Abbreviations

ACoA: anterior communicating artery

aSAH: aneurysmal subarachnoid haemorrhage

BRAT: Barrow Ruptured Aneurysm Trial

CT: computed tomography

CTA: computed tomogram angiography

DCI: delayed cerebral ischaemia

DIND: delayed ischaemic neurological deficit

DSA: digital subtraction angiography

GCS: Glasgow Coma Scale

GOS: Glasgow Outcome Scale

HDU: high dependency unit

ICA: internal carotid artery

ICG: indocyanine green

ISAT: International Subarachnoid Aneurysm Trial

ITU: intensive therapy unit

MCA: middle cerebral artery

MRA: magnetic resonance angiography

mRS: modifield Rankin Scale

OR: odd ratio

PCoA: posterior communicating artery

STASH: SimvasTatin in Aneurysmal Subarachnoid Haemorrhage

WFNS: World Federation of Neurosurgical Societies

95% CI: 95% confidence interval

Highlights

This is an important study after the publication of ISAT and BRAT for the management of aSAH, where coiling is generally believed to be superior, and is the first line treatment for aneurysm obliteration in many neurosurgical centres worldwide.

ISAT study randomized aneurysms suitable for both coiling and clipping, while the data has since been generalized to the entire cohort of cerebral aneurysms including the wide neck, complex aneurysms. Currently, in many UK centres, over 90% of aneurysms are coiled, as the perception has been coiling is better, and every attempt should be made to coil aneurysms (even subtotally), with surgery only a last resort. We hope that our data will help to modify this viewpoint.

In the current era of aSAH management, apart from patients' admission status, SAH blood load and the development of DCI, treatment modality with either coiling or clipping was not associated with poor outcome difference at 6 months.

The key message is that in the event of any perceived difficulty with coiling, then one can comfortably offer clipping without the concern for a long-term disadvantage for clipping. The short-term advantages for coiling are still very apparent.

What factors determine treatment outcome in aneurysmal subarachnoid haemorrhage in the modern era? – a post hoc STASH analysis

Mario Teo[1,2], Mathew R Guilfoyle[3], Carole Turner[3], Peter J Kirkpatrick[3], for the STASH Collaborators

1. Department of Neurosurgery, Institute of Neurological Science, Glasgow, UK;
2. Department of Neurosurgery, Southmead Hospital, Bristol, UK;
3. Academic Division of Neurosurgery, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Corresponding Author:

Mr Mario Teo FRCS (NeuroSurg)
Department of Neurosurgery
Southmead Hospital,
Bristol,
BS10 5NB
United Kingdom
Tel: +44 117 9505050
Email: marioteo@doctors.org.uk

Keywords: Neurosurgical clipping, Endovascular coiling, aSAH, post hoc analysis, propensity-matched analysis

Abstract

Introduction: The management of aneurysmal SAH has changed dramatically in the last few decades with the publication of a few major studies including The International Cooperative Study on the Timing of Aneurysm Surgery Study, International Subarachnoid Aneurysm Trial (ISAT). The aim of this study is to analyse the outcome of patients with aSAH based on a contemporary series, identify the risk factors for poor outcome, and focusing on patients with good grades aSAH (to match the ISAT cohort).

Method: Baseline demographic and outcome data (mRS) was available on the 803 patients recruited from the STASH (Simvastatin in aneurysmal subarachnoid haemorrhage) trial for post hoc analysis, using chi square test or two-sample t-test. Logistic regression analysis was performed to assess the risk factors for poor outcome at 6 months. Propensity matched analysis comparing coiling and clipping, and subgroup analysis of good grades patients (WFNS I-II) were also performed.

Result: Logistic regression analysis showed that the treatment modality (i.e coiling or clipping) was not associated with poor outcome at 6 months ($p=0.839$). The risk factors associated with poor outcome at 6 months were poor admission WFNS grade ($p<0.0001$), Fisher grade on initial CT scan ($p=0.013$), and the development of delayed cerebral ischaemia (DCI) ($p<0.0001$). Subgroup analysis for good grades patients only showed 82% of patients post coiling, and 78% of patients post clipping were classed as good outcome at 6 months ($p=0.181$).

Conclusion: In the current era of aSAH management, apart from patients' admission status, SAH blood load and the development of DCI, treatment modality with either coiling or clipping was not associated with poor outcome difference at 6 months.

Introduction

The management of aneurysmal subarachnoid haemorrhage has changed dramatically in the last few decades. The International Cooperative Study on the Timing of Aneurysm Surgery was the first large-scale, prospective, observational study to look at the issue of timing, and they also addressed factors that influenced outcome at 6 months stratified by Glasgow Outcome Scale (GOS). With 3521 patients recruited out of 8879 patients with SAH between 1980 and 1983,[1,2] 75% of those admitted within 3 days were in good condition, with a 58% good recovery at 6 months, and 25% death rate. Initial bleed, vasospasm and rebleeding were the major causes of death and disability. A number of key prognostic factors identified included admission Glasgow coma scale (GCS) (75% who were alert on admission had good recovery, compared to 11% who were comatose) and age (only 26% of those between 70 and 87 years had a good outcome). The results also showed that at 6 months, 69% who had surgery had good outcome, with alert patients preoperatively had a favourable prognosis if operated between days 0-3 or after day 10. Subgroup analysis then showed that 71% versus 62% of patients operated on between days 0-3 versus days >10 had good recovery ($p<0.01$).[3]

This study confirmed that older, poor-grade patients with pre-existing medical conditions have a bleak prognosis. It also prompted an international change on the timing to early surgery for good grade patients.

The International Subarachnoid Aneurysm Trial (ISAT)[4-6] was the first large scale randomized trial of endovascular coiling vs. microsurgical clipping of ruptured aneurysms. 2143 patients from the initial 9559 patients screened were randomized, and a statistically significant outcome difference (using mRS) of 7% was found at one year in favour of coiled patients. Of the enrolled patients, 88% were good grades (WFNS class I or II), 95% were anterior circulation aneurysm, and 90% were smaller than 10mm. The trial result has since been generalized to most patients with aSAH in many parts of the world, with over 90% of cerebral aneurysms managed by endovascular coiling in many UK neurosurgical centres. [7,8]

With technological advances over the last two decades, changing practice in the management of aSAH patients, increasing proportion of patients coiled, and improvements in both microsurgical and endovascular techniques there is a need for to reassess the factors determining patients' outcome in a contemporary series.

The Simvastatin in aneurysmal subarachnoid haemorrhage (STASH) trial was an international, multicentre, parallel group, double-blinded, randomized phase 3 trial. It was designed to determine whether simvastatin 40mg could improve the long-term outcome of patients with aSAH. 803 patients were recruited from 35 neurosurgical units (23 in the UK and 12 non-UK sites) between January 2007 and February 2013. Details of the study are described in a previous paper. [9]

The aim of the present study was to analyse the STASH cohort to identify risk factors for poor outcome and to compare the outcome between those managed by neurosurgical clipping and endovascular coiling. focusing on patients with good grade aSAH (in line with the ISAT cohort).

Materials and Methods

Trial design and participants

Baseline demographic and outcome data were available on the 803 patients recruited from the STASH trial for post hoc analysis.

Inclusion criteria were radiological confirmatory evidence of an aneurysmal subarachnoid haemorrhage (by digital subtraction angiography [DSA], CT angiography [CTA], or magnetic resonance angiography [MRA], age 18-65 years and the presentation less than 96 hours from ictus. Exclusion criteria were patient taking statin therapy at presentation, pregnancy, no reasonable prospect of survival, known renal or hepatic impairment, patient not fully independent before bleed, strong suspicion of drug or alcohol misuse, patient unlikely to be amenable to follow-up, patient taking warfarin-type drugs, patient taking contraindicated medication (amiodarone, amlodipine, verapamil, or potent CYP3A4 inhibitors), or suspected additional life-threatening disease.

Of the 803 patients, coiling only was performed in 513 patients (64%), clipping only in 254 patients (32%), both coiling and clipping in 14 patients (2%), 22 patients had no treatment or were treated by other means. For the purpose of this post-hoc analysis, patients with single modality treatment of coiling or clipping were included, i.e. 767 patients.

Outcomes

The primary outcome was the distribution of modified Rankin Scale (mRS) at 6 months by means of a standardized questionnaire. Secondary outcomes were death at 6 months, delayed ischaemic deficit, delayed ischaemic deficit requiring rescue therapy, admission to an intensive care unit, incidence of sepsis, discharge destination, quality of life as measured by the SF-36 (short form health survey questionnaire) at 6months. These secondary outcomes were preselected to provide supportive evidence related to the primary outcome. We defined delayed ischaemic deficit as a deterioration of two or more points on the Glasgow Coma Scale or the development of new neurological deficit that could not be attributed to any other cause including sepsis. We defined sepsis when clinical symptoms (eg raised temperature, raised white cell count, tachycardia, or raised respiratory rate) had microbiological confirmation. Use of hypervolaemic and inotropic rescue treatment was that adopted by every centre and did not follow any prescribed definition.

Statistical Analysis

Conventional dichotomy of favourable mRS (0-2) versus unfavourable mRS (3-6) was used for outcome analysis.

Comparison table of the baseline characteristics of patients who underwent coiling or clipping was shown. Statistical analysis was performed using chi square test or two-sample t-test as appropriate, to identify risk factor associated with poor outcome at 6 months (primary outcome). Logistic regression analysis was performed to correct for confounding factors to further assess the risk factors for poor outcome at 6 months. Results are presented as an adjusted common odds ratio (OR) with the corresponding 95% confidence interval (CI), with values of the common OR more than 1 indicating risk factors associated with poor outcome.

Propensity Matched Analysis

To compare the outcomes of patients who had aneurysms secured by endovascular coiling with those who underwent microsurgical clipping a propensity matched analysis was undertaken. This procedure essentially matches patients treated with coiling or clipping who have similar baseline factors to mimic, as closely as possible, the balanced groups that would be expected had the patients been randomly allocated to their respective aneurysm treatment.

The propensity score was constructed using logistic regression of aneurysm treatment (clipping vs. coiling) against age, sex, admission WFNS grade, Fisher grade, need for mechanical ventilation on admission, aneurysm location, and randomization group (control vs. statin). An optimal matching algorithm then generated a cohort with equal number of patients treated with coiling and clipping with balanced baseline covariates. Outcomes were then compared between the matched groups. All procedures were performed in R (v.3.2.3) using the MatchIt package.[10]

Subgroup Analysis

In order to simulate the baseline demographics of the ISAT cohort using this dataset, further analysis focused on patients with good grade aSAH (WFNS grade I and II) was performed to compare the treatment outcome between those managed by neurosurgical clipping and endovascular coiling. Baseline demographics, primary and secondary outcome, and 6 months quality of life score were compared using chi-square test, two-sample t-test as appropriate.

Result

80% of patients managed by endovascular coiling were good grade on admission (WFNS I, II) compared to 60% in the neurosurgical arm, figure 1. More patients in the clipping arm had intraparenchymal haemorrhage (23%) compared 9% in the coiled group. The remaining baseline characteristics were well matched (Table 1).

Good outcome at discharge was observed in 67% of patients post coiling compared to 47% in the post-clipping group (p=0.0001) (Figure 1B).

Comparison of outcome at 6 months is shown in Table 2. Apart from the location of aneurysms, all other factors (age, WFNS grade, Fisher grade, treatment used, ictus to treatment time, delayed cerebral ischaemia, sepsis) show statistically significant association with poor outcome. 32% of older patients (age over 50 years) (120/400) were associated with poor outcome compared to 25% (91/382) of younger patients (age 18-50 years) (p=0.028). 53% of patients with poor grade SAH had poor outcome at 6 months, compared to 19% of patients with good grade SAH (p<0.0001). 34% of patients who underwent clipping had poor outcome compared to 25% of patients who underwent coiling (p=0.017).

To address the issue of confounding factors, logistic regression analysis was performed (Table 3). The risk factors which were associated with poor outcome were poor WFNS grade on admission, Fisher grade on initial CT scan and the development of delayed cerebral ischaemia. Treatment modality was not shown to be associated with poor outcome at 6 months (p=0.839).

Propensity Matched analysis

Using the optimal propensity score matching procedure a subgroup of 498 patients (249 coiled and 249 clipped) were selected. Age, sex, admission WFNS grade, Fisher score, and proportion of patients ventilated were not significantly different between the matched groups (Table 4). However, the distribution of aneurysms could not be fully matched due to the larger number of middle cerebral aneurysms that were clipped. Nonetheless, there was no significant difference in the incidence of confirmed DIND or sepsis between the matched groups. Moreover, 6 month mRS scores and overall favourable neurological outcome was not significantly different between coiling and clipping (Table 4).

Subgroup analysis

560 patients were good grade (WFNS I & II) on admission. Of these, 408 (73%) had endovascular coiling and 152 (27%) had neurosurgical clipping. Baseline clinical and demographic characteristics were shown in Table 5. The proportion of WFNS grade I and II, Fisher grade for SAH blood load on CT scan, and imaging modality was well matched in both groups. The distribution of aneurysms selected for coiling and clipping varied. The anterior communicating artery aneurysms were most commonly coiled (36%) compared with the middle cerebral artery aneurysms most commonly treated surgically (36%). Time from ictus to treatment of aneurysms was similar for both groups.

Immediate procedural related problems or complications (intraoperative rupture, uncontrolled brain swelling, major vessel occlusion, thromboembolic event) were low in both groups, and no statistically significant differences were detected.

The rate of confirmed delayed cerebral ischaemia was lower in patients who had endovascular coiling (11%) compared to patients who had neurosurgical clipping (21%), (p=0.001). There was also a lower risk of developing sepsis for patients post coiling (13%) compared to clipping (23%), (p=0.001). A lower proportion of patients post coiling were admitted to HDU/ITU (41% vs 53%, p=0.012), needed extended hypervolaemic therapy (16% vs 30%, p=0.001), or required inotropic support (17% vs 30%, p=0.001). The rate of patients needing other rescue therapy for delayed cerebral ischaemia (angioplasty, intra-arterial papaverine or nimodipine) was similar between the two groups, (Table 6).

The mean length of hospital stay for coiling group of patients was 16.3 days (range 5-119 days), compared to patients who underwent clipping 18.9 days (range 4-120 days). 74% of patients managed by endovascular coiling was discharged home, compared to 66% of surgical patients, but this difference is not statistically significant (p=0.110).

At discharge, favourable outcome (mRS 0-2) was observed in 76% of post coiled patients, compared to 66% of patients post clipping (p=0.06, Table 6, Figure 2). This rate subsequently improved. At 6 months 82% of patients post coiling, and 78% of patients post clipping were classed as good outcome (p=0.181, Table 6, Figure 2). At 6 months, 3% of post coiling patients, and 5% of post clipping patients had died.

SF-36 at 6 months was available for 87% of patients in both treatment arms (356/408 for coiled patients, and 132/152 for clipped patients). The mean physical score, mental score and overall scores were lower in the coiling arm. The differences noted were statistically significant, (Table 6).

Discussion

Initial analysis showed that older age, poor WFNS grade, high Fisher grade on initial CT head scan, treatment used (clipping), ictus to treatment time, development of delayed cerebral ischaemia and sepsis were associated with poor outcome at 6 months post aneurysmal SAH in this post-hoc study using the STASH trial cohort recruited from 35 neurosurgical units (23 in the UK and 12 non-UK sites) between January 2007 and February 2013. However, after correcting for confounding factors using logistic regression analysis, WFNS grade, fisher grade on CT scan and the development of delayed cerebral ischaemia remained highly significant risk factors associated with poor outcome. Several studies have also confirmed the important role of WFNS grade, initial CT fisher grade in determining patients' outcome post aSAH.[1,2,11-14]

There is a trend towards worse outcome for older patients (over 50 years old), (odds ratio 1.342, 95% confidence interval 0.947-1.904, p=0.098) but not statistically significant as previously shown by other studies.[1,2,15] Such a finding is not unexpected as our cohort excluded patients over 65 years, who have been shown on many previous studies to be associated with very poor outcome.[1,2]. Previous studies showed that level of consciousness, WFNS grade, rate of rebleeding, rate of hydrocephalus worsened with advancing age.[15] However, more recent studies showed that over 75 years as the critical age for poor outcome,[16,17] and there are now increasing evidence of subgroups of very elderly patients being treated aggressively with good long term outcome.[18,19]

Previous studies[1,2,20] showed that the timing of surgery was associated with better outcome and prompted an international change on the timing to early surgery for good grade patients. The results showed that at 6 months, 69% who had surgery had good outcome, with alert patients preoperatively had a favourable prognosis if operated between days 0-3 or after day 10. Subgroup analysis from the North American cohort then showed that 71% versus 62% of patients operated on between days 0-3 versus days >10 had good recovery (p<0.01).[3] Nowadays, combined with the options of endovascular treatment, most patients (693/749, 93%) in our study had aneurysms secured early on (within 96 hours post ictus), a very different practice to the era during The International Cooperative Study on the Timing of Aneurysm Surgery. Inherently, there are many confounding factors that determine the timing of surgery or coiling (>96hours) for the 7% of patients in this study, i.e. those who undergo delayed treatment are generally limited by other medical factors. Therefore it was not surprising that the timing of treatment was shown to be statistically significant predictor for poor outcome initially, with the effect lost after correction for confounding factors.

Contrary to the ISAT[4-6] study from 2002, which suggested endovascular coiling was preferable to neurosurgical clipping, this post hoc analysis of a contemporary series of patients from the STASH trial data showed no statistically significant differences between clipping and coiling at 6 months, using both propensity matched analysis and subgroup analysis of good grade patients only to simulate the ISAT cohort. Furthermore subgroup analysis showed the outcome differences noted at discharge were lost in patients with good grade aSAH managed by either treatment modality.

In the ISAT study, the ictus to treatment time was different between the two treatment modalities (mean 3.1 days for coiling, 3.7 days for clipping) and hence more patients suffered aneurysmal rebleed prior to treatment.[6,21] In this study, time to treatment was comparable in both groups. This, coupled with modern day technology incorporating better microscopic visualization, the use of intraoperative indocyanine green (ICG) and neurosurgical clipping now performed by expert neurovascular neurosurgeon, may account for the improvement in outcome observed.

In comparison to the ISAT[4-6] and BRAT[22,23] study (Table 7), the proportion of patients with good outcome has increased for both treatment modalities. ISAT[4-6] reported 76% of patients post coiling, and 69% post clipping had good outcome at 1 year, compared to 81% and 78% respectively in our cohort at 6 months. Such improvement is promising, considering that when ISAT was performed, only a select group of aneurysms were included (88% were good grades (WFNS class I or II), 95% were anterior circulation aneurysm, and 90% were smaller than 10mm). Likewise the BRAT[22,23] study demonstrated a similar outcome; but with only 49% of good grade patients and with a greater proportion of posterior circulation aneurysms, they could still achieve a very comparable outcome to the ISAT study (Table 7). In the current era, when interventional neuroradiologists are treating the more complex and challenging aneurysms, to retain the same results is very reassuring. The more remarkable finding is that the results for neurosurgical clipping have improved even further, aided by the advent of technology, we are now in an era where good outcome could be comparable to endovascular treatment.

Our subgroup analysis showed that patients who underwent neurosurgical clipping had a higher risk of developing delayed cerebral ischaemia, although this finding was not supported by the propensity score analysis conducted. Nevertheless, a recent meta-analysis showed that delayed cerebral ischemia was more common after clipping (OR 1.43; 95% CI 1.07-1.91), but ischemic infarct, shunt-dependent hydrocephalus, and procedural complications did not differ significantly between coiling and clipping.[24] Provided that patients are adequately managed, the development of delayed cerebral ischaemia in patients who had clipping did not translate into longer-term poor outcome. Despite the use of nimodipine, which has been shown to reduce the risk of delayed cerebral ischaemia, about 25% of patients still developed it post aSAH.[25,26] The overall level of delayed cerebral ischaemia (16%) in our cohort is lower than previously reported, and this could be attributed to more aSAH patients being treated by coil embolisation (DIND rate 21% in patients post clipping, and 11% post coiling).

The propensity-score matching analysis demonstrates that patients of similar age, sex, and severity of presenting haemorrhage (based on WFNS grade and Fisher score) have a comparable risk of developing delayed ischaemic deficits irrespective of the modality chosen to secure their aneurysm. Similarly, neurological outcome at six months amongst the matched groups was not dependent on whether the patient was clipped or coiled. These findings do not imply that clipping and coiling are equivalent or interchangeable for all aneurysms. The inference should be that current selection criteria in determining which patients are best clipped or coiled result in equally good outcomes for both groups and there remains a clear role for both modalities. Despite the many advantages of propensity score matching analysis, one of the limitation is that it only accounts for observed covariates, and hidden bias could remain or be exaggerated after matching.[27] Therefore propensity-score matching is still not a substitute for randomization.

Good grade patients who were coiled experienced a lower SF36 score in terms of physical, mental & overall wellbeing. Such differences could be related to the psychological worry related to the longer term follow up required for the surveillance of these aneurysms to ensure they remaining static. Conversely, in our experience, most patients who underwent neurosurgical clipping could be generally reassured of complete aneurysm obliteration.

Coiling or clipping should not be perceived as competing treatment modalities for securing cerebral aneurysms. They are complementary as both treatments have different roles in the management of aSAH. In the event of aneurysms suitable for both treatment modalities, coiling was shown to have better outcome by 7% according to the ISAT study, so endovascular treatment should be the preferred treatment. However in patients with cerebral aneurysms with anatomical configuration either less optimal or unsuitable for endovascular treatment, clipping should be offered as the first treatment modality. As shown in this paper, good grade patients do not experience a significant disadvantage post clipping, therefore neurosurgeons should not perceive clipping as the last resort only after attempted coiling.

In order to ensure that we deliver the highest standard of care for our patients, we need to continue to improve and strive to minimize technical related complications. With an increasing number of cerebral aneurysms being secured by endovascular coiling, training for the next generation of neurovascular surgeons can be challenging. However, with the advent of modern technology, realistic simulation surgery is a crucial tool for training. Several studies have shown that complex cases performed by high volume large centres achieved better outcome than low volume smaller units.[28-30] Therefore centralisation of neurovascular centres where neurosurgical clipping cases are performed in selected centres would increase the caseload, maintain surgeons' expertise and enhance training opportunities.

This is a post-hoc analysis from STASH study, which was not designed primarily to look at the outcome difference between the two treatments modality, as such is a limitation of the study. Furthermore, the rate of aneurysms recurrence and retreatment were not part of the STASH trial protocol, and therefore not available for analysis. However, several changes to the management of aSAH in the current era and important findings were borne out in this paper.

With regards to the longer term outcomes, many studies including large scale randomized controlled trials (ISAT and BRAT) showed that retreatment and rebleeding risks were higher in the endovascular group. In BRAT study, with up to 6 years follow up, overall retreatment rates were 16.4% for coiling and 4.6% for clipping ($p<0.0001$).[31] In the ISAT study with up to 18 years follow up, incidence of recurrent SAH was one in 641 patient-years for coiling, versus one in 2041 patient-years for clipping.[32] However, the ISAT study also confirmed the long term durability of endovascular treatment.

Conclusion

In the current era of aSAH management, apart from patients' admission status, SAH blood load and the development of DCI, treatment modality with either coiling or clipping was not associated with poor outcome difference at 6 months. In this post-hoc study of selective patients involved in the STASH trial, the effect of age and timing from ictus to intervention was lost after correction for confounding factors, a finding not unexpected as elderly patients (over 65 years) were excluded, and over 90% of patients had their aneurysms secured early on (within 96 hours post ictus).

Within the limit of a posthoc analysis, this study also showed good grade patients managed with either coiling or clipping experienced no difference in outcome at discharge or at 6 months, including physical and mental wellbeing. Endovascular coiling and neurosurgical clipping both have a role to play in the management of subarachnoid haemorrhage.

ISAT study randomized aneurysms suitable for both coiling and clipping, while the data has since been generalized to the entire cohort of cerebral aneurysms including the wide neck, complex aneurysms. Currently, in many

UK centres, over 90% of aneurysms are coiled, as the perception has been coiling is better, and every attempt should be made to coil aneurysms (even subtotally), with surgery only a last resort. We hope that our data will help to modify this viewpoint.

The key message is that in the event of any perceived difficulty with coiling, then one can comfortably offer clipping without the concern for a long-term disadvantage for clipping. The short-term advantages for coiling are still very apparent.

Declaration of interest:

The authors report no declaration of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgement

The STASH study was funded by the British Heart Foundation (SP/08/003/24065) and supported by the Cambridge Clinical Trials Unit. We also acknowledge the support of the UK Clinical Research Network, the Stroke Research Network, and all 35 participating sites.

Reference:

1. Kassell NF, Torner JC, Haley EC, Jr., Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg 1990;73:18-36.
2. Kassell NF, Torner JC, Jane JA, Haley EC, Jr., Adams HP. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 2: Surgical results. J Neurosurg 1990;73:37-47.
3. Haley EC, Jr., Kassell NF, Torner JC. The International Cooperative Study on the Timing of Aneurysm Surgery. The North American experience. Stroke 1992;23:205-14.

4. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002;360:1267-74.
5. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2002;11:304-14.
6. Molyneux AJ, Kerr RS, Yu LM, et al. 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;366:809-17.
7. Teo M, Martin S, Ponweera A, et al. Results of surgical clipping in a neurointerventional dominant department. Br J Neurosurg 2015;29:792-8.
8. National Study of Subarachnoid Haemorrhage.2004.
9. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol 2014;13:666-75.
10. Ho DE, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. Journal of Statistical Software 2011;42:28.
11. Shimoda M, Oda S, Tsugane R, Sato O. Prognostic factors in delayed ischaemic deficit with vasospasm in patients undergoing early aneurysm surgery. Br J Neurosurg 1997;11:210-5.
12. Ogungbo B, Gregson BA, Blackburn A, Mendelow AD. Trends over time in the management of subarachnoid haemorrhage in newcastle: review of 1609 patients. Br J Neurosurg 2001;15:388-95.
13. Soehle M, Chatfield DA, Czosnyka M, Kirkpatrick PJ. Predictive value of initial clinical status, intracranial pressure and transcranial Doppler pulsatility after subarachnoid haemorrhage. Acta neurochirurgica 2007;149:575-83.
14. Shirao S, Yoneda H, Kunitsugu I, et al. Preoperative prediction of outcome in 283 poor-grade patients with subarachnoid hemorrhage: a project of the Chugoku-Shikoku Division of the Japan Neurosurgical Society. Cerebrovascular diseases 2010;30:105-13.
15. Lanzino G, Kassell NF, Germanson TP, et al. Age and outcome after aneurysmal subarachnoid hemorrhage: why do older patients fare worse? J Neurosurg 1996;85:410-8.
16. Proust F, Gerardin E, Derrey S, et al. Interdisciplinary treatment of ruptured cerebral aneurysms in elderly patients. J Neurosurg 2010;112:1200-7.
17. Park J, Woo H, Kang DH, Kim Y. Critical age affecting 1-year functional outcome in elderly patients aged >/= 70 years with aneurysmal subarachnoid hemorrhage. Acta neurochirurgica 2014;156:1655-61.
18. Horiuchi T, Tanaka Y, Hongo K. Surgical treatment for aneurysmal subarachnoid hemorrhage in the 8th and 9th decades of life. Neurosurgery 2005;56:469-75; discussion -75.
19. Asano S, Hara T, Haisa T, et al. Outcomes of 24 patients with subarachnoid hemorrhage aged 80 years or older in a single center. Clinical neurology and neurosurgery 2007;109:853-7.

20. Kassell NF, Torner JC. The International Cooperative Study on Timing of Aneurysm Surgery--an update. Stroke 1984;15:566-70.
21. Bakker NA, Metzemaekers JD, Groen RJ, Mooij JJ, Van Dijk JM. International subarachnoid aneurysm trial 2009: endovascular coiling of ruptured intracranial aneurysms has no significant advantage over neurosurgical clipping. Neurosurgery 2010;66:961-2.
22. Spetzler RF, McDougall CG, Albuquerque FC, et al. The Barrow Ruptured Aneurysm Trial: 3-year results. J Neurosurg 2013;119:146-57.
23. McDougall CG, Spetzler RF, Zabramski JM, et al. The Barrow Ruptured Aneurysm Trial. J Neurosurg 2012;116:135-44.
24. Li H, Pan R, Wang H, et al. Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. Stroke; a journal of cerebral circulation 2013;44:29-37.
25. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. Bmj 1989;298:636-42.
26. Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev 2007:Cd000277.
27. Sainani KL. Propensity scores: uses and limitations. PM & R : the journal of injury, function, and rehabilitation 2012;4:693-7.
28. Naylor R, Wyatt M, Mitchell D. High volume surgery outcomes suggest there is safety in numbers. . Health Service Journal 2012.
29. Reshaping surgical services: principles for change. The Royal College of Surgeons of England. Royal College of Surgeons of England, 2013. at http://www.rcseng.ac.uk/policy/documents/reshaping-surgical-services.)
30. Zhu W, Liu P, Tian Y, et al. Complex middle cerebral artery aneurysms: a new classification based on the angioarchitecture and surgical strategies. Acta neurochirurgica 2013;155:1481-91.
31. Spetzler RF, McDougall CG, Zabramski JM, et al. The Barrow Ruptured Aneurysm Trial: 6-year results. J Neurosurg 2015;123:609-17.
32. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RSC. 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). The Lancet 2015;385:691-7.

Appendix

Table 1. Baseline clinical and demographic characteristics for the whole cohort of STASH patients, stratified by the treatment modality of endovascular coiling, neurosurgical clipping or both.

Table 2. Analysis for comparative factors that determine 6 months outcome for patients with aSAH according to STASH cohort.

Table 3. Logistic regression analysis for risk factors associated with poor outcome (mRS 3-6) at 6 months.

Table 4. Comparison of propensity-score matched treatment groups between coiling and clipping.

Table 5. Baseline clinical and demographic characteristics for the good grade aSAH patients, stratified by the treatment modality of endovascular coiling, neurosurgical clipping.

Table 6. Outcome measures comparison for good grade aSAH patients stratified by endovascular coiling or neurosurgical clipping only

Table 7. Comparison between current cohort with ISAT and BRAT study.

Figure 1. Distribution of scores for the whole cohort of STASH patients stratified by treatment modalities. (A) WFNS admission grade. (B) mRS at discharge. (C) mRS at 6 months. (mRS= modified Rankin Scale)

Figure 2. Distribution of scores for the good grade aSAH patients stratified by treatment modalities. (A) WFNS admission grade. (B) mRS at discharge. (C) mRS at 6 months. (mRS= modified Rankin Scale)

Table 1

	Clipping (n=254)	Coiling (n=513)	p-value
UK participants	189 (29%)	456 (71%)	<0.0001
Non-UK participants	65 (53%)	57 (47%)	
Mean age (Range), yrs	50 (20-69)	50 (20-65)	N.S
Male /Female	93/161	149/364	0.034
Ethnic origin			
White	213(84%)	479 (93%)	<0.00001
Asian	19 (7%)	17 (3%)	
Black	4 (2%)	8 (2%)	
Hispanic	17 (7%)	5 (1%)	
Other	1(<1%)	4 (1%)	
WFNS SAH grade			
I	98 (39%)	271 (53%)	<0.00001
II	54 (21%)	137 (27%)	
III	22 (9%)	9 (2%)	
IV	50 (20%)	53 (10%)	
V	30 (12%)	43 (8%)	
Motor deficit	53 (21%)	42 (8%)	<0.00001
Cranial nerve deficit	31 (12%)	40 (8%)	0.047
Ventilated	64 (25%)	94 (18%)	0.026
Fisher grade			
1	3 (1%)	11 (2%)	0.008
2	26 (10%)	82 (16%)	
3	74 (29%)	179 (35%)	
4	151 (59%)	241 (47%)	
Intraparenchymal haemorrhage	58 (23%)	48 (9%)	<0.00001
Intraventricular haemorrhage	94 (37%)	175 (34%)	0.429
Subdural haemorrhage	8 (3%)	9 (2%)	0.216
Cerebral infarct	3 (1%)	2 (<1%)	0.200
Hydrocephalus	31 (12%)	80 (16%)	0.209
Imaging modality			
MRA	2 (1%)	8 (2%)	0.375
CTA	200 (79%)	386 (75%)	0.283
DSA	69 (27%)	180 (35%)	0.027
Location of aneurysm			
ACoA	68 (27%)	179 (35%)	<0.0001
PCoA	46 (18%)	137 (27%)	
ICA	13 (5%)	52 (10%)	
MCA	110 (43%)	60 (12%)	
Posterior circulation	12 (5%)	60 (12%)	
Other	5 (2%)	25 (5%)	
Mean time ictus to Tx (range)days	1.8 (0-17)	1.6 (0-10)	N.S

Table 1. Baseline clinical and demographic characteristics, stratified by treatment modality

Table 2

	Good outcome at 6 months mRS 0-2 n=538		Poor outcome at 6 months mRS 3-6 n=211		p value
Age of patients					0.028
18-50 years	280	75%	91	25%	
>50 years	258	68%	120	32%	
WFNS grade on admission					<0.0001
1-2	442	81%	104	19%	
3-5	96	47%	107	53%	
Fisher Grade on admission					<0.0001
1-2	106	88%	14	12%	
3	192	79%	51	21%	
4	240	62%	146	38%	
Aneurysm location					0.576
Anterior circulation	474	72%	184	28%	
Posterior circulation	49	73%	18	27%	
Other	15	63%	9	37%	
Treatment					0.017
Clipped only	165	66%	85	34%	
Coiled only	373	75%	126	25%	
Ictus to treatment (hours)					0.008
0-24	47	58%	34	42%	
25-48	239	73%	89	27%	
49-96	216	76%	68	24%	
>96	36	64%	20	36%	
Delayed cerebral ischaemia	61	49%	64	51%	<0.0001
No DCI	477	76%	147	24%	
Sepsis	101	54%	86	46%	<0.0001
No	437	78%	125	22%	

Table 2. Factors determing 6 months outcome

Table 3
Click here to download Table(s): Table 3 logistic regression CT July2016.docx

Variable	Coefficient	Standard error	p value	Odds ratio	95% confidence interval
Age >50 years	0.295	0.178	0.098	1.342	0.947 - 1.904
WFNS grade (3-5)	1.133	0.204	<0.0001	3.106	2.082 - 4.633
CT Fisher grade	0.347	0.140	0.013	1.414	1.075 - 1.861
Clipping	0.038	0.189	0.839	0.963	0.666 - 1.391
Delayed cerebral ischaemia	0.921	0.225	<0.0001	2.512	1.618 - 3.900

Table 3. Binary logistic regression analysis for risk factors associated with poor outcome (mRS 3-6) at 6 months.

Table 4

Click here to download Table(s): Table 4 Propensity matched analysis.docx

	Coiling	Clipping	
N	249	249	
Age (years, mean [SD]	49.4 [9.4]	49.9 [10.3]	P=0.748
Sex (% female)	61.8	63.9	P=0.711
WFNS Grade (%)			P=0.107
I	41.8	38.6	
II	23.7	21.3	
III	3.2	8.8	
IV	18.1	19.7	
V	13.3	11.6	
Fisher Grade			P=0.961
1	1.2	1.2	
2	9.2	10.4	
3	20.1	28.5	
4	59.4	59.8	
Ventilated (%)	26.9	24.9	P=0.682
Aneurysm Location (%)			P<0.001
ACoA	41.4	26.9	
PCoA	22.9	17.7	
ICA	5.6	4.8	
MCA	22.9	43.8	
Posterior	5.2	4.8	
Other	2.0	2.0	
Delayed Ischaemic Deficit (%)	18.9	23.3	P=0.272
Sepsis (%)	25.7	33.7	P=0.062
mRS at 6 months (%)			P=0.957
0	19.7	20.5	
1	28.9	27.3	
2	19.7	18.1	
3	11.6	14.9	
4	5.2	5.2	
5	3.6	2.8	
6	11.2	11.2	
Good outcome (%)	68.3	65.9	P=0.634

Table 4. Comparison of propensity-score matched treatment groups between coiling and clipping.

Table 5

Click here to download Table(s): Table 5 Good grades only coil vs clip July2016.docx

Good grade aSAH only	Clipping (n=152)	Coiling (n=408)
UK participants	115 (24%)	368 (76%)
Non-UK participants	37 (48%)	40 (52%)
Mean age (years) (Range)	49(20-66)	50(20-65)
Male sex	52 (34%)	111 (27%)
Ethnic origin		
White	132 (87%)	384 (94%)
Asian	12 (8%)	14 (3%)
Black	2 (1%)	4 (1%)
Hispanic	6 (4%)	3 (1%)
Other	0	3 (1%)
WFNS SAH grade		
I	98 (64%)	271 (66%)
II	54 (36%)	137 (34%)
Motor deficit	5 (3%)	10 (2%)
Cranial nerve deficit	11 (7%)	17 (4%)
Ventilated	7 (5%)	15 (4%)
Fisher grade		
1	3 (2%)	11 (3%)
2	24 (16%)	80 (20%)
3	59 (39%)	160 (39%)
4	66 (43%)	157 (38%)
Intraparenchymal haemorrhage	14 (9%)	28 (7%)
Intraventricular haemorrhage	42 (28%)	116 (28%)
Subdural haemorrhage	1 (1%)	6 (1%)
Cerebral infarct	2 (1%)	2 (1%)
Hydrocephalus	9 (6%)	37 (9%)
Imaging modality		
MRA	1 (1%)	5 (1%)
CTA	113 (74%)	305 (75%)
DSA	50 (33%)	149 (37%)
Location of aneurysm		
ACoA	45 (30%)	144 (36%)
PCoA	37 (24%)	111 (27%)
ICA	10 (7%)	41 (10%)
MCA	54 (36%)	45 (11%)
Posterior circulation	5 (3%)	48 (12%)
Other	1 (1%)	19 (5%)
Mean time, ictus to Tx (days) (range)	1.8 (0-17)	1.6 (0-10)

Table 5. Baseline demographic characteristics for good grade patients, stratified by the treatment modality

Table 6

Click here to download Table(s): Table 6 good grade outcome coil vs clip RevJuly2016.docx

Good grade aSAH only	Clipping (n=152)	Coiling (n=408)	p value
Immediate procedural problems	5 (3%)	21 (5%)	0.353
Intraprocedure bleed	1 (1%)	5 (1%)	0.562
Uncontrolled swelling	1 (1%)	2 (1%)	0.809
Major vessel occlusion	2 (1%)	4 (1%)	0.732
Thromboembolic event	5 (3%)	5 (1%)	0.101
Other event	13 (9%)	25 (6%)	0.310
Suspected delayed ischaemia	42 (28%)	65 (16%)	0.002
Confirmed delayed ischaemia	32 (21%)	43 (11%)	0.001
Drop in GCS	37 (24%)	64 (16%)	0.018
Focal deficit	29 (19%)	62 (15%)	0.268
Proven radiological infarct	27 (18%)	37 (9%)	0.004
Other causes of deterioration			
Sepsis	36 (24%)	51 (13%)	0.001
Epilepsy	3 (2%)	8 (2%)	0.992
Hypoxia	1 (1%)	5 (1%)	0.562
Rebleed	1 (1%)	6 (1%)	0.441
Hydrocephalus (needing EVD)	15 (10%)	57 (14%)	0.197
Other	14 (9%)	27 (7%)	0.295
Rescue therapy			
Extended hypervolaemic therapy	45 (30%)	67 (16%)	0.001
Inotropic support	45 (30%)	70 (17%)	0.001
Angioplasty	4 (3%)	5 (1%)	0.239
Intrarterialpapeverine or nimodipine	1 (1%)	7 (2%)	0.348
Steroids	9 (6%)	23 (6%)	0.898
ITU or HDU stay	81 (53%)	169 (41%)	0.012
ITU or HDU mean stay, days (range)	10 (1-29)	9 (1-81)	
Mean length of hospital stay, days (range)	18.9 (4-120)	16.3 (5-119)	0.088
Discharge destination			0.110
Home	101 (66%)	303 (74%)	
Non-neurosurgical ward	21 (14%)	49 (12%)	
Rehabilitation	21 (14%)	32 (8%)	
Other	2 (1%)	11 (3%)	
Died	7 (5%)	11 (3%)	
Modified Rankin Scale score at discharge			0.060
mRS 0	32 (21%)	90 (22%)	
mRS 1	39 (26%)	158 (39%)	
mRS 2	29 (19%)	62 (15%)	
mRS 3	28 (18%)	47 (12%)	
mRS 4	12 (8%)	28 (7%)	
mRS 5	5 (3%)	10 (2%)	
mRS 6	7 (5%)	11 (3%)	

Modified Rankin Scale score at 6 months			0.181
mRS 0	47 (31%)	90 (23%)	
mRS 1	43 (29%)	147 (37%)	
mRS 2	27 (18%)	88 (22%)	
mRS 3	19 (13%)	47 (12%)	
mRS 4	4 (3%)	10 (3%)	
mRS 5	2 (1%)	3 (1%)	
mRS 6	8 (5%)	11 (3%)	
SF-36 at 6 months			
Number of patients	132	356	
Physical score mean (range)	64.8 (10-100)	57.3 (4-100)	0.001
Mental score mean (range)	64.2 (11-100)	58.6 (2-100)	0.028
Overall score mean (range)	64.8 (10-100)	59.3 (4-100)	0.026

Table 6. Comparison of outcome measures for patients with WFNS Grades 1 and 2 on admission

Table 7
Click here to download Table(s): Table 7 compare table ISAT BRAT July2016.docx

Trial	Good outcome at 1 year/6months Coil (%)	Clip (%)	WFNS/HH Grade at presentation 1-2 (%)	3-5 (%)	Aneurysm location Ant (%)	Post (%)
ISAT	76	69	88	12	97	3
BRAT	79	69	49	51	83	17
STASH - post hoc (good grade)	81	78	100		91	9
STASH -post hoc (whole cohort)	74	66	73	27	91	9

Table 7. Comparison of STASH with ISAT and BRAT study.

Figure 1

Click here to download Figure(s): Figure 1 whole STASH cohort.docx

A. WFNS grade of patients with aSAH on admission

B. mRS at discharge

C. mRS at 6 months

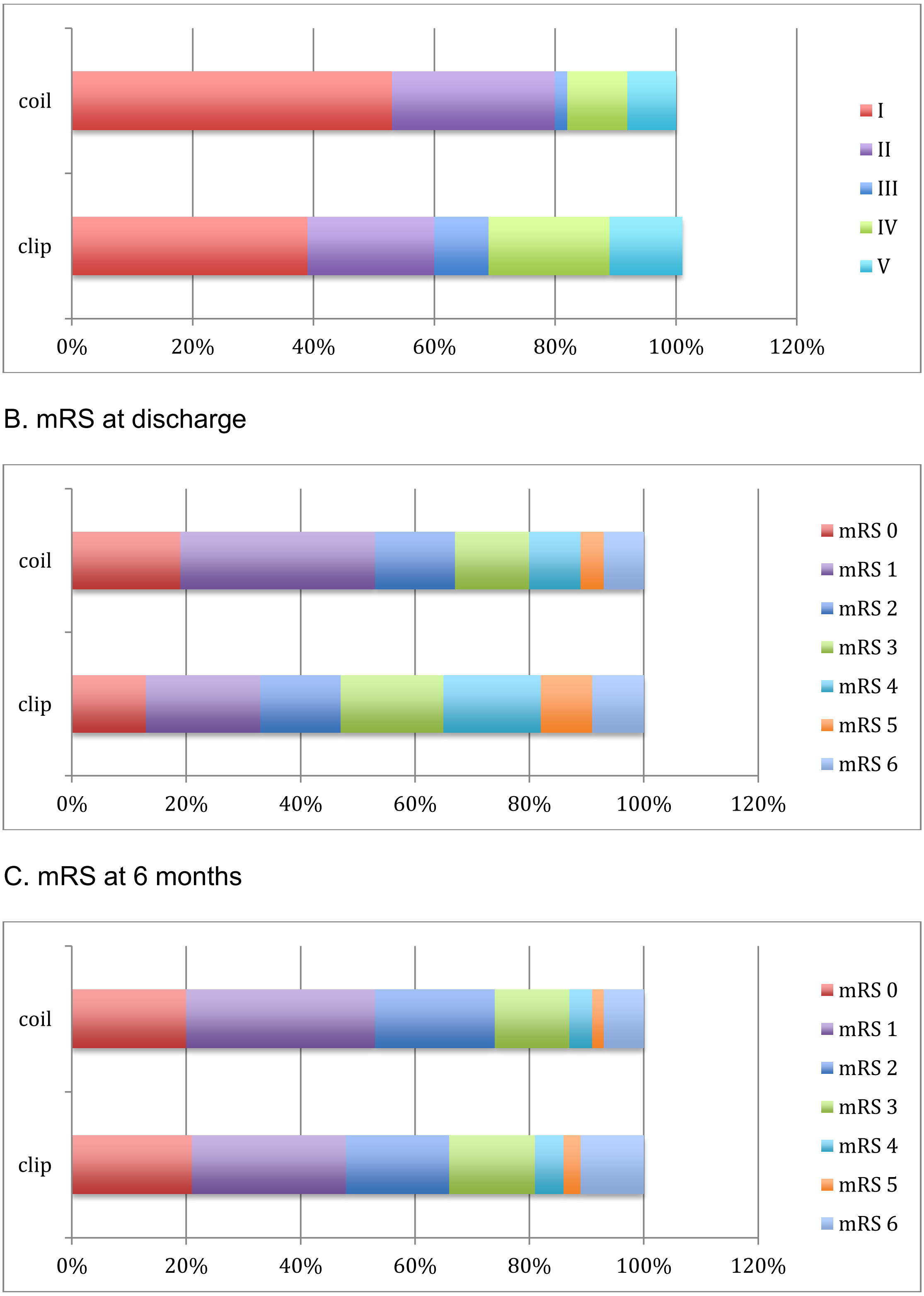
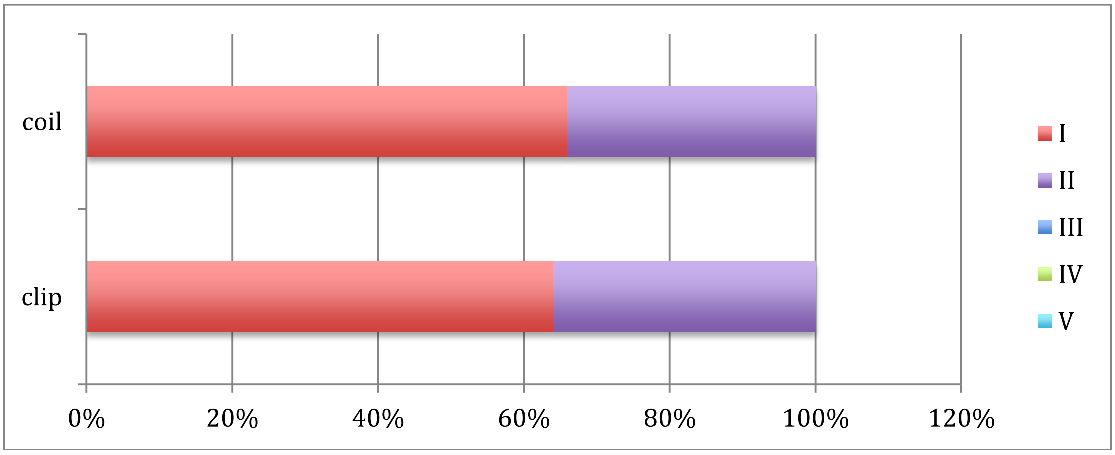


Figure 1. Distribution of scores for the whole cohort of STASH patients stratified by treatment modalities. (A) WFNS admission grade. (B) mRS at discharge. (C) mRS at 6 months. mRS= modified Rankin Scale

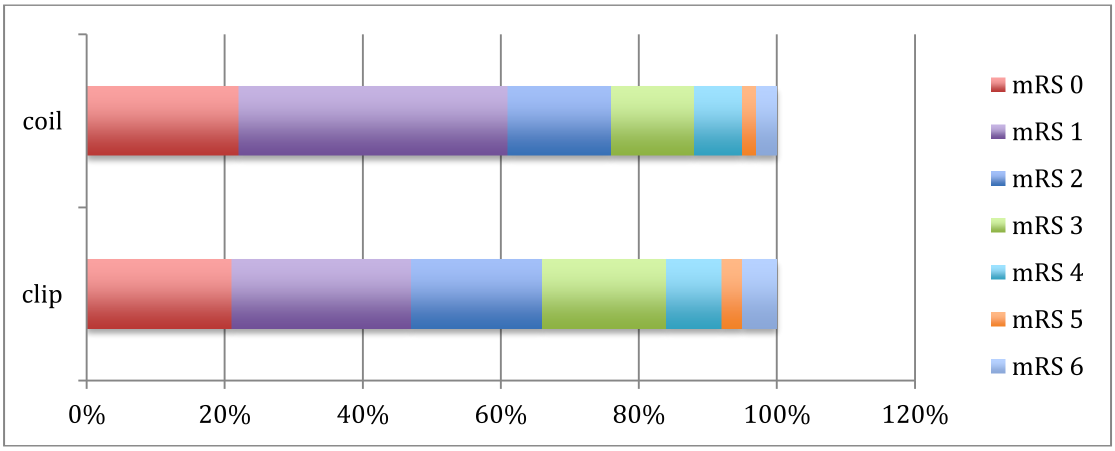
Figure 2

Click here to download Figure(s): Figure 2 good grade coil vs clip.docx

A. WFNS grade of good grade patients with aSAH on admission



B. mRS at discharge



C. mRS at 6 months

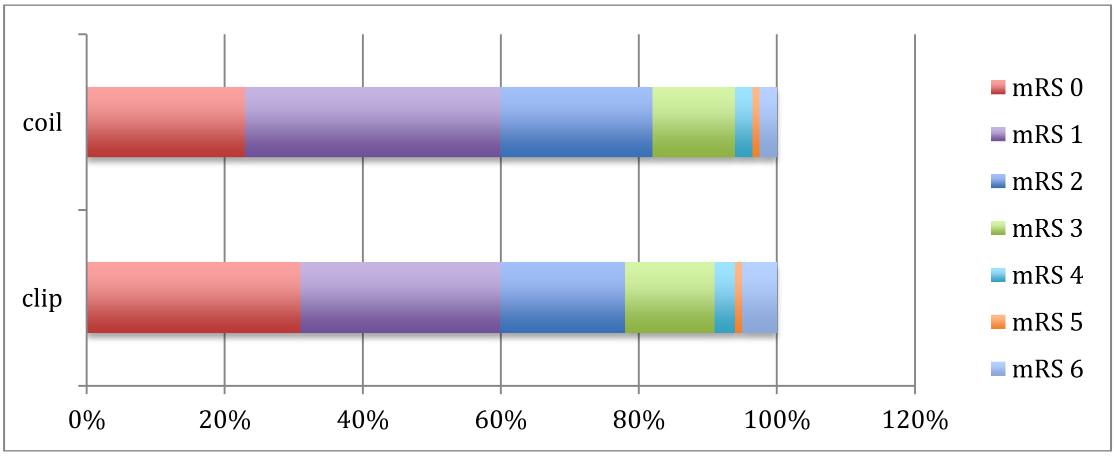


Figure 2. Distribution of scores for the good grade aSAHpatients stratified by treatment modalities. (A) WFNS admission grade. (B) mRS at discharge. (C) mRS at 6 months. mRS= modified Rankin Scale

Acknowledgement

STASH Investigators—Writing Committee: P.J. Kirkpatrick, C.L. Turner, G.D. Murray, P.J. Hutchinson. Steering Committee: Professor Sir G. Teasdale, Chairman; Professor G.D. Murray, Statistician; Mr P.J. Kirkpatrick, Chief Investigator; Professor A.D. Mendelow, Co-Investigator; Professor K. Muir, Independent; Professor M. Smith, Independent; Mr P. McCabe, Lay Member, CEO Headway, London; Professor J. Pearson, BHF Representative. Data Management Committee: Professor G. Ford, Chairman; Mr A. Vail, Statistician; Mr A. King, Independent; Dr P. Tyrrell, Independent; Dr H. Richards, Statistician; Dr S. Bond, Independent Statistician. Trial Management Team: Mr P.J. Kirkpatrick, Chief Investigator; Mrs C.L. Turner, Trial Manager; Dr C. Smith, Trial Coordinator; Dr E. Warburton, Independent Medical Advisor. Center Investigators: P.J. Kirkpatrick, C.L. Turner, C. Smith (Addenbrooke's Hospital, Cambridge); A. Belli, D. Bulters, M. Brown (Southampton University Hospital, Southampton); G. Critchley, G. Spurling, J. Gaylard (Hurstwood Park Neuro- logical Centre, Brighton); M. Javadpour, P. Eldridge, L. Murray (Walton Centre, Liverpool); R. Nelson, R. Taylor, S. Hierons (Frenchay Hospital, Bristol); A.D. Mendelow, B. Tobin, K. Storey (Royal Victoria Infirmary, Newcastle); D. Walsh, B. Mistry, J. Aeron-Thomas (King's College Hospital, London); C. Puppo (Montevideo, Uruguay); M. Papadopoulos, L. Montague (St George's Hospital, London); P. Gan, G. Flint, J. Hurley (Queen Elizabeth Hospital, Birmingham); E. Ronne, I. Stjernling (Uppsala, Sweden); E. Wang, E.L. Cheng, K.W. Low (NNI Singapore); S. Ross, R. Bellfield, L. Mandizvidza (Leeds General Infirmary, Leeds); P. Whitfield, N. Persad (Derriford Hospital, Plymouth); N. Suttner, M. Teo, K. McGuigan, L. Cloughley (Southern General Hospital, Glasgow); H. Patel, A. Ingham, K. Shaw (Salford Royal Infirmary, Manchester); R. Vindlacheruvu (Queen's, Romford); J. Millo, O. Warner, R. Teal (John Radcliffe, Oxford); F. Bernard, C. Sirois (Hopital Sacre Coeur, Montreal); S. Joshi, S. Nyabadza (University Hospital Coventry and Warwickshire, Cov- entry); J. Grieve, N. Kitchen, V. Bassan, P. Rayson (National Hospital for Neurology and Neurosurgery, London); A. Alasheev, A. Zeitlin (Burdenko Institute, Moscow); M. Findlay, L. Sonnema, B. Poworoznik (University of Alberta, Edmonton, Canada); J. Quintero (Medellin, Colombia); S. Eljamel, M. Teo (Ninewells Hospital, Dundee); F. Rasulo (Brescia, Italy); I. Ng, J.L. Lai, K.W. Low (Singapore General Hospital, Singapore); B. Mathew, J. Grieg (Hull Royal Infirmary, Hull); R. Hanel, A. Richie (Mayo Clinic, Florida); I. Fleetwood, E. Reardon-White, G. Hampton (Queen Elizabeth11, Halifax, Canada); S. Lewis, L. Miralia (Shands Hospital, Gainesville, Florida); H. Brydon, H. Maguire (University Hospital of North Staffordshire, Stoke-on-Trent); U. Patel, H. Sanderson, K. Birchall, P. Bayliss (Royal Hallamshire Hospital, Sheffield); K. O'Neill, T. Sachs (Charing Cross Hospital, London); R. Kett-White, L. Quinn (Morriston Hospital, Swansea).