Prognostic Factors and Treatment Effect in the CHIMES Study

Siwaporn Chankrachang, MD,* Jose C. Navarro, MD,† Deidre A. de Silva, FRCP,‡ Somchai Towanabut, MD,§ Carlos L. Chua, MD,|| Chun Fan Lee, PhD,¶ Narayanaswamy Venketasubramanian, FRCP,# K. S. Lawrence Wong, MD,** Marie-Germaine Bousser, MD,†† Christopher L. H. Chen, FRCP,‡‡ and for the CHIMES Study Investigators

Background: Stroke trials often analyze patients with heterogeneous prognoses using a single definition of outcome, which may not be applicable to all subgroups. We aimed to evaluate the treatment effects of MCL601 among patients stratified by prognosis in the Chinese Medicine Neuroaid Efficacy on Stroke Recovery (CHIMES) study. *Methods:* Analyses were performed using data from the CHIMES study, an international, randomized, placebo-controlled, double-blind trial comparing MLC601 with placebo in patients with ischemic stroke of intermediate severity in the preceding 72 hours. All subjects with baseline data and the modified Rankin Scale (mRS) score at 3 months were included. *Results:* Data from 1006 subjects were analyzed. The predictive variables for mRS score greater than 1 at month 3 were age older than 60 years ($P < .001$), baseline National Institutes of Health Stroke Scale score 10-14 ($P < .001$), stroke onset to initiation of study treatment of more than 48 hours ($P < .001$), and female sex ($P = .026$). A higher number of predictors was associated with poorer mRS score at month 3 for both placebo ($P < .001$) and treatment ($P < .001$) groups. The odds ratio (OR) for achieving a good outcome increased with the number of predictors and reached statistical significance in favor of MLC601 among patients with 2 to 4 predictors combined (unadjusted OR = 1.44, 95% confidence interval, 1.02-2.03; adjusted OR = 1.60, 95% confidence interval, 1.10-2.34). *Conclusions:* Age, sex, baseline National Institutes of Health Stroke Scale score, and time to first dose are predictors of functional outcome in the CHIMES study. Stratification by prognosis showed that patients with 2 or more predictors of poorer outcome have better treatment effect with MLC601 than patients with single or no prognostic factor. These results have implications on designing future stroke trials. **Key Words:** Acute stroke—stroke recovery—MLC601—NeuroAiD—prognosis—clinical trial.

From the *Chiang Mai University, Amphur Muang, Chiang Mai, Thailand; †University of Santo Tomas Hospital, España Boulevard, Manila, Philippines; ‡National Neuroscience Institute-Singapore General Hospital Campus, Singapore General Hospital, Singapore; §Prasat Neurological Institute, Rajthevi, Bangkok, Thailand; ||Philippine General Hospital, University of the Philippines Manila, Manila, Philippines; ¶Singapore Clinical Research Institute, Singapore; #Raffles Neuroscience Centre, Raffles Hospital, Singapore; **Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR, China; ††Lariboisière University Hospital, Paris, France; and ‡‡Department of Pharmacology, National University of Singapore, Clinical Research Centre, Singapore.

Received November 6, 2014; accepted November 19, 2014.

The CHIMES study was supported by the CHIMES Society and grants received by C.L.H.C. from the National Medical Research Council of Singapore (NMRC/1288/2011 and NMRC/1096/2006). The authors received funding for the trial and accommodation and transportation support for meetings from the CHIMES Society. J.C.N. has minor shares in E*Chimes, the Philippine distributor of NeuroAiD. Moleac, Singapore provided grants to the CHIMES Society of which the society had sole discretion on use.

Address correspondence to Christopher L.H. Chen, FRCP, Department of Pharmacology, National University of Singapore, Clinical Research Centre, Building MD11, Level 5, #05-09, 10 Medical Drive, Singapore 117597, Singapore. E-mail: phccclh@nus.edu.sg.

1052-3057/- see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.11.017

Introduction

Some of the difficulties in translating acute stroke treatments from bench to bedside have been attributed to discrepancies between preclinical and clinical study designs.[1-3] Unlike preclinical studies, stroke clinical trials often include heterogeneous patients[4] who are usually analyzed together using a single definition of "good" outcome that may not be applicable to all patient subgroups.

Using a prognosis-based approach to target patient selection or define and adjust desired outcomes have been proposed by several groups.[5-9] Trials that implemented such approach have identified cohorts with specific prognostic profiles likely to benefit or be harmed by treatments.[10-12]

MLC601 has been shown to have both neurorestorative and neuroprotective properties in animal and cellular models.[13] Clinical trials suggest that MLC601, as an add-on to standard treatment, could be effective in improving functional outcome and motor recovery and is safe for patients with primarily nonacute stable stroke.[14]

In a recent publication, the favorable treatment effect of MLC601 in patients with acute ischemic stroke recruited from the Philippines in the Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study was hypothesized to be because of inclusion of patients with poorer prognosis.[15] In this analysis, we aimed to evaluate if treatment effect of MCL601 varies among acute stroke patients with differing prognostic profiles in the CHIMES study cohort and if stratification by anticipated prognosis may identify patients more likely to benefit from MLC601.

Methods

Analyses were performed using data from the CHIMES study, an international, randomized, placebo-controlled, double-blind trial that compared MLC601 with placebo in patients with ischemic stroke of intermediate severity in the preceding 72 hours (clinicaltrials.gov NCT00554723).[16-18] Subjects were allocated to either MLC601 or placebo for 3 months as add-on to standard stroke care (ie, antiplatelet therapy, control of vascular risk factors, appropriate rehabilitation) and followed for 3 months. The primary outcome measure used in this study was the modified Rankin scale (mRS) score at 3 months. Of 1099 subjects in the CHIMES study, 1006 with complete baseline data and an mRS score at month 3 were included in this post hoc analysis. Logistic regression analyses were performed to identify predictors of mRS score greater than 1 and to assess the association between number of predictors and mRS. Sensitivity, specificity, positive predictive values, negative predictive values, and receiver operating characteristic for mRS score less than 2 versus 2 or more at month 3 were calculated. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were used to estimate treatment effects overall and according to number of predictors. ORs were also adjusted by logistic regression for baseline prognostic factors, that is, age, sex, National Institutes of Health Stroke Scale (NIHSS), prestroke mRS, and duration from stroke onset to initiation of study treatment.

Results

Baseline characteristics of patients were similar between the treatment groups as previously described.[16,18] The predictive variables for mRS score greater than 1 at month 3 were age older than 60 years ($P < .001$), baseline NIHSS score of 10-14 ($P < .001$), stroke onset to initiation of study treatment of more than 48 hours ($P < .001$), and female sex ($P = .026$). Increasing number of predictors at baseline was associated with worse mRS score at month 3 for both placebo ($P < .001$) and treatment ($P < .001$) groups (Fig 1). A high response rate in the placebo group (>50% with mRS score < 2) was seen among subjects with one or no predictor of poorer mRS. Having more than 1 predictor has a sensitivity of 72%, specificity of 61%, positive predictive value of 68%, and negative predictive value of 64% for a poorer outcome of mRS score greater than 1 at 3 months (Table 1). Receiver operating characteristic area under the curve was .7211.

The overall OR of MLC601 for achieving an mRS score less than 2 at month 3 was 1.15 (95% CI, .89-1.47). Stratification according to number of predictors of poorer outcome showed ORs increasing with the number of predictors and reached statistical significance in favor of MLC601 among subjects with 2 or more predictors (OR = 1.44, 95% CI, 1.02-2.03) and was higher in those with 3 or more predictors (OR = 2.21, 95% CI, 1.22-4.0; Fig 2). Adjustment for baseline prognostic factors generally increased the ORs.

Discussion

Age, stroke severity, sex, and time delay to treatment have been identified as predictors of outcome after a stroke in this and many previous studies.[19] Aside from sex, these factors are often eligibility criteria in stroke clinical trials. In addition to being individually predictive of outcome in the CHIMES cohort, we found a strong graded association between the number of predictors and mRS status at 3 months.

The CHIMES study showed an overall OR of achieving mRS score less than 2 in favor of MLC601, although this did not reach statistical significance.[16] This may be because of inclusion of patients with relatively good prognosis. In the CHIMES study, patients were included if they were 18 years and older, had a baseline NIHSS score of 6 to 14, and stroke onset in the preceding 72 hours. The

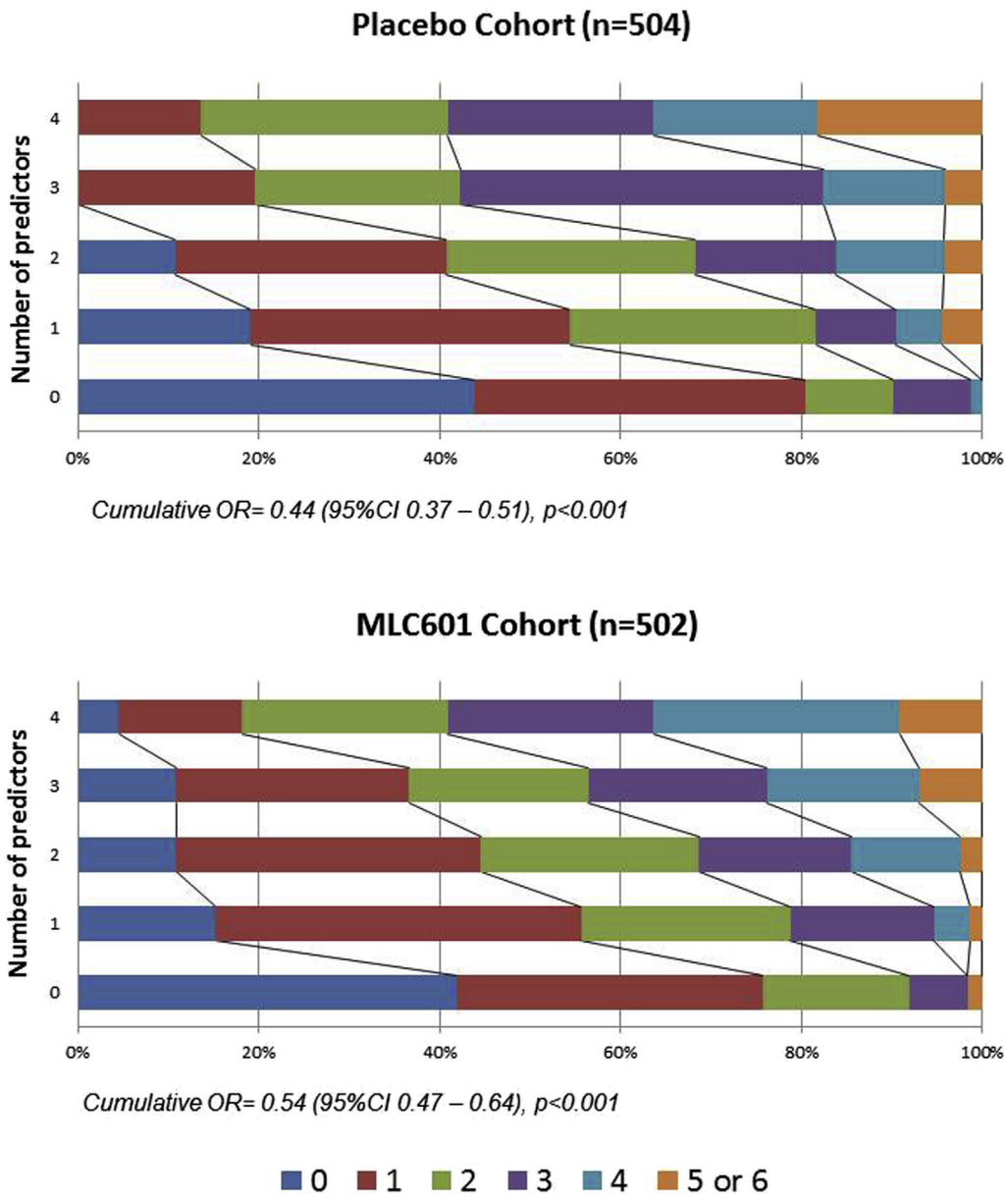

Figure 1. *Relationship between number of predictors and the mRS score at month 3 among MLC601- and placebo-treated patients in the CHIMES study. Abbreviations: CHIMES, Chinese Medicine Neuroaid Efficacy on Stroke Recovery; CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio.*

stroke severity and treatment window eligibility criteria were chosen to target inclusion of patients who would have the potential to improve over time. Although successfully excluding very severe patients with poor prognosis for recovery from our cohort, that is, only less than 5% dead or completely disabled, the NIHSS cutoff appeared to have led to selection of many patients with excellent prognosis with almost half in the placebo group achieving functional independence (mRS score < 2) and more than two thirds achieving an mRS score of 0 to 2 at month 3. Such high response rate in the placebo arm and inclusion of subjects with prognostic heterogeneity have been shown to affect the potential of detecting treatment effects in clinical trials.[11,20,21]

Indeed, our present analysis on the entire CHIMES cohort shows that MLC601 may be beneficial in patients with predicted poorer outcome based on baseline prognostic variables. This supports the hypothesis from a recently published subgroup analysis of the Filipino cohort that the favorable treatment effects of MLC601 may have been because of inclusion of more patients with poorer prognosis.[15] Clinicians are familiar with the concept that the potential of a patient to recover from a disorder or derive benefit from a treatment depends on disease severity and prognosis. Such potential benefit expectedly would not be as obvious in patients who either would spontaneously recover fully regardless of intervention or are too severe to realistically improve completely.[22]

Table 1. *Sensitivity, specificity, PPV, and NPV according to number of prognostic factors*

Number of predictors	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
>0	94.2	28.7	61.1	80.5
>1	71.5	60.9	68.5	64.2
>2	35.4	90.4	81.5	54.0
>3	6.9	98.7	86.4	47.1

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Our results have implications for the design of future stroke trials as also raised by other groups.[2-12] In clinical trials, caution must be observed when deciding on the outcomes and a threshold for assessing such outcomes to be defined as "good response."[5] In addition, adjusting outcomes according to baseline prognosis would improve the statistical power of detecting an effect,[8] which in our study generally increased the estimates of the treatment effects.

The anticipated prognosis and potential to respond to treatment should be considered in selecting a study population. Although not always successful,[23-25] targeting patients with greater potential to benefit from therapy may reduce the sample size required in trials without affecting the power.[7] Based on the mRS distribution in our sample, approximately 7000 subjects would be needed to have 90% power to detect an overall OR of 1.15. The sample size required, however, could be greatly reduced to 1200 for detecting an OR of 1.44 by recruiting only subjects with more than 1 predictor and further reduced to 300 for an OR of 2.21 with inclusion of only subjects with more than 2 predictors. As patients with poor prognostic predictors are not uncommon in stroke, prognosis-based patient selection may be feasible. Eligibility criteria that are too restrictive, however, may lead to more screen failures, slow recruitment, and less generalizable results. Careful balancing of eligibility criteria or their combinations is needed to achieve prognostic homogeneity.

On the other hand, the concern with the strategy of reducing sample size is that it gives little room to accommodate any variation in the outcomes that may not have been expected from earlier phase studies, which it was based on. Larger sample sizes can help mitigate this risk. In large stroke trials where patient homogeneity may not be practical and may need to be balanced with the disadvantages of having more stringent eligibility, some have proposed a prognosis-based responder analysis, which may be implemented by defining a realistic, clinically important difference relative to the expected outcome of study subjects. In this analysis, also called sliding dichotomy, subjects are grouped into a number of bands according to baseline prognosis, wherein each band is analyzed according to a customized predefined "good" and "bad" outcome on a scale.[6] This was performed in the International Surgical Trial in Intracerebral Hemorrhage studies but failed to show statistical significance.[25,26]

There are some limitations in this study. The prognostic variables we identified will need to be externally validated in another data set, although each was already often shown to be important predictive variables in many other studies.[19] The analyses were post hoc, and the trial was not originally planned for such prognosis-based analysis. However, the data used were collected before unblinding.

In summary, prognostic factors for functional outcomes are age, sex, stroke severity, and stroke onset to treatment delay. Using such factors in a prognosis-based stratified analysis showed that MLC601 had a treatment effect among patients with at least 2 predictors of poor outcome. Future trial designs should consider selection of patients with moderate baseline stroke severity and in whom treatment could not be instituted earlier than 48 hours from onset.

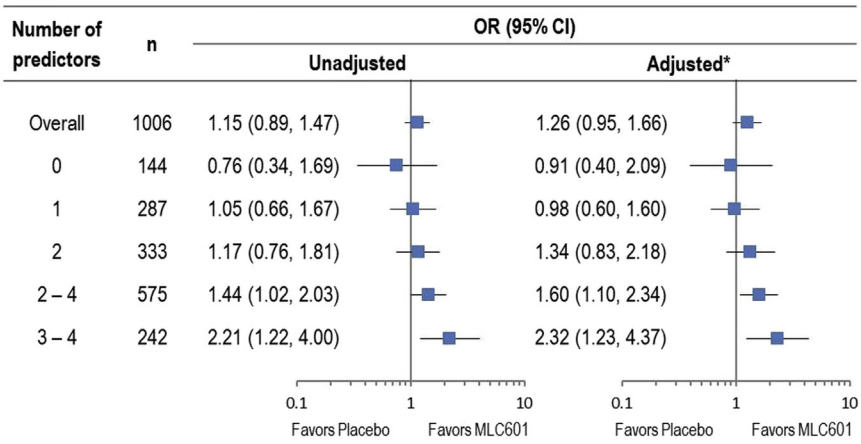

Figure 2. *Treatment effects according to number of predictors in the CHIMES study. Abbreviations: CHIMES, Chinese Medicine Neuroaid Efficacy on Stroke Recovery; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.*

** Adjusted for baseline NIHSS, age, gender, pre-stroke mRS, and stroke onset to first dose*

Acknowledgments: CHIMES Study Investigators—Philippines: Jose C. Navarro, Herminigildo H. Gan, Annabelle Lao, Alejandro Baroque II, Johnny Lokin, John Harold B. Hiyadan, Ma. Socorro Sarfati, Randolph John Fangonillo, Neil Ambasing, Carlos Chua, Ma. Cristina San Jose, Joel Advincula, Eli John Berame, and Maria Teresa Canete; Singapore: Narayanaswamy Venketasubramanian, Sherry H. Y. Young, Marlie Jane Mamauag, San San Tay, Shrikant Pande, Umapathi Thirugnanam, Rajinder Singh, Hui Meng Chang, Deidre Anne De Silva, Bernard P. L. Chan, Vijay Sharma, and Teoh Hock Luen; Thailand: NiphonPoungvarin, Sombat Muengtaweepongsa, Somchai Towanabut, Nijasri Suwanwela, Songkram Chotickanuchit, Siwaporn Chankrachang, and Samart Nitinun; Sri Lanka: H. Asita de Silva, Udaya Ranawake, and Nirmala Wijekoon; Hong Kong: K. S. Lawrence Wong; Malaysia: Gaik Bee Eow.

References

1. Cheng YD, Al-Khoury L, Zivin JA. Neuroprotection for ischemic stroke: two decades of success and failure. NeuroRx 2004;1:36-45.
2. Grotta J. Neuroprotection is unlikely to be effective in humans using current trial designs. Stroke 2002;33:306-307.
3. Lees KR. Neuroprotection is unlikely to be effective in humans using current trial designs: an opposing view. Stroke 2002;33:308-309.
4. Muir KW. Heterogeneity of stroke pathophysiology and neuroprotective clinical trial design. Stroke 2002; 33:1545-1550.
5. Berge E, Barer D. Could stroke trials be missing important treatment effects. Cerebrovasc Dis 2002;13:73-75.
6. Murray GD, Barer D, Choi S, et al. Design and analysis of phase III trials with ordered outcome scales—the concept of the sliding dichotomy. J Neurotrauma 2005;22:511-517.
7. Weir CJ, Kaste M, Lees KR, Glycine Antagonist in Neuroprotection (GAIN) International Steering Committee and Investigators. Targeting neuroprotection clinical trials to ischemic stroke patients with potential to benefit from therapy. Stroke 2004;35:2111-2116.
8. Optimising the Analysis of Stroke Trials (OAST) CollaborationGray LJ, Bath PM, et al. Should stroke trials adjust functional outcome for baseline prognostic factors? Stroke 2009;40:888-894.
9. Gorelick PB. How baseline severity affects efficacy and safety outcomes in acute ischemic stroke intervention trials. Ann N Y Acad Sci 2012;1268:85-94.
10. Roozenbeek B, Lingsma HF, Perel P, et al, IMPACT (International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury) Study Group, CRASH (Corticosteroid Randomisation After Significant Head Injury) Trial Collaborators. The added value of ordinal analysis in clinical trials: an example in traumatic brain injury. Crit Care 2011;15:R127.
11. Fiebach JB, Al-Rawi Y, Wintermark M, et al. Vascular occlusion enables selecting acute ischemic stroke patients for treatment with desmoteplase. Stroke 2012;43: 1561-1566.
12. Gregson BA, Murray GD, Mitchell PM, et al. Update on the Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II): statistical analysis plan. Trials 2012; 13:222.
13. Heurteaux C, Widmann C, Moha ou Maati H, et al. NeuroAiD: properties for neuroprotection and neurorepair. Cerebrovasc Dis 2013;35(Suppl 1):1-7.
14. Siddiqui FJ, Venketasubramanian N, Chan ESY, et al. Efficacy and safety of MLC601 (NeuroAiD®), a traditional Chinese medicine, in poststroke recovery: a systematic review. Cerebrovasc Dis 2013;35(Suppl 1):8-17.
15. Navarro JC, Gan HH, Lao AY, et al. Baseline characteristics and treatment response of patients from the Philippines in the CHIMES Study. Int J Stroke 2014; 9(Suppl A100):102-105.
16. Chen CLH, Young SHY, Gan HH, et al. Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES). A double-blind, placebo-controlled, randomized study. Stroke 2013;44:2093-2100.
17. Venketasubramanian N, Chen CL, Gan RN, et al. A double-blind, placebo-controlled, randomized, multicenter study to investigate CHInese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES Study). Int J Stroke 2009;4:54-60.
18. Chen CL, Venketasubramanian N, Lee CF, et al. Effects of MLC601 on early vascular events in patients after stroke: the CHIMES study. Stroke 2013;44:3580-3583.
19. Rabinstein A, Rundek T. Prediction of outcome after ischemic stroke: the value of clinical scores. Neurology 2013;80:15-16.
20. Hacke W, Furlan AJ, Al-Rawi Y, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. Lancet Neurol 2009; 8:141-150.
21. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2008;358:2127-2137.
22. Duncan PW, Goldstein LB, Matchar D, et al. Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. Stroke 1992; 23:1084-1089.
23. Diener HC, Cortens M, Ford G, et al. Lubeluzole in acute ischemic stroke treatment: a double-blind study with an 8-hour inclusion window comparing a 10-mg daily dose of lubeluzole with placebo. Stroke 2000; 31:2543-2551.
24. Lyden P1, Shuaib A, Ng K, et al. Clomethiazole Acute Stroke Study in ischemic stroke (CLASS-I): final results. Stroke 2002;33:122-128.
25. Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet 2013; 382:397-408.
26. Mendelow AD, Gregson BA, Fernandes HM, 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.