that the more complex the technique needs to be, the higher the chance of having silent or symptomatic complications. Their last conclusion is that a higher rate of CEC-s in post treatment venous samples may represent more aggressive endothelial damage and, subsequently, higher risk of post-treatment complications might be of true clinical significance should the technique become easy and simple enough to be used in clinical practice.*

Istvan Szikora, Budapest, Hungary



## Safety and Efficacy of Neuroform for Treatment of Intracranial Aneurysms: A Prospective, Consecutive, French Multicentric Study

Genric JC, Biondi A, Pletin M, Mounayer C, Lobotesis K, Bonafé A, Costalat V; French SENAT Investigators  
AJNR Am J Neuroradiol. 2013 Jun-Jul;34(6):1203-8. Epub 2013 Jan 24

In this prospective, multicentric study named SENAT\*, several well-known French neurointerventionalists from ten centers studied the periprocedural as well as the midterm outcome after stent assisted coiling utilizing the Neuroform™ Stent System (Stryker Neurovascular). They investigated such treatment in 107 unruptured, mostly (92%) wide-necked aneurysms in an equal number of patients. Each patient was evaluated clinically before and after the procedure, at discharge and after one and 12-18 months, respectively. The occlusion was graded after the procedure as well as at a follow-up examination, mostly by catheter angiography, after 12-18 months. All patients were treated medically with double anti-aggregation (clopidogrel and asa) but there was no specified protocol in the study, resulting in a variety of doses and regimes. The peri-procedural effect of the drugs was not monitored, or at least not reported.

The authors report 6% of technical failures even though these incidents were managed, for example by implanting a second stent, and did not cause any adverse events. After the procedure, 66% of the treated aneurysms were completely occluded, whereas 21% revealed a residual neck and in 13% there was a residual aneurysm. In 93 patients investigated after 12-18 months, 74% had a complete occlusion, whereas 13 patients had residual aneurysms (14%), of whom four (4%) needed subsequent retreatment. The rate of aneurysm recurrence, i.e. moving from complete occlusion to residual neck/aneurysm, or, from residual neck to residual aneurysm, was 10%, whereas a progressive occlusion, i.e. moving from a residual to complete occlusion or to a smaller residual, was 14%.

Four patients (4%) suffered from symptomatic peri-procedural complications

but only two of these remained symptomatic at discharge. At one-month follow-up, these patients had fully recovered. A second clinical follow-up was performed in 100 patients after 12-18 months revealing one patient with a delayed symptomatic ischemic event and one patient who had died from an unrelated cause, leading to a rate of permanent morbidity as well as of mortality at 1%. There were three patients (3%) with in-stent stenosis, all of which were asymptomatic. No patient suffered from intracranial hemorrhage but one had a severe retroperitoneal hematoma causing a secondary hemodynamic stroke with transient neurological deficit.

The authors conclude that stent assisted coiling for unruptured aneurysm, especially wide-necked aneurysm, is effective in achieving high levels of occlusion and with no increase in the morbidity/mortality rates as compared to standalone coiling

### Personal comment

*The authors have convincingly shown that stent assisted coiling is both a safe and effective method of treating unruptured, wide-necked aneurysms. For many of these aneurysms, standalone coiling is obviously not possible for anatomical reasons and the remaining endovascular option is therefore usually utilizing a balloon reconstruction technique. The balloon technique however carries its own complications and risks, and does not have the potential flow and scaffolding effects that come with a stent, effects that are also discussed in this article. Other options may be implantation of a flow-diverter or an intra-arterial embolization device even though these methods are still much less evaluated, especially long-term for the rather small, wide-necked aneurysms that were included in the SENAT-study. A direct, prospective comparison between different methods of*

*treating this type of aneurysms is, of course, very difficult to perform making studies like SENAT very important.*

*What I find especially intriguing in this study is the low level of both delayed thromboembolic, as well as hemorrhagic, complications. A fear when leaving foreign material in the cerebral vasculature is obviously that it may cause ischemic events and that the necessary anti-aggregation may result in intracranial and other serious hemorrhages. If both these complications are almost negligible, the rate being seemingly not higher than for standalone coiling, then perhaps the indication for the technique may even be widened, especially if, like in this study, both the angiographic and clinical outcomes are excellent. Perhaps then a stent, as discussed in this study, makes the result more stable and predictable and, consequently, could also be applied for aneurysms with less wide necks. In our institution, we prepare all our unruptured aneurysm patients with double anti-aggregation before the procedure and are more liberal to implant a stent even for non wide-necked aneurysms in case standalone coiling seem to result in a non-satisfactory immediate result.*

*In summary, this is a well-performed and important study with an interesting result. The only question that may be asked is if the results can also be transferred to less experienced centers. The neurointerventionalists who participated in SENAT are all very skilled and working in well-organized interventional settings. Whether the outcome will be the same from this slightly more complicated procedure in smaller centers with less experience and caseload remains an open question.*

**Tommy Andersson, Stockholm, Sweden**

\* Sponsored by Stryker Neurovascular



## End Controversy - Clipping of Asymptomatic Intracranial Aneurysm That is <7mm: Yes or No?

Robert D. Brown Jr

Stroke. 2013 Jun;44(6 Suppl 1)

Unruptured intracranial aneurysms (UIAs) constitute a significant public health problem in the United States, with 2% of the population being affected, and it is a growing concern given the increasing frequency of detection on noninvasive brain imaging. Available natural history data suggest that key risk factors for hemorrhage among patients with UIAs include aneurysm size, location, and potentially presence of a daughter sac, and Japanese or Finnish race/ethnicity. In addition, there are some data that suggest a family history of subarachnoid hemorrhage may predict a heightened risk of hemorrhage in a patient with a small UIA. Other morphological characteristics are being studied as potential predictors of rupture. In patients managed conservatively, repeat imaging is typically recommended, and it is apparent that there is a risk of aneurysm growth, even among patients with small aneurysms, <7mm in diameter. There is limited data available on the long-term rupture risk in a patient with an enlarging aneurysm because early treatment is typically recommended. The data that does exist indicates that the rupture risk may be high. Interventional treatment with surgical clipping or endovascular management is available for all patients with a small UIA.

Once an UIA is identified, the natural history for that UIA must be carefully compared with the risks of endovascular or surgical intervention to decide on the best management recommendation. Several aneurysm and patient-related factors need to be carefully considered, including aneurysm size, location, symptom status, other aneurysm morphology characteristics, presence of a daughter sac and occurrence of aneurysm growth, and patient issues, including family history of subarachnoid hemorrhage, overall medical status, age, and the patient's overall perspective on management after hearing an unbiased summary of the natural history and interventional risks.

In the absence of direct clinical trial data comparing conservative management with surgical or endovascular intervention for small UIAs <7mm in diameter, the following is an appropriate general management strategy: endovascular coiling or surgical clipping should be considered in selected

patients, mainly in younger patients, particularly with higher risk features, including symptomatic aneurysms, or those with features, such as posterior communicating or vertebrobasilar location, presence of a daughter sac, suggestion of aneurysm enlargement on repeat imaging, and those with a strong family history of intracranial aneurysm rupture. All patients should be assisted in smoking cessation if they are smokers, and use antihypertensive medications if necessary to control blood pressure.

### Personal comment

*In the commentary by Robert Brown, two different statements are confronted about whether or not to treat smaller than 7mm unruptured intracranial aneurysms (UIA). The main origin of this question rises in the still unknown biology of intracranial aneurysms. We have learned a lot about them and certainly how to treat them, in the last decade but there is still a black box regarding their nature, their growing mechanisms and rupture causes. There is no correct answer yet about to treat or not to treat, but interesting points are addressed in this paper.*

*The ISUIA trial gave us certain clues on how to manage these group of patients, with a recommendation of not to treat aneurysms under 7mm because of their almost 0% risk of bleeding at certain locations. But this, as referred in the article is very variable. Several papers have showed a higher bleeding risk in certain population as Finland or Japan. So maybe it is not easy to extrapolate all data to the general practice around the world with different genetic and epidemiologic patterns. More over, the follow up period of the 2003 ISUIA was around 5 years; short, if we consider young patients or the increasing survival age around the world. Maybe this could overweight the morbidity/mortality of preventive treatment of these aneurysms.*

*On the other side there is still doubt about treating these aneurysms mainly because*

*of the morbidity of interventions. Since 2002, endovascular techniques are the most employed choice in UIA treatment in the USA<sup>1</sup>, with high-level evidence showing better functional and clinical outcomes in coiled than clipped patients<sup>2</sup>. Therefore, endovascular coiling should be the main alternative to expectant management of UIA when there is an experienced team in this field. But it is also true that results may vary between centers and experience. We don't have yet the right answer on what is the "tolerable" morbi/mortality.*

*An interesting point of view is the usual small size of ruptured aneurysms where almost 77% of ruptured intracranial aneurysms could have less than 10mm of diameter<sup>3</sup>. In our local experience of endovascular treated aneurysms between 1997 to 2012, 56% (628/1115) of these were ruptured and 81% of the ruptured lesions were classified as small (less than 10mm). This could be really against ISUIA statements, but an interesting theory postulates that aneurysm rupture occurs shortly after its formation, so they do not reach larger sizes. If they don't rupture they stabilize and the probability for remaining in that state is high<sup>4</sup>. On the other hand, large UIA has greater risk of rupture in cohorts because some of these larger aneurysms are diagnosed in a growing stage, a well-known rupture predictor<sup>5, 6</sup>.*

*There is no doubt that we need more tools and more predictors, beyond the size, morphology or other epidemiological data. Computer Flow Dynamics (CFD) could be one of these tools, but although it has given us a lot of interesting findings, like the wall shear stress and its interaction with the wall biology and rupture risk, there is still a need for stronger data to rely on and introduce it in daily practice.*

*Finally, the patient's point of view must be considered in decision-making. Patients with an unruptured intracranial aneurysm have an impaired quality of life, quite similar*



to diseases like rheumatoid arthritis, cervical spondylotic myelopathy and minor stroke<sup>7</sup>. In some cases, refractory distress and impaired quality of life of patients would justify treatment of UIA. But we must take this with care. Maybe we need more patient education or better counseling.

We think that a conservative management policy based on risk profile is appropriate in the treatment of small UIA. Nevertheless, we always consider and analyze each single case, considering morphology, epidemiology, life style and patient's personal decision. In the case of indication

for treatment, endovascular therapy is our first choice.

**Rodrigo Rivera, Juan Gabriel Sordo, Rodrigo Riveros and Pablo Giacaman, Santiago, Chile**

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## Endovascular Therapy for Asymptomatic Unruptured Intracranial Aneurysms JR-NET and JR-NET2 Findings

Tomoyoshi Shigematsu; Toshiyuki Fujinaka; Toshiki Yoshimine; Hirotochi Imamura; Akira Ishii; Chiaki Sakai; Nobuyuki Sakai; for the JR-NET Investigators  
*Stroke.* 2013;44: 2735-42

National registration studies (the Japanese Registry of Neuroendovascular Therapy [JR-NET] and JR-NET2) have determined the current status and outcomes of neuroendovascular therapy (neuro-EVT). The authors analyzed short-term outcomes of EVT for asymptomatic unruptured intracranial aneurysms (UIAs)\*.

Periprocedural information about EVT for 4767 asymptomatic UIAs was extracted from 31968 registered procedural records of all EVT in the JR-NET and JR-NET2 databases. The authors assessed the features of the aneurysms and procedures, immediate radiographic findings, procedure-related complications, and clinical outcomes at 30 days after the procedures.

80.0% of UIAs were located in the anterior circulation, and the most frequent were paraclinoid. The diameter of 2.5%, 32.9%, 51.9%, 12.0%, and 0.7% of the UIAs was  $<3$ , 3 to 4, 5 to 9, 10 to 19, and  $>20$ mm respectively. EVT failed in only 2.1%. Adjunctive techniques were applied in 54.8% of procedures. The immediate radiographic outcomes of 57.7%, 31.9%, and 10.0% of the UIAs comprised complete occlusion, residual necks, and residual aneurysms, respectively.

Complications that were associated with 9.1% of procedures comprised 2.0% hemorrhagic and 4.6% ischemic, and the 30-day morbidity and mortality rates were 2.12% and 0.31%, respectively. The authors conclude that radiographic results of EVT for asymptomatic UIAs in Japan were acceptable, with low mortality and morbidity rates.

### Personal comment

*This is a difficult study, mainly just a description of what occurs if an aneurysm is treated via the endovascular approach in Japan. The authors extracted information about the outcomes of EVT for asymptomatic UIAs from those of all EVTs that were retrospectively registered by physicians at several neurointerventional centers but they do not represent the nationwide total. Furthermore, aneurysms that were treated more than once could not be excluded from the present study. The results are biased because the treating physicians assessed radiographic and clinical outcomes and procedure related complications. Decisions on treatment indications might have also introduced*

*inclusion bias.*

*This report simply describes the outcomes of EVT for asymptomatic UIAs, which did not include surgically treated or untreated UIAs, and the population of patients with asymptomatic UIAs was not representative of the total. Just one example of that: the vast majority of aneurysms were paraclinoid ones. However, one would expect AcomA aneurysms to be the largest group.*

*In summary, I do not understand why this report was published in STROKE. From a scientific point of view this study does not add anything new, despite the perception that the total complication rate (9.1%) was relatively high.*

*To be honest, the authors themselves mentioned these drawbacks and saw that we clearly need more prospective and unbiased data.s.*

**Michael Forsting, Essen, Germany**

\* Study supported by research grants for cardiovascular diseases from the Ministry of Health, Labor, and Welfare of Japan





## Results of endovascular treatment of middle cerebral artery aneurysms after first giving consideration to clipping

Adib A. Abila, Shady Jahshan, Peter Kan, Maxim Mokin, Travis M. Dumont, Jorge L. Eller, Kenneth V. Snyder, L. Nelson Hopkins, Adnan H. Siddiqui, Elad I. Levy  
*Acta Neurochir* (2013) 155:559–568

The authors of this article have carried out a retrospective analysis of the results of endovascular treatment of a series of 34 aneurysms of the middle cerebral artery. This series is a subgrouping (22.8%) from a total of 149 aneurysms in that same location compiled over the period between 2005 and 2009. 115 of the aneurysms were treated by clipping, though the authors do not compare the clinical and morphological outcomes of these with the endovascular series. All the endovascular and surgical procedures were carried out by neurosurgeons. Indications for endovascular treatment were patients who refused craniotomy, elderly patients who were at anaesthesia risks, and cases in which the aneurysm neck was highly conducive to endovascular treatment.

Of the patients who were treated endovascularly, 42.4% (14 patients) presented with subarachnoid haemorrhage (SAH). Endovascular complications occurred in 14 procedures (41.2%). The complications encountered were bleeding in seven cases (20.6%), carotid dissections that required stenting in two (5.9%), and thromboembolism in five (11.8%). Periprocedural mortality for the cases treated endovascularly was 5.9%, and late rebleeding occurred in 14.3% of cases.

The authors express the opinion that, while the Barrow Ruptured Aneurysm Trial predicted better clinical outcomes for embolized aneurysms than for clipped aneurysms, this does not hold true for all anatomical locations, aneurysms of the middle cerebral artery in particular. The conclusion reached by the article is that surgical clipping is the treatment of choice for middle cerebral artery aneurysms.

### Personal comment

*The view that aneurysms in the territory of the middle cerebral artery present special difficulties for endovascular treatment is widely held. It is also true that indications for surgery are more frequent for aneurysms in this territory than for aneurysms at other sites. Still, the high rate of complications in the series considered, particularly the iatrogenic aneurysm rupture rate and the number of carotid dissections, is noteworthy.*

*This data suggests that the endovascular surgeons who carried out the procedures were still in the lower part of their learning curve. This could be related to the age of the series considered in this article, cases treated five to 10 years ago. Today a mortality rate of 6% for endovascular procedures is unacceptable under any circumstances.*

*The age of the series of Abila et al. could also account for the preference for surgery over endovascular treatment of aneurysms of the middle cerebral artery, by not having been in a position to take advantage of the significant technical developments and advances in materials that have taken place in the endovascular treatment of cerebral aneurysms in recent years. The Materials and Methods section of the article considered makes no mention of flow diverter devices, advanced stenting techniques, complex intraaneurysmal devices, multicatheter techniques, or*

*complex remodeling methods currently in daily use<sup>1,2,3,4</sup>. The therapeutic arsenal and experience in handling endovascular techniques at many centres around the world have significantly increased the indications for endovascular treatment of cerebral aneurysms. At the same time, morphological outcomes of endovascular treatments have improved, and all this offers better medium and long-term clinical outcomes than transcranial procedures.*

*Without denying the usefulness of conventional surgery for particularly complex lesions or lesions that are difficult to access, there are many today who consider that endovascular treatment should be the first option for all cerebral aneurysms, carried out by a team well trained in all neurointerventional techniques.*

### Jorge Olier, Pamplona, Spain

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## Comparative Effectiveness of Unruptured Cerebral Aneurysm Therapies: Propensity Score Analysis of Clipping Versus Coiling

Jennifer S. McDonald, Robert J. McDonald, Jiaquan Fan, David F. Kallmes, Giuseppe Lanzino, Harry J. Cloft  
Stroke. 2013;44:988-994

Endovascular therapy has increasingly become the most common treatment for unruptured cerebral aneurysms in the United States. The authors evaluated a national, multi-hospital database to examine recent utilization trends and compare periprocedural outcomes between clipping and coiling treatments of unruptured aneurysms.

They used the Premier Perspective Database to identify patients hospitalized between 2006 and 2011 for unruptured cerebral aneurysm who underwent clipping or coiling therapy. A logistic propensity score was generated for each patient using relevant patient, procedure, and hospital variables, representing the probability of receiving clipping. Covariate balance was assessed using conditional logistic regression. Following propensity score adjustment using 1:1 matching methods, the risk of in-hospital mortality and morbidity was compared between clipping and coiling cohorts.

A total of 4899 unruptured aneurysm patients (1388 clipping, 3511 coiling) treated at 120 hospitals were identified. Following propensity score adjustment, clipping patients had a similar likelihood of in-hospital mortality (odds ratio [OR], 1.43; 95% confidence interval [CI], 0.49–4.44;

$P=0.47$ ) but a significantly higher likelihood of unfavorable outcomes, including discharge to long-term care (OR, 4.78; 95% CI, 3.51–6.58;  $P<0.0001$ ), ischemic complications (OR, 3.42; 95% CI, 2.39–4.99;  $P<0.0001$ ), hemorrhagic complications (OR, 2.16; 95% CI, 1.33–3.57;  $P<0.0001$ ), postoperative neurological complications (OR, 3.39; 95% CI, 2.25–5.22;  $P<0.0001$ ), and ventriculostomy (OR, 2.10; 95% CI, 1.01–4.61;  $P=0.0320$ ) compared with coiling patients.

The conclusion of the paper is that, among patients treated for unruptured intracranial aneurysms in a large sample of hospitals in the United States, clipping was associated with similar mortality risk but with a significantly higher periprocedural morbidity risk compared with coiling.

### Personal comment

*This is a nice and huge study dealing with unruptured aneurysms throughout the US. The results are not surprising, they confirm what we already know:*

- *if properly selected, coiling is associated with a lower morbidity*
- *discharge to long-term care 17% clipping versus 4% coiling*

- *ischemic complications, 10% clipping versus 3.6% coiling*
- *postoperative neuro complications, 7.7% clipping versus 2.4 % coiling*

*However, this study, of course, has a major bias. My experience from the last decade is that the more difficult aneurysms are selected for surgery. No wonder, that the outcome in the coiling group is so significantly better. And don't draw the conclusion that due to this study all patients need coiling instead of clipping. There were clear reasons to clip one third of the patients, the majority in this group were probably not good candidates for endovascular therapy.*

*Anyhow, despite these drawbacks, this study again nicely shows that endovascular therapy should be first-line treatment for the vast majority of patients with unruptured intracranial aneurysms.*

Michael Forsting, Essen, Germany



## Natural History of Asymptomatic Unruptured Cerebral Aneurysms Evaluated at CT Angiography: Growth and Rupture Incidence and Correlation with Epidemiologic Risk Factors

J. Pablo Villablanca, Gary R. Duckwiler, Reza Jahan, Satoshi Tateshima, Neil A. Martin, John Frazee, Nestor R. Gonzalez, James Sayre, and Fernando V. Vinuela  
Radiology. 2013 Jul 2. [Epub ahead of print]

This paper looks at the relationship between aneurysm size and epidemiologic risk factors along with growth and rupture using computed tomographic (CT) angiography. Patients with known asymptomatic, unruptured aneurysms were followed up longitudinally with CT angiography. Epidemiological data looked at risk factors for growth and rupture, age, sex, cigarette smoking, aneurysm size, diabetes, family history, hypercholesterolemia, history of prior rupture, hypertension, mural aneurysm calcification, aneurysm location and multiplicity and presence of vascular malformation.

The authors followed up 165 with 258 aneurysms at a mean follow-up of 2.24 year from diagnosis. 48 of 258 aneurysms,

18% in 38 patients grew larger. Spontaneous rupture occurred in four of 228 (1.8%) intradural aneurysms with a risk of aneurysm rupture per year of 2.4% with growth and 0.2% without growth. There was a 12 fold higher risk of rupture for growing aneurysms. Analysis of epidemiologic risk factors and their relation to aneurysm growth revealed that both tobacco smoking and initial aneurysm size were independent covariates associated with aneurysm growth. Other risk factors listed above were not significant

### Personal comment

*The study does confirm what many of us do routinely in our practice in the management of asymptomatic unruptured aneurysms, ie longitudinal follow-up either*

*with CT angiography or, in some of the larger aneurysms, with 3T MRA. Growth of even small aneurysms would suggest an indication for treatment as these do appear in this study and others to have a higher risk of rupture. Both CT angiography and MRA are very capable of looking at changes in shape and also the formation of blebs, which have also been associated with a higher risk of rupture in other studies. As regards epidemiology, as always cessation of smoking as shown in previous studies is mandatory.*

Andy Clifton, London, UK

## Effect of antiplatelet therapy on thromboembolism after flow diversion with the Pipeline Embolization Device

Robert S. Heller, Venkata Dandamudi, Michael Lanfranchi, and Adel M. Malek  
J Neurosurg. 2013 Dec;119(6):1603-10

Data regarding the incidence of acute procedure-related thromboembolic complications following deployment of the Pipeline Embolization Device (PED) remains unknown. Therefore, data in all patients receiving a PED for treatment of an intracranial aneurysm were prospectively maintained in a database. The incident rate of procedural embolism was established on DWI MR images, and univariate analysis was then performed to determine any associations of embolic events with measured variables. Twenty-three patients with 26 aneurysms were eligible for inclusion in the study. Thirty-one PEDs were deployed in 25 procedures. Procedural embolic events were found in the target parent vessel territory in 13 (52%) of 25 procedures, with no patients harboring lesions contralateral to the deployed PED. The number of embolic events per procedure ranged from three to 16, with a mean of 5.4. There was no significant difference between cases with and without procedural embolism in platelet inhibition by ASA (mean 15% vs 12% residual activation;  $p = 0.28$ ), platelet inhibition by clopidogrel (mean 41% vs 41% residual activation;  $p =$

0.98), or intraprocedural heparin-induced anticoagulation (mean activated clotting time 235 seconds vs 237 seconds;  $p = 0.81$ ). By multivariate analysis, the authors identified larger aneurysm size ( $p = 0.03$ ) as the single variable significantly associated with procedural embolism. There was no significant relationship between aneurysm size and the number of embolic events ( $p = 0.32$ ) or the total burden of the embolism lesion area ( $p = 0.53$ ). Acute embolism following use of the PED for treatment of intracranial aneurysms is more common than hypothesized. The only identifiable risk factor for embolism appears to be greater aneurysm size, perhaps indicating significant disturbed flow across the aneurysm neck with ingress and egress through the PED struts. The strength of antiplatelet therapy, as measured by residual platelet aggregation, did not appear to be associated with cases of procedural embolism.

### Personal comment

*The authors did a great job and tried to figure out how many ischemic events do*

*occur and why they occur during placement of PED. The findings of the current study indicate a high rate of silent procedure-related ischemic events, as measured by diffusion-weighted MRI. Greater aneurysm size was found to be significantly associated with the occurrence of these events. Effectiveness of antiplatelet inhibition alone was not sufficient to explain the rate of events, though it is possible that a threshold effect may contribute to the observed findings. These results support a need for close observation of patients treated using flow diverter devices given the higher rate of periprocedural ischemic lesions, compared with equivalent conventional stent-mediated coiling procedures. The results point to a clear need for furthering the understanding of the fundamental mechanism of platelet and thrombus interactions with the PED device within the vessel wall.*

Michael Forsting, Essen, Germany



## Endovascular Treatment of Intracranial Aneurysm in Elderly Patients: A Systematic Review and Meta-Analysis

Sturiale CL, Brinjikji W, Murad MH, Lanzino G

Stroke 2013;44:1897-1902

The authors report a meta-analysis of the literature to assess clinical and angiographic outcomes in elderly patients. The review is based on 21 studies and a total of 1511 patients  $\geq$  65 years old. 71.5% of these patients presented with subarachnoid hemorrhage and 89% were treated with coiling alone.

The overall perioperative mortality rate was 14% (23% in patient with SAH) while the permanent perioperative morbidity rate was 8%. About outcomes, 78% of the patients had good recovery or moderate disability at 12 months after embolization; angiographic result of total or sub-total occlusion at follow-up >12 months was obtained in 86% of cases.

### Personal comment

*Endovascular treatment has become the first option in the therapy of intracranial aneurysms and demographic changes make the chance to manage older patients more common: These are some of the reasons why the meta-analysis of the Rochester group provides us with useful data and topics to think about in our work. In patients > 65 years old with SAH, the main factor to consider is that the endovascular treatment leads to a good*

*clinical outcome in a large proportion of the patients (66%) at the price of a periprocedural mortality of 23%. Bearing in mind that the different clinical status (H&H, WFNS grade) remains an important predictive factor for the patient outcome, these results make an attempt of endovascular treatment of the ruptured aneurysm mandatory in any elderly patient. Actually it would be important to stratify clinical outcomes versus aneurysm location, both to clarify whether there is still the benefit of a possible neurosurgical approach for clipping<sup>1</sup> and to define the indications for treatments, such as stent-assisted coiling and flow-diverters.*

*Things are more complex in patients > 65 years old with unruptured aneurysm. For decades we have witnessed different evaluations of the risk of bleeding in unruptured aneurysms and of the relevance of any associated risk factors such as hypertension, so frequent in elderly. From ISUIA<sup>2</sup> to the recent UCAS<sup>3</sup>, we have data about the natural risk of aneurysm bleeding that we must compare with the risk of our intervention in our institutions and the life*

*expectancy of the patient. However, in the treatment decision, our daily experience is based also on the evaluation of other factors (that are difficult to extrapolate from large trials) such as particular vascular anatomy and aneurysm morphology (e.g. daughter sac), general clinical condition and emotional status of the patient.*

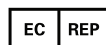
*Therefore this meta-analysis provides useful data to share with elderly patients and their families, In assessing the benefit of the endovascular therapy in an area that, in my opinion, will see an increase in the number of procedures in the next years.*

Lucio Castellan, Genova, Italy

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