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*Stroke*. 2012;43:1496-1504; originally published online April 17, 2012;
doi: 10.1161/STROKEAHA.111.640284
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

# Individual Patient Data Subgroup Meta-Analysis of Surgery for Spontaneous Supratentorial Intracerebral Hemorrhage

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***Background and Purpose***—By 2010 there had been 14 published trials of surgery for intracerebral hemorrhage reported in systematic reviews or to the authors, but the role and timing of operative intervention remain controversial and the practice continues to be haphazard. This study attempted to obtain individual patient data from each of the 13 studies published since 1985 to better define groups of patients that might benefit from surgery.

***Methods***—Authors of identified published articles were approached by mail, e-mail, and at conferences and invited to take part in the study. Data were obtained from 8 studies (2186 cases). Individual patient data included patient's age, Glasgow Coma Score at presentation, volume and site of hematoma, presence of intraventricular hemorrhage, method of evacuation, time to randomization, and outcome.

***Results***—Meta-analysis indicated that there was improved outcome with surgery if it was undertaken within 8 hours of ictus ($P=0.003$), or the volume of the hematoma was 20 to 50 mL ($P=0.004$), or the Glasgow Coma Score was between 9 and 12 ($P=0.0009$), or the patient was aged between 50 and 69 years ($P=0.01$). In addition, there was some evidence that more superficial hematomas with no intraventricular hemorrhage might also benefit ($P=0.09$).

***Conclusions***—There is evidence that surgery is of benefit if undertaken early before the patient deteriorates. This work identifies areas for further research. Ongoing studies in subgroups of patients such as the Surgical Trial in Lobar Intracerebral Hemorrhage (STICH II) will confirm whether these interpretations can be replicated. **(*Stroke*. 2012;43: 1496-1504.)**

**Key Words:** intracerebral hemorrhage ■ meta-analysis ■ surgery

**See related article, p 1460.**

Spontaneous supratentorial intracerebral hemorrhage (ICH) has a high morbidity and mortality and places a significant burden on health and social services. The role and timing of operative neurosurgical intervention remain controversial and the practice and timing of surgery continue to be haphazard. Operative intervention is thought to be beneficial in stopping bleeding, preventing rebleeding, and removing the mass effect to prevent secondary brain damage. To date 14 trials have been undertaken to investigate the role of surgery for spontaneous ICH with varying conclusions (online-only Data Supplement, a summary of trials). The first randomized trial was published in 1961 (McKissock[1]) and suggested that there was no significant advantage for surgery. As the use of the CT scan in stroke increased and operative techniques and care facilities improved, more trials were undertaken with 4 small single-center trials reported between 1989 and 1992.[2–5] Further small studies reported between 1998 and 2006,[6–10] and 4 large studies were published in 2001,[11] 2004,[12] 2005,[13] and 2009.[14] Few studies have shown statistically significant differences and some have favored surgery, whereas others have favored conservative treatment. The meta-analysis of the published outcomes from these studies shows a significant benefit from surgery both for the outcome of mortality[15] and for the combined outcome of death or disability (online-only Supplemental Figures).[16] However, there are many differences between the studies in the types of population included and in the outcomes measured.

The aim of this study was to pool all available original data from all trials of surgery versus conservative treatment in spontaneous ICH to carry out an individual patient data meta-analysis. Such pooled raw data make it possible to test

Received October 6, 2011; final revision received December 9, 2011; accepted December 14, 2011.

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**The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.640284/-/DC1.**

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*Stroke* **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.111.640284**

subpopulations of patients with ICH and their response to surgery. There were no raw data available from studies before 1985.

## Methods

### Study Selection and Data Items

The randomized controlled trials of surgery for ICH since CTs became available were identified from the ongoing Cochrane Review of Prasad et al.[17] Presentation of the study design at conferences and reviewing of relevant literature led to the identification of 2 further articles: those of Pantazis et al[10] and Wang et al.[14] The authors of the published articles were contacted by mail, e-mail, and at stroke and neurosurgery conferences and were invited to take part in the study. They were asked to describe the format of their data sets and indicate which variables were available. Data requested included patient's age and sex, Glasgow Coma Score (GCS) at presentation, volume and site of hematoma and presence of intraventricular hemorrhage (IVH), method of evacuation of hematoma, time to randomization, and outcome at 3 to 6 months.

### Definition of Outcome

Different outcome measures were used by different studies. Glasgow Outcome Scale had been used by 3 studies,[3,7,13] whereas the extended Glasgow Outcome Scale had only been used by Mendelow.[13] The Barthel Index was used by 3 studies,[6,7,13] and the Rankin Scale was the measure most commonly available in the data provided by 6 studies.[2,6–8,12,13] Batjer[4] had used "independent at home" and Hosseini[9] had used Karnofsky. Chen[11] had used a 5-category variable based on the Barthel Index: death, vegetative state, Barthel Index <60, Barthel Index >60, and excellent with no neurological deficit.

The primary outcome for this analysis was defined as an unfavorable outcome. An unfavorable outcome was defined as death plus the vegetative state or severe disability on the 5-point Glasgow Outcome Scale. If this was not available, then a Rankin Scale score of ≥3 was considered as unfavorable; and if this was not available, an outcome of Barthel Index of ≤90 was considered unfavorable. An outcome of moderate disability on the Glasgow Outcome Scale implies that an individual is able to carry out shopping tasks and use public transportation. Thus, a favorable outcome was regarded as being independent outside the home. This differs from the prognosis-based outcome derived from the extended Glasgow Outcome Scale that was used in the Surgical Trial in Intracerebral Hemorrhage (STICH).[13] The outcome classification from the Chen[11] trial did not provide sufficient information to code directly in this way so the classification of "excellent" was the only category defined as a favorable outcome. These decisions were made before the analysis of the data.

### Prespecified Subgroup Analysis

For the analysis, each of the continuous baseline variables was grouped. Categories were chosen to reflect the admission criteria in the trials, previous publications, and criteria generally used in making treatment decisions. Age was grouped into 3 categories: <50, 50 to 69, and ≥70 years. GCS was grouped into 3 groups: 3 to 8, 9 to 12, and 13 to 15; volume was classified into 4 groups: <20 mL, 20 to 50 mL, 50 to 80 mL, and ≥80 mL. These decisions were made before the analysis of the data.

The data were analyzed using SPSS to crosstabulate the outcome by treatment group for each baseline variable group and the values entered into the Revman program to calculate the ORs and to demonstrate the Forest plots.

## Results

### Study Selection

Numerous attempts were made to contact each first author by mail and e-mail. Where this method was unsuccessful, further attempts were made using third-party contacts made at conferences or through other researchers and by holding meetings with the trialists during conferences. This was a long process. Contact was established with the authors of all studies. Hattori[12] was unable to take part. Batjer's[4] and Chen's[5] data were not retrievable. The main authors of each of the other contacted studies agreed to be involved in this study and to provide data for it. Full data sets have been supplied by Juvela, Morgenstern, Zuccarello, Teernstra, Chen, Mendelow, and Wang.[3,6–8,11,13,14] After an exhaustive search in various universities taking >1 year, the original data of Auer[2] was not located but comprehensive tables from a contemporary thesis analysis of the original data were obtained.[18] Hosseini[9] supplied some aggregate data but of insufficient detail to include in an individual patient data analysis. In addition, the study has still not been published and therefore not yet subjected to peer review. Pantazis[10] supplied full data for only 92 of his 108 cases. He was unable to locate the data for the other 16 cases and therefore the decision was made not to include these data in case it was a biased selection of the cases.

Full data sets therefore have been supplied by 7 authors (2086 patients) and grouped data by an eighth author (100 patients).

**Table. Characteristics of Data Sets**

| Author | Year | No. of Cases | Male, % | Age, y | GCS | Volume of Hematoma, mL | Time to Randomization, h | Lobar Hematoma, % | IVH Present, % | Favorable Outcome, % (Responders) |
|---|---|---|---|---|---|---|---|---|---|---|
| Auer | 1989 | 100 | NR | 49%<50 | 48%≤8 | 49%<50 | NR | 45 | 32 | 25 |
| Juvela | 1989 | 52 | 58 | 51 (42–58) 24–65 | 12 (7–14) 4–15 | 58 (36–77) 17–152 | NR | 15 | 62 | 12 |
| Morgenstern | 1998 | 34 | 65 | 51 (43–63) 22–77 | 11 (10–14) 5–15 | 50 (30–76) 11–170 | 4 (1–6) 0–11 | 24 | NR | 19 (31) |
| Zuccarello | 1999 | 20 | 55 | 64 (59–70) 27–80 | 12 (9–14) 4–15 | 33 (19–61) 16–105 | 7 (4–10) 2–19 | 50 | 50 | 45 |
| Chen | 2001 | 500 | 72 | 58 (49–65) 12–74 | 11 (9–13) 7–15 | 30 (22–45) 12–130 | 35%<8<br>22%>24 | 5 | 4 | 23 |
| Teernstra | 2003 | 70 | 57 | 70 (61–74) 46–87 | 9 (7–11) 4–15 | 59 (33–81) 10–132 | 4 (2–9) 0–62 | 54 | 31 | 11 |
| Mendelow | 2005 | 1033 | 57 | 62 (52–70) 19–93 | 12 (9–14) 5–15 | 38 (24–62) 4–210 | 20 (10–36) 2–72 | 35 | 39 | 18 (965) |
| Wang | 2009 | 377 | 63 | 56 (50–65) 40–75 | 12 (10–14) 9–15 | 32 (28–37) 25–44 | 3 (2–8) 1–67 | 0 | 19 | 45 |

Median (quartiles), and minimum and maximum values of continuous variables. Percentage of categorical variables.
GCS indicates Glasgow Coma Score; IVH, intraventricular hemorrhage; NR, not recorded.

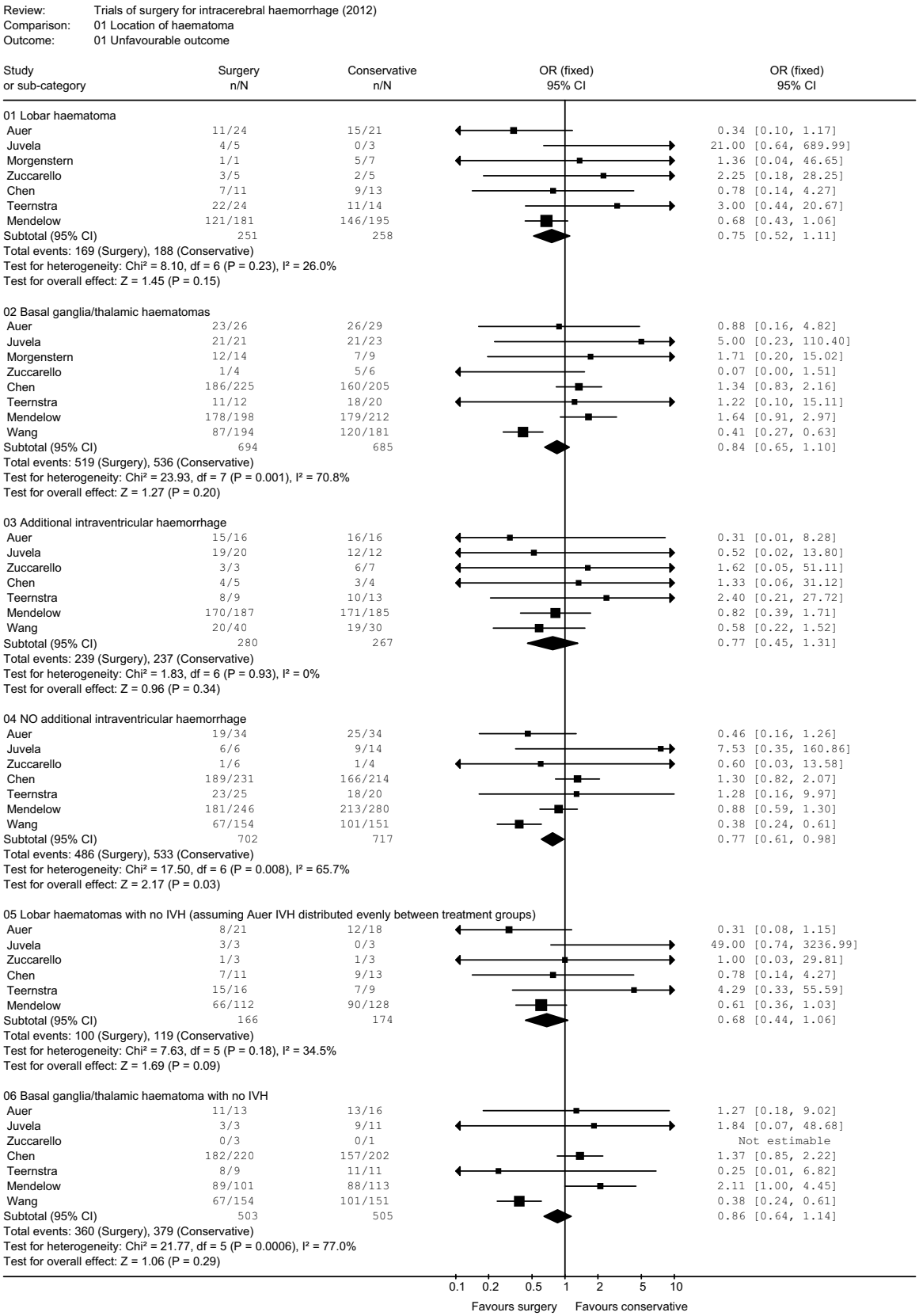



**Figure 1.** Meta-analysis by location of the hematoma.

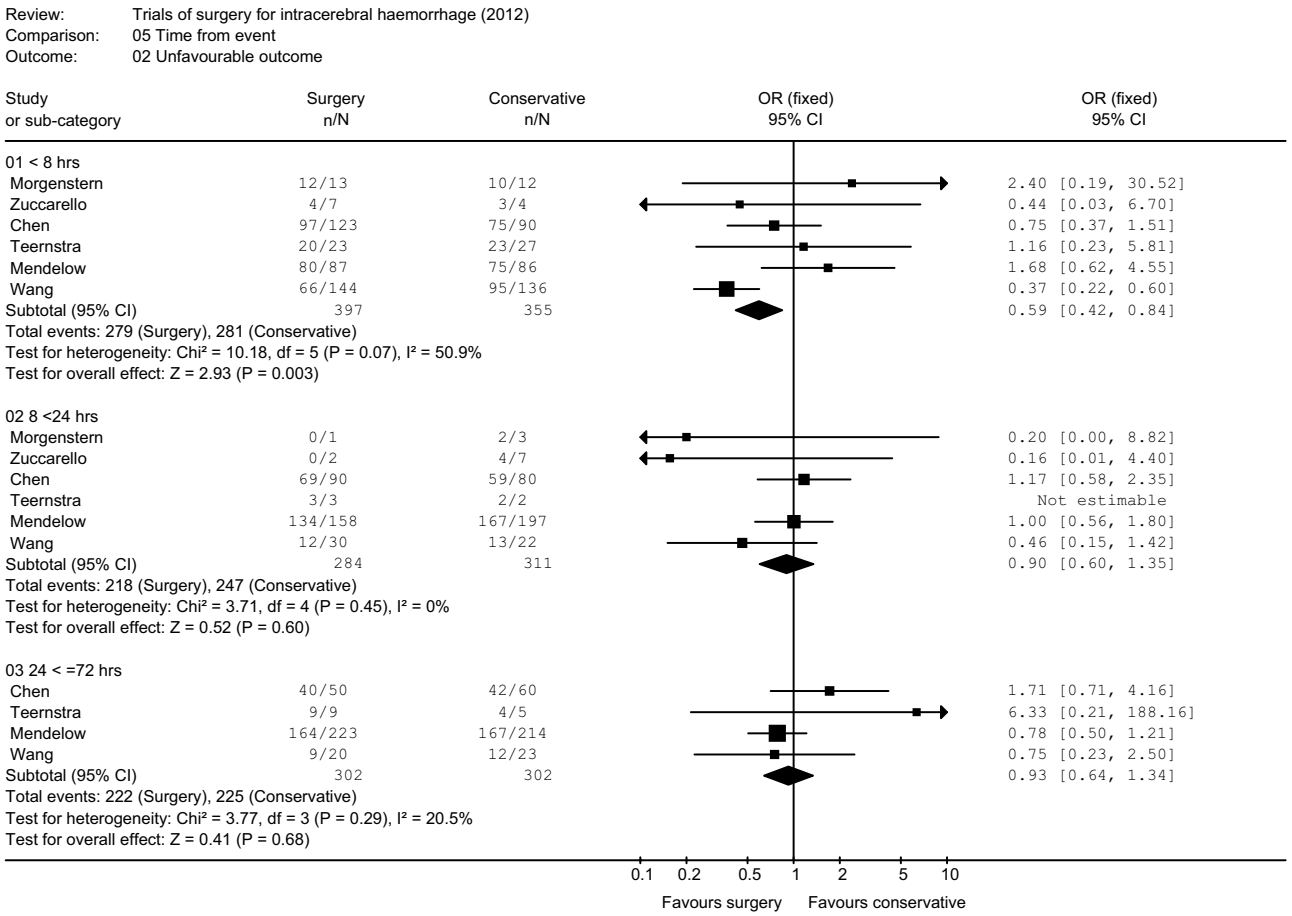



**Figure 2.** Meta-analysis by time of randomization.

## Study Characteristics

The Table summarizes the characteristics of the patients in each of the trials. Only 1 data set contained details of the depth of the hematoma from the cortical surface.[13] This would give an indication of the amount of healthy tissue that has to be passed through to reach the clot. Seven studies had recorded presence or absence of IVH but only 1 of these had any measure of the severity of the IVH.[13]

Because only dichotomized data were obtained from Auer, it is not always possible to include his data in the tables. He categorized GCS as 3 to 8 and 9 to 15, age as ≤60 years or >60 years, and volume as <50 mL or ≥50 mL.

## Location of Hematoma: Lobar or Deep and Presence of IVH

All studies recorded location of hematoma. Outcome was recorded for 509 patients with lobar hematoma (Figure 1). The majority of the patients (376 [74%]) were from the Mendelow et al trial and the overall OR was 0.75 (95% CI, 0.52–1.11; $P=0.15$) showing a nonsignificant trend toward surgery giving a favorable outcome. Outcome was recorded for 1379 patients with basal ganglia or thalamic hematomas. The studies of Chen, Mendelow, and Wang contribute most patients to this analysis: 430, 410, and 375, respectively. The OR was 0.84 (95% CI, 0.65–1.10) demonstrating no significant difference ($P=0.20$) in outcome according to whether the patients were allocated to surgery or conservative treatment. However, the test for heterogeneity demonstrates a significant difference among these studies suggesting that the results seen for the Wang study differ from those seen in the other studies.

Seven studies recorded presence or absence of IVH. In total, there were 1419 patients with no IVH: 526 from Mendelow, 445 from Chen, and 305 from Wang. The OR was 0.77 (95% CI, 0.61–0.98; $P=0.03$) indicating a significantly more favorable outcome with surgery than with conservative treatment when there was no IVH. There were 547 patients with IVH, 373 being from the Mendelow trial. The OR was similar at 0.77 (95% CI, 0.45–1.31), but there was no evidence for an improvement in outcome from surgery for the ICH when there was IVH due to the reduced power because of a smaller sample size.

Further analysis was undertaken studying only those patients with lobar hematomas who did not have IVH. Full data were available from 5 studies (301 cases) with incomplete data from the fourth (Auer; 39 cases). From the reported analyses we know that there were 6 patients who had lobar hematomas and IVH in his data set and that 31 of 32 patients with IVH had an unfavorable outcome. Thus, we can investigate a range of differences assuming all 6 patients were in the conservative group or all 6 were in the surgical group or there were 3 in each group. All these analyses give an OR favoring surgery with significance levels varying between $P=0.04$ and $P=0.15$. Assuming that the patients with IVH in

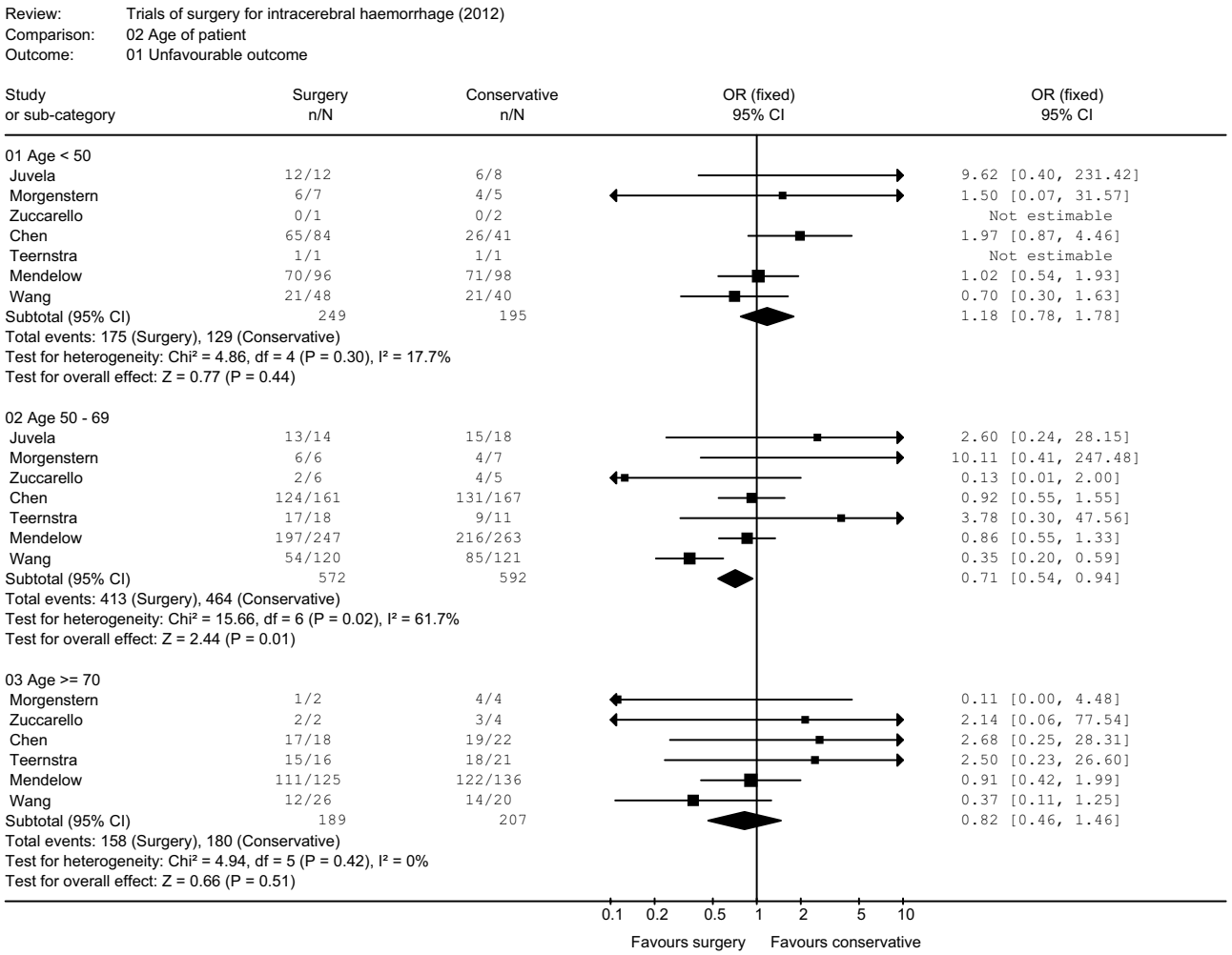



**Figure 3.** Meta-analysis by age of the patient.

Auer's data were equally distributed between the 2 groups gives an OR 0.68 (95% CI, 0.44–1.06; $P=0.09$).

Analysis of patients with a basal ganglia or thalamic hematoma and no IVH had an OR of 0.86 (95% CI, 0.64–1.14; $P=0.29$). There was a great deal of heterogeneity in these data ($P=0.0006$) with only the Wang and Teernstra data demonstrating any tendency toward a favorable outcome with surgery.

## Time to Randomization

Two studies recruited patients in a 48-hour time window, but the data were not recorded for individual patients.[2,3] Time was, therefore, only available for 6 studies and for 1 of the studies, this had been recorded in a limited way as <8 hours, 8 to 24 hours, and 24 to 72 hours. Because of this lack of full data, this categorization was therefore used for the analysis. Approximately one third of the patients fell into each categorization (752 patients were randomized within 8 hours, another 595 in 8–24 hours, and the other 604 in 24–72 hours). Only 4 studies included patients randomized >24 hours after ictus (Figure 2). These analyses suggested that early operation (within 8 hours of ictus) was beneficial with an OR of 0.59 (95% CI, 0.42–0.84; $P=0.003$).

## Age of the Patient

In total 444 patients were aged <50 years and the Chen study with one third of these patients had double the number in the surgery group compared with the conservative group. The studies tended to favor conservative rather than surgical therapy (Figure 3) with the overall OR for patients <50 years being a nonsignificant 1.18 (95% CI, 0.78–1.78; $P=0.44$). Among the 1164 patients in the intermediate age group of 50 to 69 years, the OR was significantly in favor of surgery at 0.71 (95% CI, 0.54–0.94; $P=0.01$), but again there was evidence of heterogeneity. For the 396 patients aged ≥70 years, it was 0.82 (95% CI, 0.46–1.46; $P=0.51$). In general, older patients fared worse than younger patients; 85% of patients aged ≥70 years had an unfavorable outcome compared with 75% of those aged 50 to 69 years and 68% of patients aged <50 years.

## GCS at Randomization

There were 394 patients with a GCS of 3 to 8 (Figure 4). The OR in favor of conservative treatment was 1.30 (95% CI, 0.49–3.48; $P=0.60$). All studies showed no significant difference in outcome between surgery and conservative treatment although tending to favor conservative treatment. Chen showed imbalances in the allocation of patients in this GCS

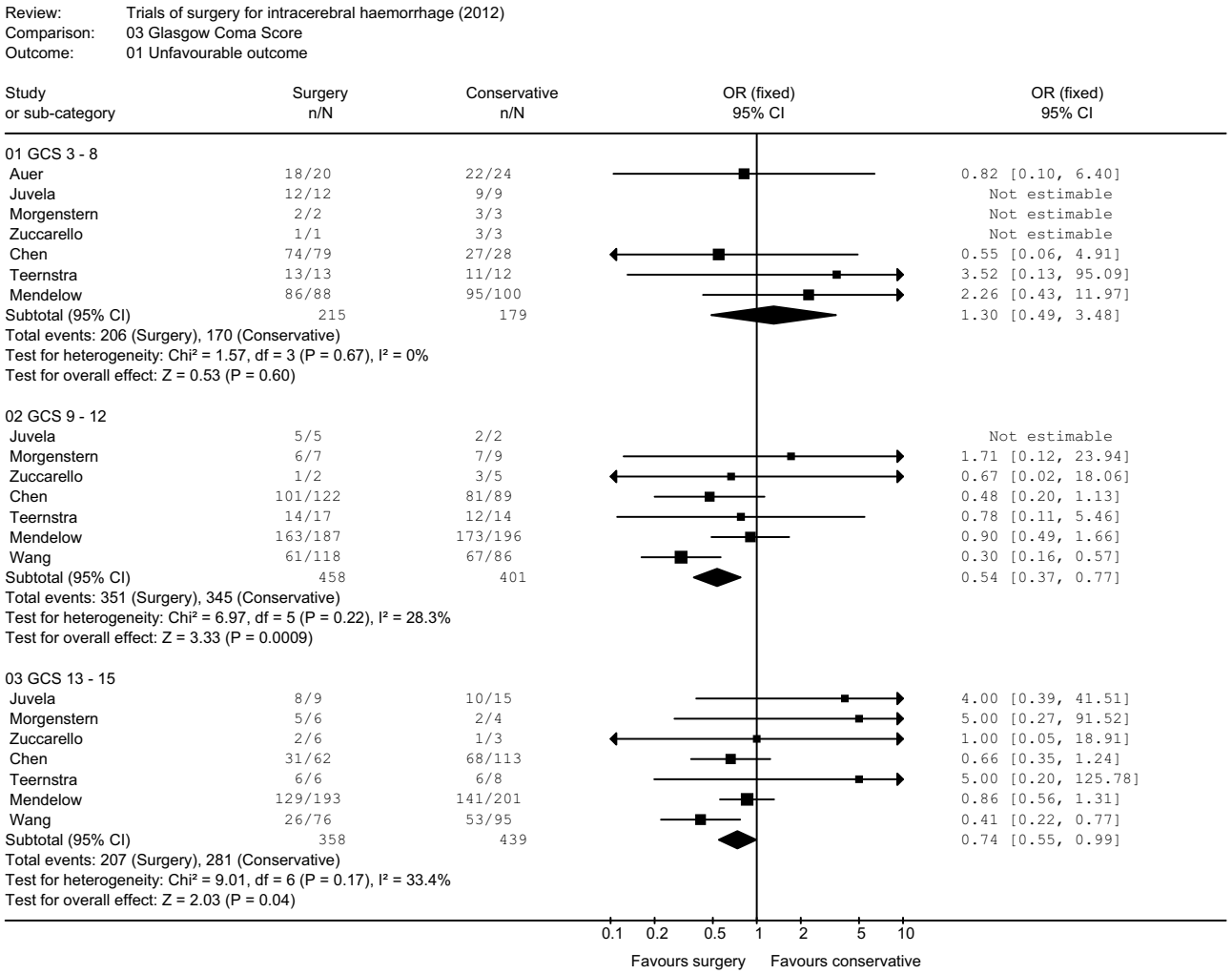



**Figure 4.** Meta-analysis by Glasgow Coma Score.

range: 79 allocated to surgery and 28 to conservative treatment.

There were 859 patients with a GCS between 9 and 12. This group of patients demonstrated a significantly improved outcome with surgery (OR, 0.54; 95% CI, 0.37–0.77; $P=0.0009$). All individual studies showed a tendency toward improved outcome with surgery for this group of patients and the test for heterogeneity was nonsignificant ($P=0.22$).

There were 797 patients with a GCS between 13 and 15. These patients also showed a significant difference in outcome between surgery and initial conservative treatment (OR, 0.74; 95% CI, 0.55–0.99; $P=0.04$).

In general, patients in a coma had a poorer outcome than conscious patients: 95% of patients with a GCS ≤8 had an unfavorable outcome compared with 81% of patients with a GCS of 9 to 12, and 60% of patients with a GCS of 13 to 15.

### Volume of Hematoma

There were 209 patients with a hematoma of <20 mL, 1233 with a hematoma of 20 to 49 mL, 373 with a hematoma of 50 to 79 mL, and 183 patients with a hematoma of ≥80 mL. The only category showing a significant treatment effect was the group with the volume of between 20 and 49 mL (Figure 5). The OR for this group was 0.69 (95% CI, 0.54–0.89; $P=0.004$). The smallest volume of hematomas (<20 mL) was the only category to show a tendency to favor conservative treatment. There is no evidence of a significant benefit for surgery at other volumes. In general, larger volumes were associated with worse outcomes: 93% of patients with a hematoma of ≥80 mL had an unfavorable outcome compared with 69% of patients with a hematoma of <20 mL.

## Discussion

### Summary of Evidence

This study set out to obtain the raw data from as many of the prospective randomized controlled trials of surgical treatment for spontaneous supratentorial ICH as possible. This has allowed exploration of clinically plausible hypotheses and prespecified subgroup analysis ideas in larger data sets than was available in the individual trials.

This study considered 1 intervention: removal of the clot by physical means. This clot removal by surgery includes craniotomy, aspiration, endoscopic aspiration, suction, and catheter aspiration. The intervention has been explored in terms of site, additional IVH, age of the patient, volume of hematoma, GCS, and timing of the intervention.

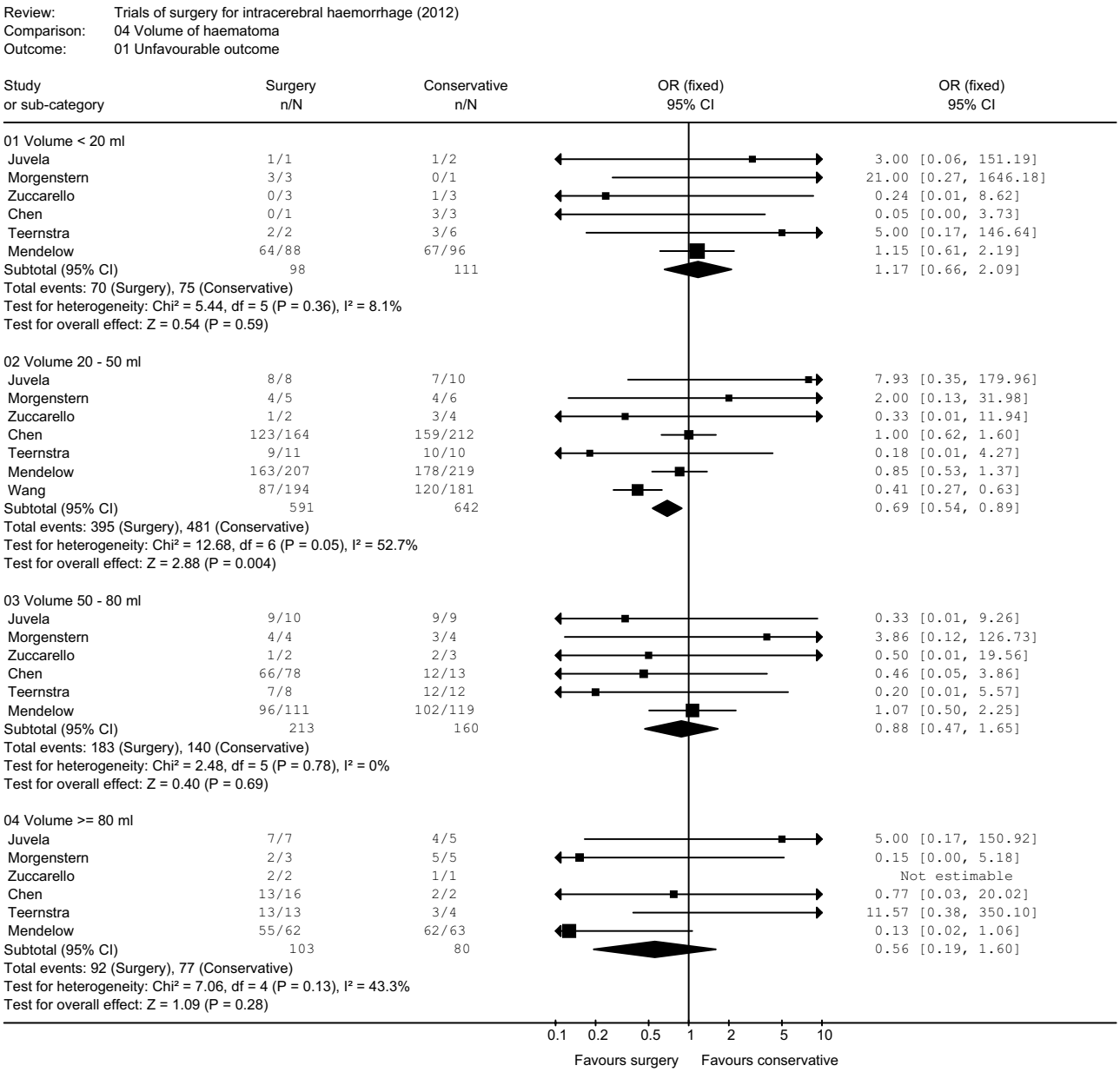



**Figure 5.** Meta-analysis by volume of the hematoma.

The overall data have permitted us to re-evaluate the prognostic features associated with ICH but it should be remembered that the interventions of surgery may have influenced these. Nevertheless, the well-known prognostic factors are clearly evident in these data. A separate analysis of the control arm of clinical trials of interventions (pharmacological and surgical) is underway and will be reported separately. Advancing age, volume of clot, and level of consciousness remain powerful predictors of outcome in this data set.

The treatment of spontaneous supratentorial ICH has remained and will remain controversial until a definitive prospective randomized controlled trial comes up with firm evidence in favor of a particular treatment. To date, both medical and surgical trials have failed to do this. Traditional treatment of ICH has been to observe the patient's clinical condition and to consider and offer surgery once the patient deteriorates. This means that secondary brain damage has taken place before the intervention of surgery. It would be more logical to intervene before the onset of secondary brain damage and this has been the theory behind many of the surgical trials over the past 50 years. Other aspects of intervention include prevention of expansion of the clot and treatment of the source of bleeding. Medical therapies have been aimed at these last 2 pathophysiological events but surgery would deal with all 3. Analysis of trials to date has suggested that there is a treatment effect but none has been conclusive. Meta-analysis of these trials gives some indication as to the effectiveness but the different methods, treatment intervals, outcome assessments, and methods of treatment make comparison difficult. Future studies should aim to standardize the collection of data. Actual measurements

should be recorded rather than grouped data such as the grouped time to randomization recorded in the Chen study.[11] All recognized predictive variables should be recorded and outcome should be measured at 6 months as well as any additional outcome points. Outcome should be measured using the extended version of the Glasgow Outcome Scale as well as modified Rankin Scale and other recognized assessments of outcome.

Overall there is no evidence that hematomas located in the deeper regions, basal ganglia or thalamus, may benefit from surgery, although more recent studies using minimally invasive techniques combined with clot lysis using urokinase suggest that this may prove to be a fruitful area for further research.[14,19,20]

There is, however, a suggestion that patients with lobar hematomas and no IVH might benefit from surgery. Our meta-analysis supports their selection as an appropriate population for the ongoing STICH II study.[21]

Our analysis confirms the benefits seen from surgery in the Cochrane (second edition) Review.[17] From this it has emerged that the factors that are most likely to show benefit with physical removal of the clot (that is different types of surgery) are earlier intervention (timing), the treatment of lobar and superficial hematomas, and the exclusion of patients with ventricular hemorrhage and/or hydrocephalus. The question of early intervention has been the central theme of the STICH trials and this is the first indication that early surgery is beneficial. It would in fact be logical to hypothesize that the earlier the clot is removed, the better. However, there have been studies that have suggested that ultraearly surgery might lead to worse outcomes[22] so further work is needed. This will be a prespecified subgroup in STICH II.[21]

### Limitations

Meta-analysis can be useful to identify trends and to set up hypotheses for further trials. The results have to be interpreted with caution because of the different methods used in each of the individual trials. Methods to evaluate studies that use meta-analysis have been proposed, the most recent being the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations,[23] which updates the Quorum (Quality of reporting of Meta-analyses) statement.[24] The data that we have analyzed here are difficult to report using these standards. In addition, Brand[25]has pointed out the difficulty of conducting trials in a double-blind way in the surgical arena.

## Conclusions

Our data suggest that improved outcomes can be achieved with early surgery within 8 hours of ictus, with hematomas of 20 to 50 mL, for patients with a GCS of ≥9 or for patients aged 50 to 69 years. In particular, our analyses suggest that when the GCS is ≤8, early surgery does not significantly improve outcome. Taking this argument further suggests that once the GCS has dropped to ≤8, then irretrievable damage has already occurred and surgery will not be successful in rescuing the patient.

This work has shown that the information available to date does favor earlier surgical intervention in patients with ICH. The ongoing studies STICH II, Minimally Invasive Surgery Plus rtPA for ICH Evacuation (MISTIE), and Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III) are focused on areas that this analysis shows may offer promising results.[19,21,26] Our work also endorses the American Heart Association guidelines[27] calling for more research to establish the groups that might benefit from surgery. At present the recommendations for or against surgery are based on conflicting evidence. These trials should provide robust evidence on which to base future recommendations.

## Sources of Funding

Funding for this work was provided by the National Institutes of Health (P50 NS044283-03 subaward P021-040-N633-1105) and UK Stroke Association (TSA 2004/19). The funding sources provided salary support for Dr Gregson. They had no role in writing the article or in the decision to submit.

## Disclosures

Professor Broderick has received honoraria from Genentech and PhotoThera for consulting work, Oakstone Medical Publishing for speaking as well as study medication or devices from EKOS Corporation, Genentech, Schering Plough and Novo Nordisk for NIH-funded studies. He has received monies for travel to national meetings from Genentech and Covidien. Professor Mendelow has received honoraria from Stryker, Codman, and NovoNordisc. Both place the honoraria in an educational/research fund in their departments.

## References

1. McKissock W, Richardson A, Taylor J. Primary intracerebral haemorrhage: a controlled trial of surgical and conservative treatment in 180 unselected cases. *Lancet*. 1961;2:221–226.
2. Auer LM, Deinsberger W, Niederkorn K, Gell G, Kleinert R, Schneider G, et al. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. *J Neurosurg*. 1989;70:530–535.
3. Juvela S, Heiskanen O, Poranen A, Valtonen S, Kuurne T, Kaste M, et al. The treatment of spontaneous intracerebral hemorrhage. A prospective randomised trial of surgical and conservative treatment. *J Neurosurg*. 1989;70:755–758.
4. Batjer H, Reisch J, Allen B, Plaizier L, Jen Su C. Failure of surgery to improve outcome in hypertensive putaminal hemorrhage. A prospective randomised trial. *Arch Neurol*. 1990;47:1103–1106.
5. Chen X, Yang H, Cheng Z. A prospective randomised trial of surgical and conservative treatment of hypertensive intracerebral haemorrhage. *Acta Acad Shanghai Med*. 1992;19:237–240.
6. Morgenstern LB, Frankowski RF, Shedden P, Pasteur W, Grotta JC. Surgical Treatment for Intracerebral Hemorrhage (STICH): a single-center, randomized clinical trial. *Neurology*. 1998;51:1359–1363.
7. Zuccarello M, Brott T, Derex L, Kothari R, Sauerbeck L, Tew J, et al. Early surgical treatment for intracerebral hemorrage. A randomized feasibility study. *Stroke*. 1999;30:1833–1839.
8. Teernstra OPM, Evers SMAA, Lodder J, Leffers P, Franke CL, Blaauw G. Stereotactic treatment of intracerebral hematoma by means of a plasminogen activator: a multicenter randomized controlled trial (SICHPA). *Stroke*. 2003;34:968–974.
9. Hosseini H, Leguerinel C, Hariz M, Melon E, Palfi S, Deck P, et al. Stereotactic aspiration of deep intracerebral hematomas under computed tomographic control: a multicentric prospective randomised trial. *Cerebrovasc Dis*. 2003;16S:57.
10. Pantazis G, Tsitsopoulos P, Mihas C, Katsiva V, Stavrianos V, Zymaris S, et al. Early surgical treatment vs conservative management for spontaneous supratentorial intracerebral hematomas: a prospective randomized study. *Surg Neurol*. 2006;66:492–501.
11. Chen X, Wu J, Zhou X, Zhang Y, Wang Z, Qin Z, et al. The randomized multicentric prospective controlled trial in the standardized treatment of hypertensive intracerebral hematomas: the comparison of surgical thera-

peutic outcomes with conservative therapy. *Chin J Clin Neurosci*. 2001; 4:365–368.
12. Hattori N, Katayama Y, Maya Y, Gatherer A. Impact of stereotactic hematoma evacuation on activities of daily living during the chronic period following spontaneous putaminal hemorrhage: a randomised study. *J Neurosurg*. 2004;101:417–420.
13. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*. 2005;365:387–397.
14. Wang WZ, Jiang B, Liu HM, Li D, Lu CZ, Zhao YD, et al. Minimally invasive craniopuncture therapy vs. conservative treatment for spontaneous intracerebral hemorrhage: results from a randomized clinical trial in China. *Int J Stroke*. 2009;4:11–16.
15. Mendelow A. Surgical management of intracerebral hemorrhage. In: Carhuapoma J, Mayer S, Hanley D, eds. *Intracerebral Hemorrhage*. Cambridge, UK: Cambridge University Press; 2009:165–175.
16. Mendelow A, Gregson B. Surgery for intracerebral hemorrhage. In: Mohr JP, Wolf P, Grotta J, Moskowitz M, Mayberg M, von Kummer R, eds. *Stroke: Pathophysiology, Diagnosis and Management.* V ed. Philadelphia: PA: WB Saunders; 2011.
17. Prasad K, Mendelow AD, Gregson BA. Surgery for primary supratentorial intracerebral haemorrhage. *Cochrane Database Syst Rev*. 2008;4: CD000200.
18. Deinsberger W. *Spontane Nichttraumatische Intracerebrale Haematome: Verbesserung der Prognose durch die endoskopische Haematomentleerung [MD].* Graz, Austria: Karl Franzens Universitat; 1987.
19. Morgan T, Zuccarello M, Narayan R, Keyl P, Lane K, Hanley D. Preliminary findings of the Minimally-Invasive Surgery plus rtPA for Intracerebral Hemorrhage Evacuation (MISTIE) clinical trial. *Acta Neurochir Suppl*. 2008;105:147–151.
20. Zhou H, Zhang Y, Liu L, Huang Y, Tang Y, Su J, et al. Minimally invasive stereotactic puncture and thrombolysis therapy improves long-term outcome after acute intracerebral hemorrhage. *J Neurol*. 2011; 258:661–669.
21. Mendelow AD, Gregson B, Mitchell P, Murray G, Rowan E, Gholkar A, et al. Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II) protocol. *Trials*. 2011;12:124.
22. Morgenstern LB, Demchuk AM, Kim DH, Frankowski RF, Grotta JC. Rebleeding leads to poor outcome in ultra-early craniotomy for intracerebral hemorrhage. *Neurology*. 2001;56:1294–1299.
23. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P, Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006–1012.
24. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. *Lancet*. 1999;354:1896–1900.
25. Brand RA. Standards of reporting: the CONSORT, QUORUM, and STROBE guidelines. *Clin Orthop Relat Res*. 2009;467:1393–1394.
26. Morgan T, Awad I, Keyl P, Lane K, Hanley D. Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial. *Acta Neurochir Suppl*. 2008;105:217–220.
27. Morgenstern LB, Hemphill JC III, Anderson C, Becker K, Broderick JP, Connolly ES Jr, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41:2108–2129.

Online supplement

# Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral haemorrhage

Table S1. Table of potential data sources

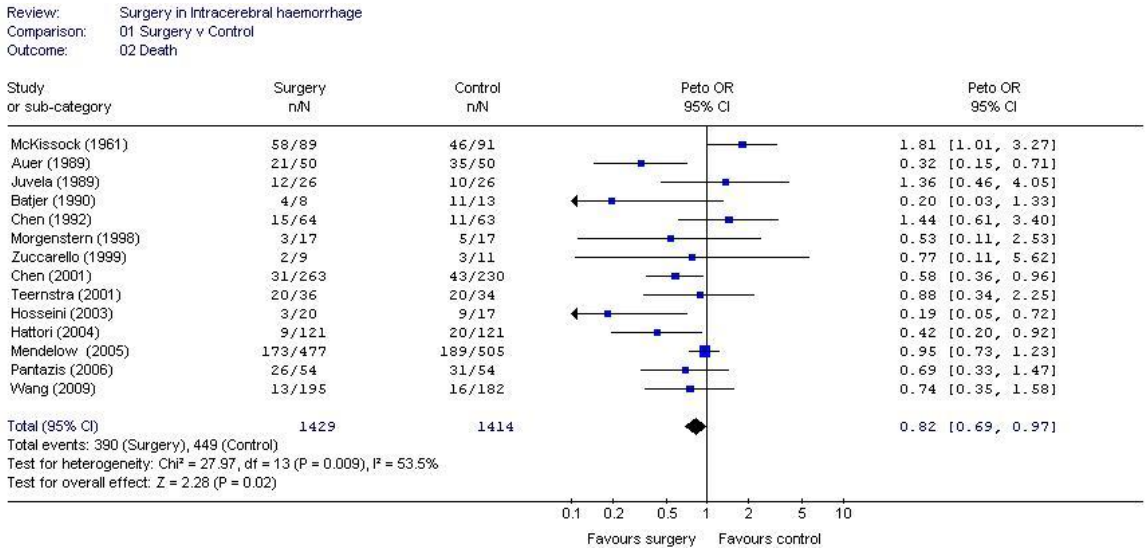
| Author (date of publication) | Years of data collection | No. of cases | Evacuation method | Time window | Outcome measure | Outcome timepoint | Location of haematoma | Other inclusion criteria |
|---|---|---|---|---|---|---|---|---|
| McKissock (1961)[1] | 1959-60 | 180 | craniotomy | >14 days | Full work/ partial disability/ full disability/ dead | 6 months | supratentorial | |
| Auer (1989)[2] | 1983-6 | 100 | endoscopic evacuation | 48 hrs | Similar to Rankin | 6 months | supratentorial | Aged 30-80 Volume >10ml |
| Juvela (1989)[3] | 1982-6 | 52 | craniotomy | 48 hrs | GOS | 6 months | supratentorial | Aged <65 |
| Batjer (1990)[4] | 1987-9 | 21 | craniotomy | 24 hrs | similar to GOS | 6 months | putaminal | Aged 30-75 Diameter > 3cm |
| Chen (1992)[5] | 1986-90 | 127 | craniectomy/ stereotaxy/ ventricular drainage | Not recorded | 5 Category dead/worse/ moderate/ fair/good | 3 to 39 months | supratentorial cerebellar | Not recorded |
| Morgenstern (1998)[6] | 1993-6 | 34 | craniotomy | 12 hrs | Barthel (Rankin) | 6 months | supratentorial | GCS 5-15 Volume >9ml |
| Zuccarello (1999)[7] | 1994-6 | 20 | craniotomy/ stereotaxy | 24 hrs | GOS | 3 months | supratentorial | Volume >10ml GCS >4 |
| Chen (2001)[8] | 1998 - 2000 | 500 | craniotomy/ burrhole (+/- streptokinase /urokinase) | 72 hrs | based on Barthel | 3-6 months | supratentorial infratentorial | Aged <70 GCS >6 Volume >10ml |
| Hossieni (2003)[9] | Not recorded | 37 | stereotactic aspiration | 24 hrs | Karnofsky | 12 months | "Deep" | Aged >30 Volume> 40ml |
| Teernstra (2003)[10] | 1996-9 | 71 | stereotactic aspiration + urokinase | 72 hrs | Rankin | 6 months | supratentorial | Aged >45 years Volume> 10ml |
| Hattori (2004)[11] | 1998-2000 | 242 | stereotactic evacuation | 24 hrs | Rankin | 12 months | putaminal | Aged 35-85 Japanese Coop Study grade 2-3 |
| Mendelow (2005)[12] | 1995-2004 | 1033 | craniotomy/ other | 96 hrs | GOS Rankin | 6 months | supratentorial | GCS>4 Diameter > 2cm |
| Pantazis (2006)[13] | 1998 - 2003 | 108 | craniotomy | 8 hrs | GOS | 12 months | supratentorial | Volume > 30 ml Aged <80 GCS <15 |
| Wang (2009)[14] | 2003-4 | 377 | minimally invasive + urokinase | 72 hrs | Rankin | 3 months | basal ganglia | Aged 40-75 GCS >8 Volume 25-40ml |

## References

1. McKissock W, Richardson A, Taylor J. Primary intracerebral haemorrhage: a controlled trial of surgical and conservative treatment in 180 unselected cases. Lancet. 1961;2:221-6.

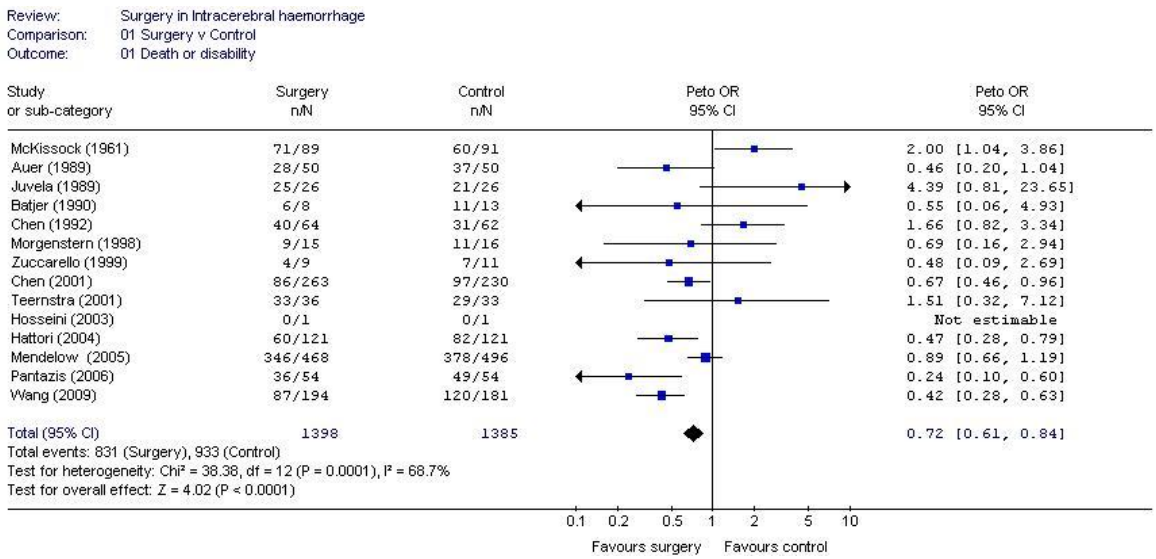
2. Auer LM, Deinsberger W, Niederkorn K, Gell G, Kleinert R, Schneider G, et al. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. Journal of Neurosurgery. 1989;70:530-5.
3. Juvela S, Heiskanen O, Poranen A, Valtonen S, Kuurne T, Kaste M, et al. The treatment of spontaneous intracerebral hemorrhage. A prospective randomised trial of surgical and conservative treatment. J Neurosurg. 1989;70:755 - 8.
4. Batjer H, Reisch J, Allen B, Plaizier L, Jen Su C. Failure of surgery to improve outcome in hypertensive putaminal hemorrhage. A prospective randomised trial. Arch Neurol. 1990;47:1103 - 6.
5. Chen X, Yang H, Cheng Z. A prospective randomised trial of surgical and conservative treatment of hypertensive intracerebral haemorrhage. Acta Acad Shanghai Med. 1992;19:237 - 40.
6. Morgenstern LB, Frankowski RF, Shedden P, Pasteur W, Grotta JC. Surgical treatment for intracerebral hemorrhage (STICH): a single-center, randomized clinical trial. Neurology. 1998;51:1359-63.
7. Zuccarello M, Brott T, Derex L, Kothari R, Sauerbeck L, Tew J, et al. Early surgical treatment for intracerebral hemorrage. A randomized feasibility study. Stroke. 1999;30:1833 - 9.
8. Teernstra OPM, Evers SMAA, Lodder J, Leffers P, Franke CL, Blaauw G. Stereotactic treatment of intracerebral hematoma by means of a plasminogen activator: a multicenter randomized controlled trial (SICHPA). Stroke. 2003;34:968-74.
9. Hosseini H, Leguerinel C, Hariz M, Melon E, Palfi S, Deck P, et al. Stereotactic aspiration of deep intracerebral hematomas under computed tomographic control: a multicentric prospective randomised trial. . Cerebrovasular Diseases. 2003;16S:57.
10. Pantazis G, Tsitsopoulos P, Mihas C, Katsiva V, Stavrianos V, Zymaris S, et al. Early surgical treatment vs conservative management for spontaneous supratentorial intracerebral hematomas: A prospective randomized study. Surgical Neurology. 2006;66:492-501.
11. Chen X, Wu J, Zhou X, YZhang Y, Wang Z, Qin Z, et al. The randomized multicentric prospective controlled trial in the standardized treatment of hypertensive intracerebral hematomas: The comparison of surgical therapeutic outcomes with conservative therapy. Chinese Journal of clinical Neuroscience. 2001;4:365-8.
12. Hattori N, Katayama Y, Maya Y, Gatherer A. Impact of stereotactic hematoma evacuation on activities of daily living during the chronic period following spontaneous putaminal hemorrhage: a randomised study. Journal of Neurosurgery. 2004;101:417-20.
13. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet. 2005; 365:387-97.
14. Wang WZ, Jiang B, Liu HM, Li D, Lu CZ, Zhao YD, et al. Minimally invasive craniopuncture therapy vs. conservative treatment for spontaneous intracerebral hemorrhage: results from a randomized clinical trial in China. Int J Stroke. 2009;4:11-6.

Figure S1. Meta-analysis of published data for all 14 trials: Mortality




Reference: Updated from: Mendelow A. Surgical management of intracerebral hemorrhage. In: Carhuapoma J, Mayer S, Hanley D, editors. Intracerebral Hemorrhage. Cambridge: Cambridge University Press; 2009. p. 165-75.

Figure S2. Meta-analysis of published data for death and disability




Reprinted from: Mendelow A, Gregson B. Surgery for Intracerebral Hemorrhage. In: Mohr JP, Wolf P, Grotta J, Moskowitz M, Mayberg M, von Kummer R, editors. Stroke: Pathophysiology, Diagnosis and Management. 5th ed: Saunders; 2011.