Published in final edited form as:
Neurocrit Care. 2011 December ; 15(3): 559–576. doi:10.1007/s12028-011-9538-3.

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: Design, Methods, and Rationale

A. I. Qureshi and
Zeenat Qureshi Stroke Research Center, University of Minnesota, Minneapolis, MN, USA. Department of Neurology, University of Minnesota, MMC 295, 420 Delaware Street SE, Minneapolis, MN 55455, USA

Y. Y. Palesch
Medical University of South Carolina, Charleston, SC, USA

A. I. Qureshi: aiqureshi@hotmail.com

Abstract

The December 2003 report from the National Institute of Neurological Disorders and Stroke (NINDS) Workshop on priorities for clinical research in intracerebral hemorrhage (ICH) recommended clinical trials for evaluation of blood pressure management in acute ICH as a leading priority. The Special Writing Group of the Stroke Council of the American Heart Association in 1999 and 2007 emphasized the need for clinical trials to ensure evidence-based treatment of acute hypertensive response in ICH. To address important gaps in knowledge, we conducted a pilot study funded by the NINDS, Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) I Trial, during 2004–2008 to determine the appropriate level of systolic blood pressure (SBP) reduction. We now have initiated a multicenter, randomized Phase III trial, the ATACH II Trial, to definitively determine the efficacy of early, intensive, anti-hypertensive treatment using intravenous (IV) nicardipine initiated within 3 h of onset of ICH and continued for the next 24 h in subjects with spontaneous supratentorial ICH. The primary hypothesis of this large (N = 1,280), streamlined, and focused trial is that SBP reduction to ≤140 mm Hg reduces the likelihood of death or disability at 3 months after ICH, defined by modified Rankin scale score of 4–6, by at least 10% absolute compared to standard SBP reduction to ≤180 mm Hg. The ATACH II trial is a natural extension of numerous case series, the subsequent ATACH I pilot trial, and a preliminary, randomized, and controlled trial in this patient population funded by the Australian National Health and Medical Research Council. Both trials recently confirmed the safety and tolerability of both the regimen and goals of antihypertensive treatment in acutely hypertensive patients with ICH, as proposed in the present trial. The underlying mechanism for this expected beneficial effect of intensive treatment is presumably mediated through reduction of the rate and magnitude of hematoma expansion observed in approximately 73% of the patients with acute ICH. The Australian trial provided preliminary evidence of attenuation of hematoma expansion with intensive SBP reduction. The ATACH II trial will have important public health implications by providing evidence of, or lack thereof, regarding the efficacy and safety of acute antihypertensive treatment in subjects with ICH. This treatment represents a strategy that can be made widely available without the need for specialized equipment and personnel, and therefore, can make a major impact upon clinical practice for treating patients with ICH.

Correspondence to: A. I. Qureshi, aiqureshi@hotmail.com.

This study was conducted for the ATACH II Investigators.

Keywords

Intracerebral hemorrhage; Clinical trial; Randomization; Acute hypertensive response; Hematoma enlargement

Introduction

It is estimated that 37,000–52,400 people in the U.S. have intracerebral hemorrhage (ICH) every year [1]. The high rate of death and disability, and the high financial burden associated with this illness mandates critical analysis of treatments with therapeutic potential. Elevated blood pressure (BP) is observed in 46–75% of patients with ICH depending on the population studied and the definition of hypertension used [2]. Furthermore, hematoma expansion in ICH patients is a common and important cause of poor outcomes, and elevated BP may predispose patients to hematoma expansion. Since expansion occurs during a time frame when therapeutic intervention is feasible, the opportunity exists to reduce BP which ultimately may reduce hematoma expansion and subsequent death and disability. Although experimental and small uncontrolled clinical studies suggest that reduction of elevated BP in ICH may be tolerated and is feasible, various BP management protocols that are in place for treatment of acute hypertensive response in ICH lack appropriate evidence, and some strategies may have deleterious effects and need to be modified.

In 1999 and 2007, the Special Writing Group of the American Heart Association (AHA) Stroke Council [3, 4] concluded that the treatment of acute hypertension in patients with ICH can be supported only by anecdotal case series (level V or Class IIa evidence) and could be considered only as a Grade C recommendation. In addition, the report from the December 2003 National Institute of Neurological Disorders and Stroke (NINDS) Workshop on priorities for clinical research in ICH [5] recommended clinical trials for evaluation of BP management in acute ICH as a leading priority. The recommendations stated that “a prospective randomized control trial needs to be performed to determine appropriate BP goals and the best strategies to achieve those goals.”

In this article, we describe the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial design and methods and provide the rationale for the choice of design parameters.

Study Objective

The primary objective of the ATACH II is to definitively determine the efficacy of intensive BP reduction for acute hypertension in subjects with supratentorial ICH. The primary hypothesis of the trial is that intensive systolic blood pressure (SBP) reduction (SBP ≤ 140 mm Hg) using IV nicardipine infusion for 24-h post-randomization reduces the proportion of death and disability (modified Rankin scale, mRS of 4–6) at 3 months by ≥10% compared with the standard BP reduction (SBP ≤ 180 mm Hg) among patients with ICH treated within 3 h of symptom onset. A simple, streamlined study design is implemented to evaluate the efficacy of intensive SBP reduction and its effect on outcomes measures at 24 h (hematoma expansion) and at 3 months from randomization (see Table 1).

The other aims of the study are to evaluate the therapeutic benefit and safety of the intensive treatment compared with the standard treatment in terms of (1) quality of life as measured by EuroQOL at 3 months; (2) the proportion of subjects with hematoma expansion (defined as increase from baseline hematoma volume of ≥33%) at 24 h using centrally read serial computed tomographic (CT) scans; and (3) the proportion of subjects with treatment-related SAEs within 72 h.

Study Design and Method

The ATACH II trial is a parallel, two-arm study, where eligible subjects are randomized to intense and standard SBP treatment in a 1:1 ratio. All the randomized subjects are treated according to the study protocol and followed for 3 months or death, whichever occurs first. Subjects are contacted by telephone at 1 month and assessed for the clinical outcomes in person at 3 months.

Pre-randomization Procedure

The specific eligibility criteria are provided in Table 2. The clinical and radiological information to assess eligibility should be complete after acquisition of CT scan. There is an anticipated period lasting no longer than 30 min between determination of eligibility and initiation of treatment titrated to SBP target of the allocated treatment group (see Table 3). In this interim period, IV nicardipine infusion preferably should be initiated with a goal to maintain SBP below 180 mm Hg, but above 160 mm Hg, consistent with existing ASA and European Stroke Initiative (EUSI) recommendations for patients with ICH [4, 6]. Initiation of nicardipine before randomization within 3 h of symptom onset and titration to allocated target within 3.5 h is acceptable would also avoid loss of time in initiating nicardipine infusion. If the patient's SBP falls below 180 mm Hg in a sustained manner without any treatment (defined by lack of any SBP value greater than or equal to 180 mm Hg within the last 60 min between Emergency Department arrival and randomization), then the patient is ineligible for the study. If the patient's SBP falls below 180 mm Hg with treatment as outlined above, the patient remains a candidate with further alteration in treatment as required to achieve the target SBP goal of the allocated group. Once eligibility is determined, randomization takes place centrally via the ATACH-II Trial Website.

Study Treatment

The goal for the standard BP reduction group will be to reduce and maintain SBP < 180 mm Hg until 24 h from randomization. The goal for the intensive BP reduction group will be to reduce and maintain SBP < 140 mm Hg for 24 h from randomization. The primary BP reduction agent for this trial is, Cardene® I.V., a patented formulation of the anti-hypertensive agent nicardipine hydrochloride, originally approved by Food and Drug Administration (FDA) in 1992 for the short-term treatment of hypertension when oral therapy is not feasible or desirable. Randomized treatment assignments will be started for each treatment group within 3.5 h of symptom onset and continued for 24 h after randomization. Nicardipine will be either prepared in concentration of 0.1 mg/ml (25 mg in 10 ml added to 240 ml of normal saline) or used from pre-mixed bags. Nicardipine will be administered as a continuous infusion with a starting dose of 5 mg/h (50 ml/h), and then increased by 2.5 mg/h (25 ml/h) every 15 min as needed, up to a maximum of 15 mg/h (150 ml/h). If SBP is greater than the target, despite infusion of the maximum nicardipine dose for 30 min, a second agent can be used (Labetalol 5–20 mg IV bolus every 15 min) for another hour.

In the standard treatment group, if the BP falls below 140 mm Hg, IV nicardipine will be reduced in a stepwise pattern until SBP returns to target range (140–180 mm Hg) or nicardipine is discontinued. In the intensive treatment group, if the BP falls below 110 mm Hg, IV nicardipine will be discontinued and fluid boluses will be given to raise BP. Another scenario may arise when a subject has high ICP and lowering BP reduces cerebral perfusion pressure (CPP) below 70 mm Hg (the minimum level of acceptable CPP according to AHA guidelines [4]). In this scenario, nicardipine infusion will be stopped, and standard treatment for elevated intracranial pressure (ICP) will be initiated. We expect this scenario to be very rare.

Post-randomization In-hospital Clinical Assessment

Neurological status is assessed by the National Institutes of Health Stroke Scale (NIHSS) score at baseline and 24 (±3) h by a qualified study investigator. The trial mandates a non-contrast head CT scan at 24 (±8) h after initiation of treatment. Additional brain-imaging are performed at the discretion of the treating physician as a part of routine care. Routine laboratory surveillance including platelet counts, hemoglobin, and hematocrit measurements, and complete chemistry panel are performed for the first 3 days. Also as a standard of care, brief history and physical examination are performed daily while the subject is in the hospital.

Post-discharge Follow-up

Post-discharge follow-up includes telephone contact at 1 month and in-person clinical evaluation at 3 month (±14 days) (see Table 4). Post-discharge telephone follow-up by the site clinical coordinator is planned at 1 month post-randomization to collect serious adverse events (SAE) and death data and to ensure that subjects are being followed-up by their primary care physicians or other pertinent health care providers. The main emphasis of the telephone interview will be on SAEs and deaths that are likely related to BP control, such as serious cardiovascular and neurological events. If during the telephone interview or upon receiving laboratory results an SAE is suspected, then the site coordinator, in consultation with the site principal investigator (PI), must decide the best strategy for evaluation, including possible additional visits to the study site for follow-up on such events.

The 3-month follow-up is planned to conduct physical and neurological examinations by a qualified investigator who did not participate in the randomization, treatment, or in-hospital clinical management of the subject. The main components of the 3-month follow-up include measurement of BP, assessment of patient disability using mRS and quality of life using Euro-QOL. The PI at each site will be responsible for ensuring the integrity of blinded follow-up examinations. Additional assessments will be made as necessary after discharge for any new neurological or non-neurological events.

Sample Size and Analysis of the Primary Outcome

For the effect size of 10% (the absolute difference between the two treatment groups in the proportion of subjects with poor outcomes) assuming the control group's proportion of 60% (obtained from the literature), and Type I and Type II error probabilities, respectively, of 0.05 and 0.10, the total sample size is 1,042 with two interim analyses for overwhelming efficacy and concurrently, for futility (see Table 5). We assume a group sequential design of O'Brien and Fleming boundary. The intention to treat (ITT) principle is applied to the primary analysis. Therefore, to safeguard against an approximate 10% drop-in/out and missing data in the two treatment groups, we inflate the sample size by a factor of 1.23 which is derived from $1/(1 - R)^2$, where R is the proportion of dropouts. Therefore, the maximum sample size for the trial is 1,280.

The primary analysis for the trial is to test, under the ITT principle, the hypothesis of superiority of intensive SBP treatment over the standard SBP treatment in eligible ICH subjects, adjusting for age, baseline Glasgow Coma Scale (GCS), and intraventricular hemorrhage (IVH) (present or absent). The primary analysis model of this study is the generalized linear model with log link function which yields relative risk, rather than the logit link function which yields odds ratio (OR). It is tested at the two-sided alpha level of 0.05. In addition, relative risk and its 95% confi-dence interval are calculated.

Interim Data Monitoring

For the interim analyses of the primary outcome, the alpha spending function approach with O'Brien and Fleming type stopping boundaries is adopted. Currently, two interim analyses, after approximately 1/3 (or 425) and 2/3 (or 850) of subjects complete the 90-day follow-up, and one final analysis are tentatively planned. For assessment of futility, we adopt the stochastic curtailment method based on conditional power. The informal criterion for determination of futility is that at each interim look, if the conditional power (defined as the probability of rejecting the null hypothesis at the final analysis given the data accumulated so far and under the assumption that the alternative is true) falls below a certain value, for example, 10%, then the DSMB may evaluate all study information (such as overall recruitment rate and secondary outcome assessment data) to consider stopping the study for futility. Depending on the DSMB request, additional interim analyses may be conducted. At any interim analysis, if we cross the stopping boundary, then the DSMB may recommend (to the NINDS) stopping the study for overwhelming efficacy of one treatment over the other, although the better treatment may not necessarily be the intensive SBP treatment. Only if the stopping boundary is crossed, before making the final decision for recommendation to stop the study, it is expected that the DSMB would request thorough analyses of secondary outcomes and subgroup analyses to confirm the findings of the primary outcome results.

CT Scan Evaluations

Baseline and 24-h CT scans are forwarded to the Image Analysis Center at the University of Minnesota for volumetric analysis. In subjects who experience neurological deterioration before 24 h, the CT scans performed earlier are forwarded to the Image Analysis Center. The neuroimaging specialist, who is blinded to the treatment assignment, clinical findings, and other CT scans from different time points for a given subject, reviews the entire CT scan and record findings on the case report forms via the ATACH II Trial website. The following data are extracted from CT scans obtained at the time of admission: (1) site of hemorrhage; (2) ventricular extension by assessing CT scans for presence or absence of blood in the ventricles; (3) parenchymal hematoma volume calculated by computerized image analysis; and (4) presence of hydrocephalus.

Rationale for Study Design Parameters

Rationale for the SBP Treatment Targets

The target for the intensive treatment group is to reduce and maintain SBP between 110 and 140 mm Hg. We do not know what threshold of SBP reduction will provide the greatest benefit for reducing the rate of hematoma expansion. However, it is reasonable to consider that the most aggressive reduction in SBP may provide the greatest benefit, provided it can be well tolerated. This assumption is supported by the results of the INTERACT study and by two studies demonstrating very low rates of hematoma expansion when SBP was maintained <140 mm Hg [7, 8]. Another study [9] assessed 76 consecutive patients with hypertensive ICH and attempted to lower SBP below 140, 150, or 160 mm Hg. Lowest rates of hematoma expansion were observed in patients with the lowest SBP. These studies suggest that the <140 mm Hg tier maybe the most efficacious SBP range for reducing hematoma expansion.

In ATACH I, we evaluated the effect of SBP reduction (relative to initial SBP) on: (1) hematoma expansion, defined as an increase in the volume of intra-parenchymal hemorrhage of >33% measured on the 24-h CT compared to the baseline CT scan; (2) relative edema expansion, defined as an increase in the edema volume/hematoma volume ratio of >40% (where 40% cutoff is the median value of all subjects); and (3) death or disability, defined by mRS of 4–6 (moderate or severe disability or death) at 3 m following

treatment. Baseline SBP was calculated using the average of maximum and minimum SBP recorded before initiation of treatment. Average SBP, derived from maximum and minimum hourly recordings, was used to determine SBP reduction compared from baseline value. The overall reduction of SBP greater than 60 mm Hg at 6 h from treatment initiation appears to be associated with smaller likelihood of bad outcome—hematoma expansion of >33%, relative edema expansion of >40%, and 90 day mRS of 4–6 as noted with RR < 1.0 (see Table 6). In summary, owing to the small sample size and the pilot study nature of ATACH-I, no statistical significance would be expected. However, the direction (and to some extent, the magnitude) of the association among SBP reduction and volumetric and clinical outcomes are generally consistent with what is anticipated and hypothesized in the ATACH-II trial.

Standard treatment is defined by existing recommendations from professional organizations. The EUSI in 2006 [6] recommended that antihypertensive treatment should be initiated in patients with ICH and chronic hypertension if SBP is ≥180 mm Hg. The Writing Group of the AHA Stroke Council [3] in 1999 recommended starting antihypertensive treatment if SBP is ≥180 mm Hg or DBP is ≥105 mm Hg. The recent update from the Writing Group in 2007 recommends that if SBP is ≥180 mm Hg or mean arterial pressure (MAP) is ≥130 mm Hg and there is no evidence or suspicion of elevated ICP, a modest reduction of BP is recommended [4]. With evidence or suspicion of elevated ICP, monitoring ICP and reducing BP should be considered using intermittent or continuous IV medications to keep CPP between 60 and 80 mm Hg.

Rationale for the 3-h Time Window for Treatment Initiation

Randomized IV nicardipine will be initiated within 3 h of symptom onset. Nicardipine may be initiated before randomization so long as SBP remains above 160 mm Hg until the patient is randomized. (All patients must be randomized within 3 h). The time window for treatment was selected on the basis of the following two observations:

1. The first 3 h represent the time interval for maximum rates of hematoma expansion (the proposed mechanism for beneficial effect of SBP reduction) after symptom onset; in one study, the mean time from symptom onset to arrival was 1.3 h in patients who underwent hematoma expansion within the subsequent hour [10]. Significant improvement in the beneficial effect of factor seven for acute hemorrhagic stroke (FAST) trial if the analysis was only limited to patients recruited within 2.5 h after symptom onset [11]; and
2. Three of the four symptomatic hematoma expansions in ATACH I occurred in patients who were recruited after 3 h, and the deterioration occurred before treatment initiation. FAST trial was a randomized, double blinded, placebo controlled study of 821 patients treated within 4 h of symptom onset with placebo, 20, or 80 μg/ kg. Patients who received 80 μg/kg of rfVIIA had significantly lower rates of hematoma expansion but without any improvement in 90-day survival or functional outcome. Subgroup analysis [12] suggested that the reduction in hematoma expansion relative to placebo was almost doubled by limiting onset to treatment to 2.5 h. Therefore, we have limited inclusion to those in whom treatment can be started within 3 h of symptoms onset. Recruiting patients with symptom onset after 3 h will result in inclusion of patients who have already either had hematoma expansion or inclusion of patients at very low risk for hematoma expansion. In ATACH I, patients were eligible if they were seen within 6 h of symptom onset. However, 50 of the 58 patients recruited presented within 3 h of symptom onset in the study. This is consistent with other studies [5] that

demonstrate minimal benefit in recruitment if the time window for recruitment is extended to within 6 h of symptom onset.

We chose an infusion to be up to 24 h after randomization (24–27 h after symptom onset), to provide adequate SBP control during the time that hematoma expansion will mostly occur. Although the rate of hematoma expansion is the highest in the first 3 h after symptom onset [10, 13], expansion occurs in 12–37% of patients between 3 and 24 h after symptom onset. Early termination of antihypertensive treatment may lead to poor control of SBP, with subsequent increase in delayed bleeding. Hematoma expansion after the first 24 h was evaluated in two studies and found to be rare [13, 14].

Rationale for the Eligibility Criteria

The list of inclusion and exclusion criteria is provided in the Table 2. Justification of salient inclusion and exclusion criteria is provided below.

The total GCS score (aggregate of verbal, eye, and motor response scores) is 5 or greater at the time of enrollment.

The ICH represents a disease with high mortality. The mortality is the highest in the first 48 h with approximately 20% of the patients dying within the first 24 h of symptom onset [15]. This also represents the time period for the proposed intervention. A high rate of early mortality would substantially decrease our ability to evaluate the effect of the therapeutic intervention in our study population. We defined entry criteria to exclude patients with high chance of futility of any care strategy. The exclusion was done based on two identifying markers having consistency of acute mortality: initial GCS score and hematoma volume. Only the patients with initial GCS score greater than 5 will be included in the study. We had previously considered only including patients with GCS score 8 or greater based on previous studies [16]. Recent studies have demonstrated that excessively high mortality with minimal chance of any recovery occurs in patients presenting with initial GCS score of less than 5 rather than those presenting with GCS scores of 5–8 [17, 18]. In a study of 153 patients with ICH, 96% of the patients with initial GCS of less than 5 were dead before 1 month [18].

It is possible that an asymmetrically high proportion of patients with low NIHSS scores can predispose the overall patient population to have a high rate of favorable outcome regardless of treatment (ceiling effect) making it difficult to discern the beneficial effect of intensive SBP reduction. It is also possible that an asymmetrically high proportion of the patients with low GCS scores can predispose overall patient population to have a high rate of death and disability regardless of treatment (floor effect) making it difficult to discern the beneficial effect of intensive SBP reduction. We reviewed the major clinical studies involving patients with ICH and were unable to find any evidence to support the existence of either “ceiling” or “floor” effect in recruitment patterns (see Table 7). The design of this study also provides adequate sample size for varying proportions of death and disability in the standard SBP-treated patients.

CT scan demonstrates intra-parenchymal hematoma with manual hematoma volume measurement less than 60 cc.

The expected proportion of patients with an initial hematoma volume that approaches futility is derived from the study by Broderick et al. [15] and Nilsson et al. [19]. The 1-month mortality in patients with initial hematoma volume greater than 60 cc was 93% for patients with deep ICH and 71% for those with lobar ICH [15]. In addition, patients with large ICH can manifest elevated BP because of a protective response (referred to as the Cushing-Kocher response) whose aim is to preserve cerebral perfusion, particularly in patients with evidence of brain stem compression [20]. The pathophysiology of this form of

hypertension is different from other forms of hypertension. Therefore, we also felt that exclusion of patients with hematoma volume greater than 60 cc would restrict the impact of heterogeneous pathophysiologies underlying acute hypertension. The FAST trial subgroup analysis [12] suggested that if patients aged less than 70 years, with baseline hematoma <60 ml, and baseline intraventricular hemorrhage volume <5 ml and time to onset less than or equal to 2.5 h were selected, the OR for poor outcome at 90 days decreased to 0.28 (95% CI 0.08–1.06). Therefore, we have limited inclusion to those in whom treatment can be started from symptom onset within 3 h and excluded patients with large hematoma >60 ml.

ICH is supratentorial and location is lobar, basal ganglionic, or thalamic based on the initial CT scan appearance.

The AHA Stroke Council [4] and EUSI guidelines [21] do not recommend routine evacuation of supratentorial ICH by standard craniotomy within 96 h of ictus. Cerebellar hematomas are unique from a surgical perspective because timely decompression can reduce morbidity and mortality related to compression of the brain stem. The AHA Stroke Council [4] and EUSI guidelines [21] recommend urgent surgery for patients with cerebellar hemorrhages with a relatively good neurological status or hematoma >3 cm who are clinically deteriorating, or who have brain stem compression and/or hydrocephalus from ventricular obstruction. Cerebellar hemorrhage is often complicated by obstructive hydrocephalus [22] with rapidly rising ICP which can be treated successfully with external ventricular drainage [23]. Therefore, it is anticipated the high rates of surgical intervention in this group of patients will lead to excessive rates of drop-outs. Pontine ICH are rare and form about 1–5% of all ICH [15, 18]. All pontine ICH greater than 5 cc were dead by 1 month in one study suggesting a very poor prognosis [15]. Another study reported a 1-month mortality of 100% for all pontine ICH [18].

Patients with intraventricular hemorrhage associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles.

Patients with IVH have higher 30-day mortality rate compared with those without intraventricular hemorrhage [24, 25]. Quantitative measures of IVH independently predict outcome in patients with supratentorial ICH [24]. We have chosen to include patients with IVH in the study because hematoma expansion can occur in IVH in patients with elevated MAP and expansion can be reduced by rfVIIA treatment [26]. Therefore, IVH represents a valid target for modification with treatments directed towards reduction of hematoma expansion. We have excluded patients with IVH with blood completely filling one lateral ventricle or more than half of both ventricles because of low prevalence and excessively high mortality documented with these characteristics [24, 27] (see Table 8). We have chosen to avoid using volumetric analysis to define eligibility because of technical difficulties in measuring intraventricular hemorrhage volume at bedside [24]. We have provided stratification to avoid imbalance of these variables. The classification was evaluated by four investigators in a previous publication [27] for the presence and the extent of ventricular blood. A review of CT scans suggested that the intraventricular extension could be classified in all the 75 patients included in the analysis. We intend to provide examples of various grades of intraventricular hemorrhage in our operations manual to facilitate adequate recognition at study sites.

Rationale for the Frequency of Follow-up

The frequency of follow-up after discharge is based on the principles of ensuring appropriate patient care and provides adequate surveillance to determine study endpoints. The frequency in part is derived from perindopril protection against recurrent stroke study [28] (PROGRESS), and the Prevention Regimen for Effectively Avoiding Second Strokes Trial

(PRoFESS) [29] two of the largest trials of oral antihypertensive treatment in post-stroke patients. Both trials used a 1–2-week visit after initiating antihypertensive medication and 1 and 3 month visits. Since, almost all the subjects recruited in the ATACH-II trial will be in the hospital for the first week of initiation of therapy, the study visits are scheduled for 1 month (via telephone) and 3 months (in person). This post-discharge evaluation schedule is consistent with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [30] that recommends follow-up and adjustment of medications at approximately monthly intervals until the target BP goal is reached once antihypertensive drug therapy is initiated.

Rationale for the Blinded Outcomes Assessment

Two strategies are used to reduce selection bias: allocation concealment and randomization [31]. Allocation concealment seeks to prevent selection bias, protects the allocation sequence until assignment, and can always be successfully implemented, regardless of intervention [31]. Determination of eligibility and procurement of patient agreement to participate will occur before randomization and treatment assignment. In surgical or endovascular treatment trials or trials of varying intensity of treatment, the nature of the treatment cannot be hidden from either the investigator or the patient, and compliance with the treatment allocated can become an issue [32]. In the present proposal, the infusion of nicardipine is titrated to target SBP, and therefore, the treating physician cannot be blinded to treatment. Blinding of treating physicians also raises safety issues for the subject precluding early detection of relationship between hemodynamic variables and adverse neurological events and delaying corrective measures. Lack of double blinding may exaggerate estimates of treatment benefits and therefore strategies must be developed during planning to minimize the bias introduced by lack of blinding [33]. We will require participating centers to designate an individual who will remain blinded to treatment assignment and will not participate in randomizing or treating patients in the trial. This individual will conduct clinical assessments of treatment efficacy in a blinded manner at 90 days after initial treatment.

Rationale for the Primary Outcome

Primary outcome is death or disability, defined by mRS of 4–6 at 3 m following treatment. We chose the mRS because of its high inter-observer reliability, superiority to other indices (e.g., Barthel index), and consistency with previous trials in patients with ICH [34]. Further reliability will be increased by training raters in using the structured interview and obtaining a mRS grade. The methodology of training in the use of structured interview has been published previously [35]. Inter-rater agreement for mRS studied among 15 raters from three stroke centers was high, i.e., agreement for differences of 1 grade on the mRS was 0.56 and for 2 grades was 0.91 [34]. Reliability will be further increased by training raters in using the structured interview and obtaining a mRS grade. Training consists of investigator explanation, a video showing an example interview that the raters scored, and two example transcripts that the raters scored. In a previous study, patients at least 6 months after stroke were first assessed using conventional mRS definitions. After completion of initial mRS assessments, raters were trained to use a structured interview, and patients were re-assessed. For the mRS, overall agreement among raters was 43% ($K = 0.25$, $K_w = 0.71$), and for the structured interview overall agreement was 81% ($K = 0.74$, $K_w = 0.91$). A dichotomous outcome was chosen to reduce the rate of misclassification and increase the sensitivity of detecting meaningful difference [36].

Rationale for the Choice of Secondary Outcomes

EuroQOL—EuroQOL, designed in Europe in 1987 [38], is a simple, standardized non-disease-specific instrument for describing and valuating health-related quality of life. One of its components is a printed "thermometer"-type visual analog scale on which respondents indicate how good or bad their health is today. Its other component, EQ-5D, consists of five questions in five different domains and allows for responses from 1 (the best outcome) to 3 (the worst). The original version contained six dimensions: mobility, self-care, chief activity, social ability, pain, and state of mind, each with three levels. The modified EQ-5D version has reduced the dimensions to five, combining chief activity and social ability into "everyday activities." We chose EuroQOL because it has higher reliability than Short Form-36 (SF-36) when used by proxy for patients, and we expect a large proportion of proxy response. In a study of over 2,000 stroke patients who were mailed versions of the EuroQOL and SF-36 more than 3 months after stroke, about half of them were unable to complete either type of questionnaire by themselves. Proxy measures of the SF-36 were inaccurate [39]. However, studies have found moderate agreement between responses from patients and those from their proxies for the domains of the EuroQol [40]. The reliability of the EuroQOL and SF-36 questionnaires after stroke was compared in a total of 2,253 patients with stroke entered by the UK hospitals in the International Stroke Trial. Patients were randomized to follow up with either the EuroQOL or the SF-36 instruments. For the five categorical domains of the EuroQOL, reproducibility was generally good (kappa ranged from 0.63 to 0.80). Reproducibility of domains of the SF-36 was qualitatively similar for all the domains except mental health (intraclass correlation coefficient $=0.28$) [41]. Another study reported validity of the EuroQOL in a series of 152 patients from a prospective registry of patients with first (or recurrent) stroke. In general, most domains of QOL information obtained from a proxy were considered sufficiently valid and unbiased to be useable in most types of trials and surveys [40]. Agreement between patient and proxy was the best when assessed ≥1 m after baseline [42].

Hematoma Expansion as Determined by Serial CT Scans—Hematoma expansion will be defined as an increase in the volume of intra-parenchymal hemorrhage of >33% as measured by image analysis on the 24-h CT compared with the baseline CT scan. The cutoff for hematoma enlargement is based on the cutoff defined by Brott et al. [10] which is the change in size associated with significant neurological deterioration. Application of this cutoff has been used in the ATACH-I trial consistently. The computerized volumetric analysis for measuring hematoma volume and detecting hematoma expansion has been used in previous studies [10, 15, 16]. The conservative percentage of 33% was chosen prospectively for two reasons in the study by Brott et al. [10]. First, a 33% change in the volume of a sphere corresponds to a 10% increase in diameter; a clear difference to the naked eye of a physician viewing serial CT scans of a subject with ICH. Second, measurement of serial CTs in subjects with ICH indicates some subjects had up to one-third less volume of hemorrhage on the 1-h CT than on the baseline CT [10]. This "decrease" is due to different positioning and angles of the CT slice images in the baseline and 1-h CTs rather than to an actual decrease in hemorrhage volume. This observation was particularly true for small hemorrhages. Therefore, the present CT definition of growth is most likely to represent true hemorrhage growth and not variability in CT imaging. The volume of ICH calculated by image analysis also correlated quite well with the volume calculated manually using the formula for an ellipsoid in a previous study ($r=0.94$) [15].

Rationale for the Minimum 10% Effect Size

Previous trials have used an absolute difference of 10% or greater as an effect size in the absence of data supporting that lower magnitudes of difference will modify clinical practices. An absolute difference of 10% translates into a relative risk reduction of 17%

while an absolute difference of 5% translates into a relative risk reduction of 8% for an expected endpoint rate of 60% in the standard SBP reduction group. Previous trials with either an absolute difference of 5% or relative difference of 8% between a new treatment and standard treatment have not changed practice patterns for ICH. In the phase II trial evaluating use of NXY-059 [43] in patients with ICH, the rate of mRS: 0–1 was 17 and 12.5% among patients treated with NXY-059 and placebo, respectively, and hence, an absolute difference of ~5%. The difference was not considered encouraging to further develop NXY-059 as a therapeutic modality in patients with ICH. Similarly, in the International Surgical Trial in Intracerebral Hemorrhage (STICH) [44], the rate of prognosis-based mRS favorable outcome was 33 and 28% in surgery and conservative treatment groups, respectively: again, an absolute difference of 5%. Subsequent to the STICH results, the ASA Stroke Council [4] and EUSI guidelines [21] do not recommend routine evacuation of supratentorial ICH by standard craniotomy within 96 h of ictus (consistent with inclusion criteria of STICH).

Clinical trials evaluating therapies with higher associated risk such as rfVIIa have used a threshold of 15% or greater reduction in death or disability to define clinical benefit [45]. The NINDS Working Group on Clinical trials in TBI [46] concluded that in many clinical trials of head injury, demonstration of effectiveness was set at 10% increase in the percentage of patients with favorable outcome defined by the Glasgow Outcome Scale (GOS). This level has not been achieved, although trends toward favorable outcome have been observed in some trials. However, effect sizes of only 3–5% would translate into only 1,000–5,000 fewer deaths from TBI each year. Similarly, the annualized mortality of ICH in 2000–2001 was 15,625 deaths [47], an absolute reduction of 5% would translate into a minor reduction of approximately 781 deaths. Setting the bar lower may achieve more “positive” outcomes of clinical trials at the expense of very large sample sizes; however, the approval of mediocre therapies may hinder the development of truly effective treatments. Research must be directed at exceeding standard therapy.

For our proposed trial, we surveyed the clinical site investigators to gather input on what percent of absolute reduction in death or disability would make a difference in their clinical practice (≥5, ≥7.5, or ≥10%). The question was posed to the 49 site investigators identified at the time. The 23 responders replied as follows: ≥5% (39%), ≥7.5% (22%), and ≥10% (39%). The selected poll also suggests that to ensure maximum effect on practice paradigms, an absolute difference of ≥10% will be required between the intensive SBP and standard SBP reduction. Fewer than half of the respondents would change practices if the absolute difference was <5%.

Finally, the 10% effect size should be considered in light of the anticipated outcome rate in the standard therapy group. The proportion of patients with mRS of 4–6 among patients with ICH has been reviewed in placebo groups of several clinical trials (see Table 9). Based on these data, we have assumed the outcome to be 60% in the standard therapy group. In this range, a 10% absolute difference has more clinical relevance than if the standard therapy proportion of poor outcome were more extreme (i.e., closer to 100% in which case a smaller effect size may be clinically important).

Another issue is whether an absolute difference of 10% or greater in the primary event can be reasonably expected in the currently proposed comparison of intensive and standard SBP reduction in patients with ICH. Given the inability of rfVIIa treatment to improve clinical outcome despite reducing the rate and extent of hematoma expansion in the FAST trial [45], careful consideration is necessary for (1) determining the extent of hematoma expansion that affects outcome; and (2) understanding the variables that can obscure the benefit of reducing hematoma expansion. Davis et al. [48] determined that 1 ml expansion of hematoma by 24 h

increased the rate of poor clinical outcome at 90 days by 7%. In the phase II study of rfVIIa [49] the placebo group underwent a 5-ml greater expansion compared with rfVIIa-treated groups with an absolute increase in rate of poor outcomes of 16% (1-ml expansion was associated with 3.2% higher rate of poor outcomes). Based on the rFVIIIA study then, to observe an absolute reduction of ≥10% in the rate of poor outcomes in our trial, a mean difference of greater than 3 ml may be required between the intensive and standard BP treatment groups. In the INTERACT study [50], the difference in the extent of hematoma expansion between the intensive and standard BP treatment groups was 1.7 ml, which may not be adequate to significantly influence clinical outcomes. However, if the analysis of the INTERACT data was confined to only patients recruited within 4 h of symptom onset, the difference in the extent of hematoma expansion would increase to 3.4 ml between the two groups, a value that can lead to the magnitude of clinical benefit sought in our trial. A subgroup analysis of the FAST [12] data suggested that if patients selected were age <70 years, with baseline hematoma <60 ml, and baseline IVH volume <5 ml and time to onset ≤ 2.5 h, the OR for poor outcome at 90 days decreased to 0.28 (95% CI 0.08–1.06) with rfVIIa. We have selected our patient population to identify the group most likely to benefit from the proposed treatment. A review of the data derived from ATACH-I suggests that the magnitude of reduction in hematoma expansion and subsequent reduction in death and disability sought in ATACH-II are possible. The effect is augmented in patients treated within 3 h of symptom onset. Since we had only 11 patients with SBP reduction ≥60 mm Hg within 3 h, caution must be used before inferring efficacy from underpowered pilot trials. Most pilot studies are small (fewer than 100 patients) and any differences in outcome must be dramatic to provide a trend [51, 52].

Rationale for the Dichotomization of mRS

A binary outcome based on mRS avoids inflation of minimal changes that are of unclear clinical significance [53]. Using binary endpoint provides simplicity and straightforward clinical interpretation. Net number needed to treat (NNT) values can be easily derived from dichotomized end points allowing conversion of trial results into the number of patients needed to achieve one additional net good outcome [53] (where “good” means exceeding the dichotomization threshold). Some reports indicate that a 1-point shift on the mRS scale is often deemed clinically significant because of the large category sizes. By using a binary outcome analysis, trialists may discard outcome information, which may lead to underestimation of treatment benefit because of reduction in statistical power. Because of the drawbacks of dichotomization, shift analysis using the proportionality of Odds Model (POM) has recently gained attention [54–56]. Shift analysis is particularly advantageous when treatments confer a relatively uniform, mild benefit to patients over a wide range of stroke severities [57]. However, unlike dichotomized outcome analysis, POM requires that the assumption of proportionality of the OR is met [58]. Otherwise, the gain in power by POM approach may not materialize and data interpretation may not be straightforward. The major difficulty in planning a study is whether assumption of proportionality of the ORs will be met upon completion of the study. We calculated the ORs by different cutoffs for some studies where scores on the full-scale mRS were available, and the results are shown in Table 10. The variations in OR based on various cutoffs used within the same study suggest a high likelihood of the proportionality assumption not being met. A statistical test for the proportionality assumption (score test) exists, but like all statistical tests, its significance is highly dependent upon sample size. Therefore, clinical judgment is needed to determine whether the proportionality assumptions hold, as is the case for the ORs in Table 10. To be conservative, it would be prudent to size the study for a binary outcome analysis, in which case the primary analysis should also be based on the binary outcome, for ease of interpretation. As a supportive analysis, POM analysis will be conducted if the proportionality assumption holds. Other options such as nonparametric tests are generally

less powerful and the ordinality of the mRS is unlikely to be linear. Furthermore, one can argue that a difference between a score of 0 and 1 is not the same as the difference between a score of 2 and 3 or between 5 and 6. Finally, as a prospectively conducted study, the summary statistic of interest in most clinical trials is the relative risk/benefit of the investigational treatment rather than the OR, and the POM yields a summary statistic that may be less relevant for clinical interpretation. Hence, we have opted to dichotomize the mRS scores mainly for simplicity (i.e., no need for model assumptions) and interpretability.

Given our decision to focus on benefit versus risk, the 0–3 vs. 4–6 represents an incremental benefit of substantive value since it compares subjects who can live independently at home to subjects who are dead or dependent. A shift in this proportion would be of significant value given the high morbidity and mortality of ICH. Increasing acceptance of this endpoint is now being found in stroke trial publications [59].

Furthermore, it is unlikely to be countered that mRS of 4–6 is a poor outcome regardless of the severity of stroke. Additional validation was provided by a prospective analysis involving 459 participants in the Kansas City Stroke Study [60]. Mean 3-month scores of physical functioning and SF-36 social functioning were significantly higher among patients with mRS of 3 compared with those with a mRS of 4.

Stratified Randomization Versus Post-stratification Adjustment

Stratified randomization prevents imbalance between treatment groups for known factors that influence prognosis or treatment responsiveness. Stratification may prevent type I error and improve power for small trials (<400 patients), but only when the stratification factors have a large effect on prognosis [61]. However, stratification is probably unnecessary for large (>200 subjects per group) superiority trials [62, 63]. The chance that the two treatment groups will differ by more than 10% for the proportion of patients with the prognostic factor is 33% for a trial of 30 patients, 24% for a trial of 50 patients, 10% for a trial of 100 patients, 3% for a trial of 200 patients, and 0.3% for a trial of 400 patients [63]. The number of strata required also depends upon the number and levels of prognostic factors. For example, stratification by three GCS score levels (5–8, 9–12, and 13–15), two hematoma volume levels (<30 and ≥30 cc), and IVH (present or absent) will have a total of 12 strata ($3 \times 2 \times 2$). Investigators recommend a minimum of 50–100 patients per stratum which can be a matter of concern with a large number of strata and a small number of patients in some stratifying variables such as IVH. Furthermore, stratification opens the door for randomizing subjects in an incorrect stratum, particularly if the stratification variable is not completely objective and if there is a narrow time window. In the ATACH II trial, we would have to create separate sets of envelopes for each stratum, which again leads to a possibility of error in selecting the envelope from the correct stratum. We chose to use an alternative to stratified randomization by adjusting the analysis for treatment effectiveness for covariates using multivariate analysis (post-stratification) [64]. At the conclusion of a trial, the outcome rates between treatment groups will be compared using a multivariate model. Comparisons between stratified randomization with adjustment and adjustment alone (post-stratification) suggest that the two procedures are comparably precise for estimating treatment contrasts when the trial size exceeds 100 patients [63, 65]. Investigators have demonstrated that choice of covariates may influence the research conclusions [65]; therefore, the covariates have been pre-specified to avoid manipulation and error [64].

Discussion

Generalizability of Results

One of the most significant expected contributions of the proposed research is the identification of specific gaps in scientific knowledge that lead to high levels of practice variation and possibly suboptimal outcomes. Such knowledge could improve physicians' adoption of optimal therapeutic practices in routine care of patients with ICH. Once identified, critical knowledge should result in quality improvement strategies within clinical practice [66, 67]. The most important step is to ask the right questions and address them with appropriate methodology. We carefully reviewed several multidisciplinary professional statements [3, 4, 6, 68] supplemented by personal knowledge of investigators through participating in and chairing several national forums to identify relevant knowledge gaps to ensure interest and high likelihood of instituting change. We developed the grant proposal in light of recommended standards from the interdisciplinary writing group of National Heart, Lung, and Blood Institute (NHLBI) [69] with emphasis on a clear and explicit definition of appropriate patient sample, clinical coherence of variables, designation of appropriate reference time before which covariates are derived and after which outcomes are measured, use of an appropriate outcome and a standardized period of outcome assessment, application of an analytical approach that takes into account the multilevel organization of data, and disclosure of methods used to compare outcomes and risk-adjustment methodology in derivation and validation samples. The personal involvement and participation [70, 71] of practicing physicians minimizes distinctions between research and clinical practice and creates a systematic and efficient mechanism to allow medical professionals to carefully document outcomes that result in individual learning and modification of practices, and that foster a scientific approach to clinical practice. By requiring a link between research and practice, effectiveness trials are one method of effectively translating evidence into practice.

A possible critical issue is that if only one of ten patients with ICH is eligible, generalization of results may be difficult. This issue is similar to that observed in other clinical trials of acute stroke (see Table 11). However, considerable variation among hospitals is seen in the rates of utilization of acute treatments for acute ischemic stroke treatment. The national average rate is estimated at approximately 1% of patients presenting to the hospital [72], but high-performing centers administer acute stroke treatment to 18% [73]. The rate of acute ischemic stroke treatment is improving at low-performing centers with increasing awareness and protocol implementations [74]. A high variation was observed in the ATACH-I study in the ratio of screened to recruited patients, with the highest-recruiting site recruiting up to 20% of patients evaluated at the hospital [75]. Therefore, we expect that if intense lowering of BP is demonstrated to be beneficial, low-performing centers will implement steps (such as those already undertaken for patients with ischemic stroke) to provide expedient treatment to a higher proportion of patients with ICH. Study of existing "leading centers" or "best practices" can generate novel potential approaches to improving provider adherence that could then be rigorously tested. We will use complementary mechanisms of training, presentations, publications, and media to disseminate knowledge generated from research that has value for incorporation into clinical practice.

Expected Impact of the Proposed Trial

The ICH remains a major public health problem, as demonstrated in a review of data from the Nationwide Inpatient Sample, which found 148,604 admissions for ICH during 1990–1991 and 175,496 during 2000–2001 in the U.S. [47]. In-hospital mortality rates did not change among the patients with ICH during the decade in the study (29.9 vs. 28.1%). Approximately 90,000 annual admissions in the U.S. (18% increase) and unchanged 7 day mortality over the aforementioned 10 years, disproportionate to other stroke subtypes,

suggest that both preventive and treatment strategies for ICH are lagging. A study of 45,330 patients with ICH in 2004 derived from the National Hospital Ambulatory Medical Care Survey found that 33,992 (75.0%) had an initial SBP ≥ 140 mm Hg [2]. The data were based on a national probability sample of visits in noninstitutional general and short-stay hospitals. In the last quarter of 2007, the INTERACT phase III was funded by the Australian National Health and Medical Research Council. The phase III study would combine the data derived from the "vanguard phase" and the "main phase" to perform the final analysis with adequate power. Table 12 highlights the differences between the two trials. The results derived from INTERACT will not address whether the benefit or lack of benefit is either augmented or unchanged in patients treated within 3 h, those with SBP ≥ 180 mm Hg, or those treated with a single agent and achieving target SBP at a high rate. Therefore, the proposed study will have direct implications for 75% of the patients with ICH in the U.S. BP treatment is a strategy that can be made widely available without specialized equipment or personnel, and can make a major impact on outcomes in ICH patients. Substantial reduction in morbidity and mortality may be possible if the estimates of treatment effect from our current pilot trial are accurate.

Acknowledgments

The study is supported by National Institutes of Health grant 1U01NS062091-01A2. The study medication is provided by EKR Therapeutics, Inc., Bedminster, NJ.

References

1. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001; 344:1450–60. [PubMed: 11346811]
2. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med. 2007; 25:32–8. [PubMed: 17157679]
3. Broderick JP, Adams HP Jr, Barsan W, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke. 1999; 30:905–15. [PubMed: 10187901]
4. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/ American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Stroke. 2007; 38:2001–23. [PubMed: 17478736]
5. Flaherty ML, Woo D, Haverbusch M, et al. Potential applicability of recombinant factor VIIa for intracerebral hemorrhage. Stroke. 2005; 36:2660–4. [PubMed: 16269646]
6. Steiner T, Kaste M, Forsting M, et al. Recommendations for the management of intracranial haemorrhage—part I: spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. Cerebrovasc Dis. 2006; 22:294–316. [PubMed: 16926557]
7. Sorimachi T, Fujii Y, Morita K, Tanaka R. Rapid administration of antifibrinolytics and strict blood pressure control for intracerebral hemorrhage. Neurosurgery. 2005; 57:837–44. [PubMed: 16284553]
8. Nishiyama T, Yokoyama T, Matsukawa T, Hanaoka K. Continuous nicardipine infusion to control blood pressure after evacuation of acute cerebral hemorrhage. Can J Anaesth. 2000; 47:1196–201. [PubMed: 11132741]
9. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke. 2004; 35:1364–7. [PubMed: 15118169]
10. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997; 28:1–5. [PubMed: 8996478]

11. Mayer, SA. Factor seven for acute hemorrhagic stroke (FAST) study. 16th European Stroke Conference: Large Clinical Trials 1; 29 May–1 June 2007; p. Abstract 1
12. Mayer SA, Davis SM, Begtrup K, et al. Subgroup analysis in the Fast trial: A subset of intracerebral hemorrhage patients that benefit from recombinant activated factor VII. Stroke. 2008; 39:528.
13. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke. 1996; 27:1783–7. [PubMed: 8841330]
14. Mayer SA, Sacco RL, Shi T, Mohr JP. Neurologic deterioration in noncomatose patients with supratentorial intracerebral hemorrhage. Neurology. 1994; 44:1379–84. [PubMed: 8058133]
15. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality [see comment]. Stroke. 1993; 24:987–93. [PubMed: 8322400]
16. Qureshi AI, Safdar K, Weil J, et al. Predictors of early deterioration and mortality in black Americans with spontaneous intracerebral hemorrhage. Stroke. 1995; 26:1764–7. [PubMed: 7570722]
17. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage [see comment]. Stroke. 2001; 32:891–7. [PubMed: 11283388]
18. Godoy DA, Pinero G, Di Napoli M. Predicting mortality in spontaneous intracerebral hemorrhage: can modification to original score improve the prediction? Stroke. 2006; 37:1038–44. [PubMed: 16514104]
19. Nilsson OG, Lindgren A, Brandt L, Saveland H. Prediction of death in patients with primary intracerebral hemorrhage: a prospective study of a defined population. J Neurosurg. 2002; 97:531–6. [PubMed: 12296635]
20. Qureshi AI, Geocadin RG, Suarez JI, Ulatowski JA. Long-term outcome after medical reversal of transtentorial herniation in patients with supratentorial mass lesions. Crit Care Med. 2000; 28:1556–64. [PubMed: 10834711]
21. Katse M, et al. European Stroke Initiative Writing C, Writing Committee for the EEC. Recommendations for the management of intracranial haemorrhage—part I: spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. Cerebrovasc Dis. 2006; 22:294–316. [PubMed: 16926557]
22. St Louis EK, Wijdicks EF, Li H. Predicting neurologic deterioration in patients with cerebellar hematomas. Neurology. 1998; 51:1364–9. [PubMed: 9818861]
23. Sumer MM, Acikgoz B, Akpinar G. External ventricular drainage for acute obstructive hydrocephalus developing following spontaneous intracerebral haemorrhages. Neurol Sci. 2002; 23:29–33. [PubMed: 12111618]
24. Tuhrim S, Horowitz DR, Sacher M, Godbold JH. Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage [see comment]. Crit Care Med. 1999; 27:617–21. [PubMed: 10199544]
25. Bhattathiri PS, Gregson B, Prasad KSM, Mendelow AD, Investigators S. Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. Acta Neurochir Suppl. 2006; 96:65–8. [PubMed: 16671427]
26. Steiner T, Diringer MN, Schneider D, et al. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. Neurosurgery. 2006; 59:767–73. discussion 773–764. [PubMed: 17038942]
27. Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC. Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. Neurology. 1994; 44:133–9. [PubMed: 8290048]
28. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001; 358:1033–41. [PubMed: 11589932]

29. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med. 2008; 359:1225–37. [PubMed: 18753639]
30. The Seventh Report of the Joint National Committee on Prevention. [Accessed April 2011] Detection, Evaluation, and Treatment of High Blood Pressure. National High Blood Pressure Education Program. 2004. http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf
31. Qureshi AI, Hutson AD, Harbaugh RE, et al. Methods and design considerations for randomized clinical trials evaluating surgical or endovascular treatments for cerebrovascular diseases. Neurosurgery. 2004; 54:248–64. discussion 264–7. [PubMed: 14744272]
32. Day SJ, Altman DG. Statistics notes: blinding in clinical trials and other studies. BMJ. 2000; 321:504. [PubMed: 10948038]
33. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what [see comment]. Lancet. 2002; 359:696–700. [PubMed: 11879884]
34. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988; 19:604–7. [PubMed: 3363593]
35. Wilson JT, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. Stroke. 2002; 33:2243–6. [PubMed: 12215594]
36. Choi SC, Clifton GL, Marmarou A, Miller ER. Misclassification and treatment effect on primary outcome measures in clinical trials of severe neurotrauma. J Neurotrauma. 2002; 19:17–22. [PubMed: 11852975]
37. Mayer SA. Recombinant activated factor VII for acute intracerebral hemorrhage. Stroke. 2007; 38:763–7. [PubMed: 17261734]
38. Group TE. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy. 1990; 16:99–208.
39. Segal ME, Schall RR. Determining functional/health status and its relation to disability in stroke survivors. Stroke. 1994; 25:2391–7. [PubMed: 7974578]
40. Dorman PJ, Waddell F, Slattery J, Dennis M, Sandercock P. Is the EuroQol a valid measure of health-related quality of life after stroke? Stroke. 1997; 28:1876–82. [PubMed: 9341688]
41. Dorman P, Slattery J, Farrell B, Dennis M, Sandercock P. Qualitative comparison of the reliability of health status assessments with the EuroQol and SF-36 questionnaires after stroke. United Kingdom Collaborators in the International Stroke Trial. Stroke. 1998; 29:63–8. [PubMed: 9445330]
42. Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. Stroke. 2004; 35:607–12. [PubMed: 14726549]
43. Lyden PD, Shuaib A, Lees KR, et al. Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT Trial. Stroke. 2007; 38:2262–9. [PubMed: 17569876]
44. 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; 365:387–97. [PubMed: 15680453]
45. 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; 358:2127–37. [PubMed: 18480205]
46. Narayan RK, Michel ME, Ansell B, et al. Clinical trials in head injury. J Neurotrauma. 2002; 19:503–57. [PubMed: 12042091]
47. Qureshi AI, Suri MFK, Nasar A, et al. Changes in cost and outcome among US patients with stroke hospitalized in 1990 to 1991 and those hospitalized in 2000 to 2001. Stroke. 2007; 38:2180–4. [PubMed: 17525400]
48. Davis SM, Broderick J, Hennerici M, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006; 66:1175–81. [PubMed: 16636233]
49. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2005; 352:777–85. [PubMed: 15728810]

50. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008; 7:391–9. [PubMed: 18396107]
51. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry. 2006; 63:484–9. [PubMed: 16651505]
52. Arnold DM, Burns KE, Adhikari NK, Kho ME, Meade MO, Cook DJ. The design and interpretation of pilot trials in clinical research in critical care. Crit Care Med. 2009; 37:S69–74. [PubMed: 19104228]
53. Adams HP Jr. Trials of trials in acute ischemic stroke. The Humana lecture. Stroke. 1993; 24:1410–5. [PubMed: 8362441]
54. Bolland K, Sooriyarachchi MR, Whitehead J. Sample size review in a head injury trial with ordered categorical responses. Stat Med. 1998; 17:2835–47. [PubMed: 9921605]
55. Kasner SE. Clinical interpretation and use of stroke scales. Lancet Neurol. 2006; 5:603–12. [PubMed: 16781990]
56. Saver JL. Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. Stroke. 2007; 38:3055–62. [PubMed: 17916765]
57. Saver JL, Gornbein J. Treatment effects for which shift or binary analyses are advantageous in acute stroke trials. Neurology. 2009; 72:1310–5. [PubMed: 19092107]
58. Brant R. Assessing proportionality in the proportional odds model for ordinal logistic regression. Biometrics. 1990; 46:1171–8. [PubMed: 2085632]
59. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007; 6:215–22. [PubMed: 17303527]
60. Lai SM, Duncan PW. Stroke recovery profile and the Modified Rankin assessment. Neuroepidemiology. 2001; 20:26–30. [PubMed: 11174042]
61. Feinstein AR, Landis JR. The role of prognostic stratification in preventing the bias permitted by random allocation of treatment. J Chronic Dis. 1976; 29:277–84. [PubMed: 773948]
62. Lipchik GL, Nicholson RA, Penzien DB. Allocation of patients to conditions in headache clinical trials: randomization, stratification, and treatment matching [see comment]. Headache. 2005; 45:419–28. [PubMed: 15953258]
63. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials [see comment]. J Clin Epidemiol. 1999; 52:19–26. [PubMed: 9973070]
64. Beach ML, Meier P. Choosing covariates in the analysis of clinical trials. Control Clin Trials. 1989; 10:161S–75S. [PubMed: 2605965]
65. McHugh R, Matts J. Post-stratification in the randomized clinical trial. Biometrics. 1983; 39:217–25. [PubMed: 6871350]
66. Rectenwald JE, Upchurch GR Jr. Impact of outcomes research on the management of vascular surgery patients. J Vasc Surg. 2007; 45(Suppl A):A131–40. [PubMed: 17544034]
67. Lipscomb J, Donaldson MS, Hiatt RA. Cancer outcomes research and the arenas of application. J Natl Cancer Inst. 2004:1–7. Monographs.
68. Priorities for clinical research in intracerebral hemorrhage: report from a National Institute of Neurological Disorders and Stroke workshop. Stroke. 2005; 36:e23–41. [PubMed: 15692109]
69. Krumholz HM, Brindis RG, Brush JE, et al. Standards for statistical models used for public reporting of health outcomes: an American Heart Association Scientific Statement from the Quality of Care and Outcomes Research Interdisciplinary Writing Group: cosponsored by the Council on Epidemiology and Prevention and the Stroke Council. Endorsed by the American College of Cardiology Foundation. Circulation. 2006; 113:456–62. [PubMed: 16365198]
70. Taylor SM, Robison JG, Langan EM 3rd, Crane MM. The pitfalls of establishing a statewide vascular registry: the South Carolina experience. Am Surg. 1999; 65:513–8. discussion 518–519. [PubMed: 10366204]
71. Isenberg SF. Community-based outcomes research: the project solo experience. Laryngoscope. 2000; 110:21–3. [PubMed: 10718410]

72. Qureshi AI, Suri MFK, Nasar A, et al. Thrombolysis for ischemic stroke in the United States: data from National Hospital Discharge Survey 1999–2001. Neurosurgery. 2005; 57:647–54. discussion 647–654. [PubMed: 16239876]

73. Qureshi AI, Kirmani JF, Sayed MA, et al. Time to hospital arrival, use of thrombolytics, and in-hospital outcomes in ischemic stroke. Neurology. 2005; 64:2115–20. [PubMed: 15985583]

74. Katzan IL, Hammer MD, Furlan AJ, Hixson ED, Nadzam DM. Cleveland Clinic Health System Stroke Quality Improvement T. Quality improvement and tissue-type plasminogen activator for acute ischemic stroke: a Cleveland update. Stroke. 2003; 34:799–800. [PubMed: 12624312]

75. Comparison of patients with intracerebral hemorrhage treated within and outside clinical trials: A report of the antihypertensive treatment of acute cerebral hemorrhage investigators. American Academy of Neurology 59th Annual Meeting; 2007; Boston. 2007.

76. Qureshi AI. Antihypertensive treatment of acute cerebral hemorrhage (ATACH): rationale and design. Neurocrit Care. 2007; 6:56–66. [PubMed: 17356194]

77. 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; 105:217–20. [PubMed: 19066112]

78. Haley EC Jr, Thompson JL, Levin B, et al. Gavestinel does not improve outcome after acute intracerebral hemorrhage: an analysis from the GAIN International and GAIN Americas studies. Stroke. 2005; 36:1006–10. [PubMed: 15831831]

79. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism [see comment]. Stroke. 1998; 29:4–11. [PubMed: 9445320]

80. Furlan A, Higashida R, Wechsler L, et al. Intraarterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism [see comment]. JAMA. 1999; 282:2003–11. [PubMed: 10591382]

81. Investigators IMSS. Combined intravenous and intraarterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study [see comment]. Stroke. 2004; 35:904–11. [PubMed: 15017018]

82. Investigators IIT. The Interventional Management of Stroke (IMS) II Study. Stroke. 2007; 38:2127–35. [PubMed: 17525387]

83. Adams HP Jr, Effron MB, Torner J, et al. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: abciximab in emergency treatment of stroke trial (AbESTT-II). Stroke. 2008; 39:87–99. [PubMed: 18032739]

84. Qureshi AI, Palesch YY, Martin R, Novitzke J, Cruz-Flores S, Ehtisham A, Ezzeddine MA, Goldstein JN, Hussein HM, Suri MF, Tariq N. Antihypertensive Treatment of Acute Cerebral Hemorrhage Study Investigators. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study. Arch Neurol. 2010; 67:570–6. [PubMed: 20457956]

Table 1

Overview of the study design

Patient screened		ED personnel
Patient meets eligibility criteria		Site investigator
Randomize subjects 1:1		WebDCU™ system at MUSC
Intensive treatment SBP ≤140 mmHg using IV nicardipine ± labetalol	Standard treatment SBP ≤180 mmHg using IV nicardipine ± labetalol	Site investigator (oversight by IOC)
Best management according to AHA guidelines and "best available evidence"		Site investigator/treating physicians (oversight by IOC)
Neurological evaluation		Site investigator/treating physicians
CT scan for hematoma expansion		Blinded central image analysis
AEs (up to discharge), SAEs, care parameters		Site investigator (adjudication by IOC)
mRS and Euro-QOL		Blinded neurological evaluation by site investigator

WebDCU™ a web-based clinical trial management system developed by the Data Coordination Unit of MUSC, *MUSC* Medical University of South Carolina, *ED* emergency department, *IOC* Independent Oversight Committee, *AEs* adverse events, *SAEs* serious adverse events, *mRS* modified Rankin scale, *Euro-QOL* European quality of life

Table 2

The inclusion and exclusion criteria of the ATACH II trial

Inclusion criteria	
1	Age 18 years or older and less than 90 years.
2	IV nicardipine can be initiated within 3 h of symptom onset.
3	Clinical signs consistent with the diagnosis of stroke, including impairment of language, motor function, cognition, and/or gaze, vision, or neglect. ICH is defined by sudden onset of focal neurological deficit presumed due to intracerebral hematoma demonstrated on CT scan.
4	Initial NIHSS score of 4 or greater.
5	The total GCS score (aggregate of verbal, eye, and motor response scores) of 5 or greater at time of enrollment.
6	CT scan demonstrates intraparenchymal hematoma with manual hematoma volume measurement <60 cc (see section above). ICH is supratentorial and location is lobar, basal ganglionic, or thalamic based on the initial CT scan appearance. If hematoma extends into two regions (e.g., basal ganglionic and lobar) then the site where majority of hematoma is located would be considered the hematoma location
7	Admission SBP > 180 mmHg on two repeat measurements at least 5 min apart.
Exclusion criteria	
8	Time of symptom onset cannot be reliably assessed.
9	Admission SBP > 240 mmHg on two repeat measurements at least 5 min apart.
10	Previously known neoplasms, AVM, or aneurysms.
11	Intracerebral hematoma considered to be related to trauma.
12	ICH is located in infratentorial regions such as pons or cerebellum.
13	Intraventricular hemorrhage associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles
14	Subject is considered a candidate for immediate surgical intervention by the neurosurgery service.
15	Pregnancy, lactation, or parturition within previous 30 days.
16	Any history of bleeding diathesis or coagulopathy.
17	Use of warfarin within the last 5 days.
18	A platelet count less than 50,000/mm^3.
19	Known sensitivity to nicardipine.
20	Pre-morbid mRS of 4 or greater.
21	Subject has a living will that precludes aggressive intensive care unit management.
22	Signed and dated informed consent by the subject, representative or surrogate cannot be obtained.

ICH intracerebral hemorrhage, *NIHSS* National Institutes of Health stroke scale, *GCS* Glasgow Coma Scale, *AVM* arteriovenous malformation, *ATACH-II* antihypertensive treatment of acute cerebral hemorrhage—II, *SBP* systolic blood pressure

Table 3

Screening/recruitment timeline guidelines

Procedures	Recommended time interval between symptom onset and intervention	Consequence of inability to achieve recommended time
Screen and determine eligibility	150 min	Exclude from randomization
Acquire consent		
Order/prepare nicardipine		
Initiate nicardipine infusion	180 min	Protocol violation
Determine randomized allocation titrate nicardipine infusion	210 min	Protocol violation
Enter current patient's randomization data in WebDCU™ database at MUSC	8 h	Unable to randomize next eligible patient

WebDCU™ a web-based clinical trial management system developed by the Data Coordination Unit of MUSC, *MUSC* Medical University of South Carolina

Table 4

Summary of required evaluation according to time points of ascertainment

	Baseline	24 h	48 h	Discharge	Day 30 (tel)	Day 90
Screening	×					
Eligibility	×					
Demo/ED examination	×					
Medical history	×					
Cardiology/EKG	×					
Vital signs	×	×				
Prior medications	×					
GCS score	×	×				
NIHSS score	×	×				×
Laboratory tests	×	×	×			
CT scan	×	×				
Nicardipine administration		×				
Hospital discharge summary				×		
Concomitant medications		×	×	×		
Concomitant procedures		×	×	×		
Concomitant acute therapies		×				
AEs		×	×	×		
mRS					×	×
SAEs		×	×	×	×	×
Follow-up					×	×
EuroQOL						×
End of study						×

GCS Glasgow Coma Scale, *NIHSS* National Institutes of Health Stroke Scale, *CT* computed tomographic, *AEs* adverse events, *mRS* modified Rankin scale, *SAEs* serious adverse events, *EuroQOL* European quality of life

Table 5

Sample size requirements under various proportions of death and disability among standard SBP reduction patients

A. Assumes an absolute reduction of 10% or greater in the intensive SBP-treated group	
Standard therapy group (%)	**Sample size estimation[a]**
45	1,244
50	1,282
55	1,296
60	**1,282**
65	1,244
B. Assuming 60% death and disability in standard therapy group	
Effect size (%)	Sample size estimation[a]
10	1,282
9	1,582
8	2,002
7	2,610
6	3,550
5	5,100

SBP systolic blood pressure, *LTFU* lost to follow-up

[a] Assume 90% power, 2-sided alpha of 0.05, 2 interim analyses for efficacy, and inflated to account for 10% LTFU The most likely value is highlighted in bold

Table 6

Relationship between absolute SBP reduction at 6 h and volume expansion at 24 h and 90 day mRS [84]

	SBP reduction ≤ 60 mmHg	SBP reduction > 60 mmHg	RR (95% CI)
All subjects	*N* = 32	*N* = 28	
Hematoma expansion (increase of >33%)[a]	19.4%	33.3%	0.58 (0.24, 1.42)
Relative edema expansion (increase of >40%)[b]	42.9%	57.7%	0.74 (0.43, 1.27)
Death or disability (mRS 4–6)[c]	32.1%	52.0%	0.62 (0.32, 1.19)
Subjects treated within 3 h of symptom onset	N = 11	N = 9	
Hematoma expansion (increase of >33%)	18.2%	37.5%	0.48 (0.10, 2.26)
Relative edema expansion (increase of >40%)	30.0%	37.5%	0.80 (0.22, 2.94)
Death or disability (mRS 4–6)	12.5%	42.9%	0.29 (0.04, 2.21)

SBP systolic blood pressure, *RR* relative risk, *CI* confidence interval, *mRS* modified Rankin scale

[a] 2 subjects are missing 24 h hematoma volume measure

[b] 6 subjects are missing 24 h edema volume measure

[c] 7 subjects are missing day 90 mRS; 2 subjects' day 90 mRS were imputed from their earlier outcome measures

Table 7

Distribution of initial NIHSS and GCS scores among previous trials of ICH

Study	Exclusion criteria		Mean/median NIHSS	Mean/median GCS	Proportion of mRS 0–2	Proportion of mRS 3–6
CHANT [43]	**1**	NIHSS score < 6	Mean 14 (range 6–33)	Mean 13.7 (range 7–15)	180	416
	2	Unconsciousness a score of 3 on 1a of NIHSSS was exclusion.				
INTERACT [50]	GCS < 5		9 (range 5–16)	Median 14 (range 12–15)	207	193
STICH [44]	GCS < 5			20% GCS 5–8; 40% GCS 9–12; 40% GCS 13–15	289	663
FAST [45]	GCS < 5		Mean 13 (±7)	Median 14–15 (range 6–15)	433	390
rVII a Phase II [49]	GCS < 5		Means 12–14 (± 6)	Median 14 (6–15)	172 * (mRS 0–3)	226 * (mRS 4–6)

NIHSS National Institutes of Health stroke scale, *GCS* Glasgow coma score, *ICH* intracerebral hemorrhage, *CHANT* cerebral hemorrhage and NXY treatment, *INTERACT* intensive blood pressure reduction in acute cerebral hemorrhage trial, *STICH* surgical treatments for ischemic heart failure Trial, *FAST* factor seven for acute hemorrhagic stroke

* Data on mRS dichotomization 0–2 to 3–6 not reported

Table 8

Qualitative classification of intraventricular hemorrhage, prevalence, and rates of associated poor outcome in patients with supratentorial ICH

Grade	Characteristics	Prevalence (%)	mRS 5–6 (%)
Grade 0	None	56	17
Grade 1	Blood in third ventricle or blood occupying less than one-third of one lateral ventricle	25	20
Grade 2	Blood occupying less than half of both lateral ventricle or two-thirds of one ventricle	21	29
Grade 3	One completely filled lateral ventricle or both ventricle more than one-half filled ventricle	11	34

Adapted from Lisk et al. [27]

ICH intracerebral hemorrhage, *mRS* modified Rankin Scale

Table 9

Proportion of patients with death or disability among placebo-treated groups in various trial recruiting ICH patients

Placebo/standard treatment patients	Number of patients	Proportion of patients with mRS 4–6 (%)	95% confidence interval
INTERACT (2008) [50]	201	47	0.40, 0.54
FAST (2008) [45]	263	54	0.48, 0.60
CHANT (2007) [43]	96	52	0.24, 0.62
rfVIIa (2005) [49]	96	69	0.60, 0.78

ICH intracerebral hemorrhage, *INTERACT* intensive blood pressure reduction in acute cerebral hemorrhage trial, CHANT cerebral hemorrhage and NXY treatment, *FAST* factor seven for acute hemorrhagic stroke, *rfVIIa* recombinant activated factor VII, mRS modified Rankin scale

Table 10

Odds ratios by different mRS cutoffs in various trials involving patients with ICH

	FAST [45][a] (*N* = 555)			ATACH[c] [76] (*N* = 51)			IVH-CLEAR[b] [77] (*N* = 99)			GAIN [78] (*N* = 564)			CHANT [43] (*N* = 595)		
mRS cut point	**OR**	**95%**	**OR limit**	**OR**	**95%**	**OR limit**	**OR**	**95%**	**OR limit**	**OR**	**95%**	**OR limit**	**OR**	**95%**	**OR limit**
0	0.80	0.32	2.01	0.69	0.04	11.68	NA	NA	NA	0.89	0.45	1.79	0.89	0.34	2.35
1	0.84	0.55	1.27	2.57	0.60	10.97	2.10	0.24	18.05	1.17	0.77	1.78	0.76	0.48	1.19
2	0.94	0.66	1.33	2.62	0.82	8.34	1.17	0.30	4.58	1.22	0.86	1.74	1.05	0.74	1.49
3	0.78	0.56	1.09	2.67	0.84	8.42	1.04	0.34	3.21	1.20	0.86	1.67	1.09	0.79	1.50
4	0.72	0.49	1.06	1.64	0.48	5.68	2.47	0.87	6.97	1.22	0.84	1.76	0.97	0.68	1.39
5	0.84	0.55	1.27	1.56	0.39	6.27	1.32	0.42	4.19	1.18	0.78	1.80	NA	NA	NA

mRS modified Rankin scale, *ATACH* anti-hypertensive treatment of acute cerebral hemorrhage, *IVH-CLEAR* clot lysis: evaluating accelerated resolution of intraventricular hemorrhage phase III, *GAIN* glycine antagonist in neuroprotection for patients with acute stroke, *CHANT* cerebral hemorrhage and NXY treatment, *FAST* factor seven for acute hemorrhagic stroke

[a]The FAST analysis is based upon comparison between placebo and 80 μg/kg dose

[b]IVH-CLEAR analysis is based on 1 m data provided by investigators

[c]ATACH analysis is based on comparison between patients with ≥60 mmHg and <60 mmHg reduction in SBP at 6 h after treatment

Table 11

Patient populations, proportion of centers, and screened and recruited patients in various acute stroke trials

Trial	Patient population	Number of centers	Screened	Recruited (%)
PROACT I [79]	Acute ischemic stroke within 6 h of symptom onset	37	1,314	105 (8)
PROACT II [80]	Acute ischemic stroke within 6 h of symptom onset	54	12,323	180 (1.4)
rfVIIa trial [49]	Acute ICH within 3 h of symptom onset	38	1,636	199 (12)
IMS I [81]	Acute ischemic stroke within 3 h of symptom onset	17	1,477	80 (5.4)
IMS II [82]	Acute ischemic stroke within 3 h of symptom onset	13	3,602	81 (2.2)
AbESTT-II [83]	Acute ischemic stroke within 5 h of symptom onset	112	9,011	801 (8.9)

PROACT I prolyse in acute cerebral thromboembolism trial, *PROACT II* prolyse in acute cerebral thromboembolism II, *IMS I* interventional management of stroke study, *IMS II* the interventional management of stroke (IMS) III trial, *rfVIIa* recombinant activated factor VII, *AbESTT-II* Abciximab in emergent stroke treatment trial-II

Table 12

Differences between the INTERACT Phase III and ATACH-II study

	INTERACT (Phase III)	ATACH-II
Inclusion within 3 h (%)	30[a]	100
Initial SBP ≥180 mm Hg (%)	47[a]	100
ICH location (supratentorial) (%)	90[a]	100
Antihypertensive agents	Uradipil or frusemide	Nicardipine
SBP goals achieved in intensive BP treatment group	42% in 1 h and 66% in 6 h[a]	90% in 2 h[b]
Recruited population	Chinese (95%)[a]	Whites (52%) and African Americans (42%)[b]
Overall patient management at sites	Recommended according to AHA guidelines	IOC monitors intensity of care through periodic reviews

ATACH-II antihypertensive treatment of acute cerebral hemorrhage—II, *ATACH-I* antihypertensive treatment of acute cerebral hemorrhage—I, *IOC* independent oversight committee, *INTERACT II (Phase III)*, *SBP* systolic blood pressure, *ICH* intracerebral hemorrhage

[a]Derived from INTERACT vanguard phase

[b]Derived from ATACH-I study