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Thrombolytic removal of intraventricular haemorrhage in treating severe stroke: Results of the CLEAR III trial, a randomised, controlled trial

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Abstract

Introduction: Intraventricular haemorrhage (IVH) is a subtype of intracerebral haemorrhage (ICH), with 50% mortality and serious disability for survivors. CLEAR III, a randomised, double-blinded, placebo-controlled trial of subjects with a routinely-placed extraventricular drain (EVD), tested whether attempting to remove IVH with alteplase vs. saline irrigation improved functional outcome.

Methods: Patients in the intensive care unit with stable, non-traumatic ICH volume <30 mL, IVH obstructing the 3rd or 4th ventricles, and no underlying pathology were adaptively randomised (1:1) to receive up to 12 doses, 8 hours apart of 1mg of alteplase or 0.9% saline via the EVD. CT scans were obtained every 24 hours throughout dosing. The primary efficacy outcome was good functional outcome, defined as a modified Rankin Scale score of ≤ 3 at 180 days (mRS) per central adjudication by blinded evaluators.

Results: The trial completed with 180-day follow-up data available for analysis from 246/251 and 245/249 subjects in the alteplase and placebo groups, respectively. The primary efficacy outcome was similar in each arm (good outcome in alteplase group 48% vs. saline 45%; RR (95% CI)=1.06 (0.88, 1.28) $p=0.554$). A difference of 3.5% (RR (95% CI)=1.08 (0.90, 1.29), $p=0.420$) was found after adjusting for IVH size and thalamic ICH. At 180 days, the treatment arm had lower case fatality (18% vs. saline 29%, HR (95% CI)=0.60 (0.41, 0.86), $p=0.006$), but greater proportion with mRS 5 (17% vs. 9%; RR (95% CI)=1.99 (1.22, 3.26), $p=0.005$). Ventriculitis (7% alteplase vs. 12%; RR (95% CI)=0.55 (0.31, 0.97), $p=0.048$), and serious adverse events (49% alteplase vs. 63%; RR (95% CI)=0.77 (0.66, 0.91), $p=0.002$), were less frequent with alteplase treatment. Symptomatic bleeding (2%, both arms; RR (95% CI)=1.21 (0.37, 3.91), $p=0.771$) was similar.

Conclusions: In patients with IVH and a routine EVD, irrigation with alteplase did not substantially improve functional outcomes at the mRS 3 cutoff compared to irrigation with saline. Protocol-based use of alteplase with EVD appears safe. Future investigation is needed to determine if a greater frequency of complete IVH removal via alteplase produces gains in functional status.

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Introduction: In patients with spontaneous intracerebral haemorrhage (ICH), intraventricular haemorrhage (IVH) is associated with devastating consequences.¹⁻⁴ Mortality is reported to be greater than 50%, with fewer than 20% of survivors having good functional outcomes. Mortality and function appear to be altered if thrombolytic is employed.^{5,6} Systematic review, Meta-analysis suggest removal of IVH improves survival and long-term functional outcome by relieving acute obstructive hydrocephalus and reducing neurotoxicity.⁵⁻⁹ We hypothesised that small ICH with large IVH describes a subgroup of ICH patients whose severe prognosis is reversible.^{1,6} Thus we organised the Phase III *Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR III)* trial.

In EVD-treated IVH subjects, we tested the hypothesis that irrigating the ventricle with alteplase would be superior to normal saline (0.9%), measured by an improved modified Rankin Scale (mRS) score 0-3 (mRS ≤ 3 , called “good outcome”), in which a score of 0 indicates no symptoms, a score of 5 indicates severe disability, and a score of 6 indicates death. This hypothesis was based on our preliminary data showing alteplase (Genentech, Inc., San Francisco, CA) can safely remove clot from the ventricle, if precautions are taken to avoid re-activating brain bleeding, in patients treated with an EVD.¹⁰⁻¹³ Although EVD placement is not standardised in practice for all cases of IVH, it is used to manage hydrocephalus and intracranial pressure (ICP). We included such patients in the CLEAR III study.

Methods

Trial Design and Participants: CLEAR III was a multicentre, randomised (1:1), prospective phase III trial¹¹ done at 73 sites in the US, Canada, Brazil, Israel, UK, Germany, Hungary, and Spain, following local and country ethics approval, testing a strategy of ventricular clearance with alteplase via EVDs placed for ICP control in subjects with a clinical diagnosis of obstructive hydrocephalus. Placement of an EVD pre-trial was a routine clinical care decision. Subjects were age 18-80 with known symptom onset within 24 hours of the initial computed tomography (CT) scan confirming IVH and 3rd or 4th ventricle obstruction. Eligibility criteria included supratentorial ICH volume ≤ 30 mL, measured by the ABC/2 method,¹² and clot stability (no measured expansion >5 mL) on repeat CT scan at least 6 hours after EVD placement.¹³ Additional eligibility criteria

included an historical mRS ≤ 1 , no limitations to care, and no ongoing coagulopathy, suspicion of aneurysm, arteriovenous malformation, or other vascular anomaly.¹³ (See supplemental appendix, section 2a.

Methodological details of the treatment protocol: Inclusion and Exclusion criteria for additional details.) All data were captured electronically and pertinent source documentation uploaded by local site personnel using an internet-based electronic data capture (EDC) system (VISION, Prelude Dynamics, LLC, Austin, Tx). The EDC provided field-level and form-to-form range and value edit checks during data entry. Independent quality assurance monitors (Emissary International, LLC, Austin, Tx) utilized the uploaded source documentation to perform risk-based, remote monitoring of key data variables. Monitored data were then exported by the data management center where additional data edit checks were applied prior to form/subject finalization. Site personnel were notified of and responded to data discrepancies identified during these review processes using the EDC system query tool, with resulting data corrections captured by the electronic audit trail.

Randomization and Blinding: All subjects and trial personnel except for the local and central pharmacists and the unblinded statistician were masked to treatment assignments. After the local PI determined eligibility and written, informed consent was obtained, site personnel randomised patients within 72 hours of ictus using a web-based enrollment system (VISION, Prelude Dynamics, LLC, Austin, Tx), which generated a treatment allocation and emailed the treatment assignment code directly to the local, trained pharmacist. All other site and coordinating center personnel remained blinded to allocation. After 100 subjects were assigned by simple randomisation, a Pocock-Simon^{14,15} covariate adaptive algorithm was implemented to balance study arms by baseline IVH size (≤ 20 mL; 20-50 mL; and >50 mL, measured on the diagnostic CT), ICH location (thalamus or other, determined by centralised CT reading). Imbalances in these factors were determined at each enrollment, and patients were randomised with a weighted coin (80/20) favoring assignment to the treatment arm, which improved balance in ICH location and ICH size.^{6,13,14} To ensure treatment balance at the site, patients were adaptively randomised only after a given site had recruited two saline and two alteplase patients. All participants remained masked during data collection and interim analyses. Masking was evaluated by the external monitor.

Treatment: Subjects received up to 12 doses, 8 hours apart, of 1 mg of alteplase or 0.9% saline via the EVD. CT scans were obtained every 24 hours throughout dosing. All subjects were managed using the American Heart Association recommendations for the treatment of spontaneous ICH as the basis for a standard approach to airway, ventilation, ICP monitoring, sedation and pharmacologic treatment of mass effect.^{16,17} Investigators were asked to remove as much clot as possible, until a stopping point was obtained: 3rd and 4th ventricles open; IVH mass effect relieved; 80% of clot was removed; or 12 doses were given.

Image analysis: To optimize accuracy and minimize investigator bias, clot volumes were analyzed by a core laboratory utilizing semi-automated segmentation and Hounsfield thresholds.¹⁸ This was performed using OsiriX software (v.4.1, Pixmeo; Geneva, Switzerland) on DICOM images of each subject's stability and treatment scans. This approach has been validated for accuracy and inter-rater reliability.¹⁹ Core lab values were utilized in all analyses. Core lab defined location as either thalamus or other (lobar, putamen, caudate).

Follow-up and Outcomes: Subjects were followed with an NIHSS assessment at Day 7, clinic visits on Days 30, 180, and 365, and phone contacts at Days 90 and 270. A site-identified, certified examiner assessed the mRS, extended Glasgow Outcome Scale (eGOS; 8 level disability scale from 8-upper good recovery to 1-death), Barthel Index (BI; 0 to 100 daily activities scale with 0 indicating no activities performed and 100 all activities performed), Stroke Impact Scale (SIS; self-reported scale of 16 activity domains from 1-most impaired to 5-not impaired), NIH Stroke Scale (NIHSS, clinic visits only; scores range from 0 to 42, with higher scores indicating a more severe neurologic deficit). CT was repeated at 30 and 365 days. The mRS assessment, the primary outcome, was video-recorded and sent to a core lab for blinded assessment by an independent panel of experts.¹³ All other assessments were secondary. Full details of mRS, eGOS, and NIHSS are given in the supplemental appendix sections 2b and 2c.

Statistical Methods

Sample Size: The trial planning was informed by data from the previously completed Phase II CLEAR studies, which recorded 30-day outcomes.⁶ Sample size planning assumed an average removal difference attributable

to alteplase of 12ml. The sample size of CLEAR III was planned to be 250 patients per group in order to provide at least 82% power to detect a risk difference of 13% in the proportion of good outcome from EVD+alteplase treatment compared to control, assuming a 22% proportion of good outcome among controls. The conjectured risk difference and good outcome rate under control were based on extrapolating from the previously completed Phase II CLEAR studies, which recorded baseline IVH clot volume and location (for ICH) and 30-day mRS outcomes.⁶ To do this, models were first fit using the data from these studies, and then used for simulating hypothetical trials at sample size 500 as described in section 2g of the supplemental appendix.

We present data in three groups: the planned intention-to-treat (ITT) primary efficacy analyses of functional outcome; additional mRS efficacy analyses including other mRS analyses of various cut points, and secondary analyses of case fatality, clot removal, and ICU care; and safety. Adjusted analyses are indicated in Table S1. The primary and key secondary analyses were designated in 2008, at the start of the trial.

ITT Efficacy Analysis: The primary aim was to assess clinical efficacy of EVD+alteplase by estimating the difference in the proportion of centrally-adjudicated mRS scores, dichotomised as ≤ 3 vs. > 3 , at 180 days. We estimated the average benefit comparing treatment vs. control, using the ITT principle. Specifically, we estimated the difference between the probability of 180-day mRS ≤ 3 , referred to as a good outcome, comparing alteplase vs. saline. In accordance with the literature on covariate-adaptive randomised designs, the estimate of the adjusted treatment effect was based upon a weighted average of the difference in proportions for each of the six strata defined by the possible baseline combinations for covariates used in randomization: IVH volume and location. Weights were set proportional to the number in each stratum (pooled across arms). The 95% confidence interval, estimated by the percentile method for the average treatment effect, was computed by the nonparametric bootstrap method, such that the covariate-adaptive design is adhered to in each resampled (i.e., bootstrap replicated) data set. Multivariable logistic regression models were used to estimate the conditional effect of treatment on good mRS outcome for baseline variables.

Secondary and Post-hoc Efficacy Analysis: Planned secondary efficacy analyses: 1) The Kaplan-Meier time-to-event analysis was used to estimate the survival functions and the log-rank test was used to compare

the survival by treatment. 2) A logistic model relating clot removed to mRS 0-3 proportion was used (Supplemental Table S2). These models were informed by univariate regression and well established clinical and epidemiologic considerations of the important prognostic factors of age, initial Glasgow Coma Scale (GCS) score (scores range from 3 to 15, with lower scores indicating reduced levels of consciousness), IVH size as a continuous variable, and the results of the planned intervention, clot removal. 3) Intensity of ICU management by treatment type was compared via Chi square or Fisher's exact test, as appropriate. Results of planned analyses of key demographic subgroups for heterogeneity of treatment effect: IVH and ICH size, location, GCS, age, gender, and race are presented.

Post hoc analyses were undertaken for two unexpected but clinically important findings: 1) when the number of subjects in mRS 5 category at 180 days was inspected for disproportion, a treatment comparison was made. 2) When inspection of protocol associated clot removal showed that alteplase achieved the hypothesised differential removal for subjects with IVH volume >20mL but not in the group with <20mL, subgroup by treatment group was undertaken. Interaction terms for treatment by baseline IVH stability volume at 20mL were considered. No correction for multiplicity was applied, as secondary analyses were considered hypothesis generating.

Safety Analysis: The safety aim of the trial was to achieve near total clot dissolution without procedure-related safety events endangering subjects beyond the risks associated with intensive medical treatment.²⁰ Analyses tested the null hypothesis that use of alteplase is safe for the treatment of IVH, relative to standard care of EVD alone under pre-specified thresholds for 30-day case fatality (40%), symptomatic rebleeding (25%), and bacterial brain infection (20%). We tested these three thresholds and all safety event rates as interim analyses after 100, 175, 250, and 350 subjects were enrolled and then for the full 500 over 180 days with Fisher's exact test. The overall occurrence rate of serious adverse events (SAEs) was tested between the two treatment groups.

Clot Removal Analysis: End of treatment (EOT) was defined as 24 hours after the last dose.¹⁸ Additionally, area under the curve (AUC) of the IVH time course from stability to EOT was calculated using the trapezoidal

rule to quantify clot removal over time. AUC values were normalised by the time elapsed from stability to EOT to account for variability in treatment times. Logistic and Cox regression analyses were done to evaluate the relationship between IVH removal, represented by the normalised AUC of IVH clot on $mRS \leq 3$, and 180-day case fatality, respectively, after adjustment for ICH clot location, age, ICH volume at stability and randomization GCS.

All analyses were conducted using two-sided tests with a Type I error rate of 0.05, performed using the statistical packages STATA 13.0 or higher (STATA Corp, College Station, TX) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). All data are presented as median [IQR: inter quartile range], unless otherwise specified.

Role of the Funding Source: The principal investigator (DFH) conceived, organized and executed this trial. He had full access to all study data and had final responsibility for the decision to submit for publication. The sponsor NIH/NINDS provided input regarding the study design during the grant review process and the NIH/NINDS-appointed DSMB provided the same during active recruitment. The NIH/NINDS-appointed DSMB and Genentech, Inc. approved the decision to submit the paper for publication.

Results

Subjects: Between September, 2009 and January, 2015, 500 patients were randomised, with the last subject completing follow-up in January, 2016 (Fig. 1). The trial completed with 180-day follow-up data available for analysis from 246/251 and 245/249 subjects in the alteplase and placebo groups, respectively. Admission demographics and clinical severity factors are shown in Table 1 and were similar between groups. Subjects arrived at hospital within 1.5 [0.8, 3.5] hours of ictus and underwent a CT by 2.3 [1.4, 4.9] hours. ICH clot location was thalamus 59%, 32% other; and 9% primary IVH (no identifiable ICH). The baseline IVH and ICH sizes were 21.8 [12.7, 36.9] mL and 7.9 [2.5, 15.0] mL, respectively. Baseline mean arterial pressure and ICP were similar by group. Subjects received first EVD at 7.5 [5.0, 12.0] hours and bleeding was determined stable by 43.5 [26.9, 57.9] hours post ictus.

Acute Protocol Period: Randomization occurred at 52.1 [39.1, 66.5] hours, with first treatment given 3.0 [1.7, 5.5] hours later. Five [3, 8] alteplase and 12 [9, 12] saline doses were given. EOT occurred at 2.5 [1.8, 3.7] and 4.7 [4.0, 5.1] days post randomization for alteplase and saline respectively. In the alteplase group, the 3rd and 4th ventricles opened more rapidly ($p < 0.0001$). Twenty percent of all subjects achieved 80% removal of IVH, 10% saline and 30% alteplase. Overall, 27% of subjects received two EVDs (dual catheters), one in each lateral ventricle. During treatment, most subjects (78%) experienced at least one ICP reading ≥ 20 mmHg. Cerebral perfusion pressure (CPP) < 70 mmHg occurred in 62% of subjects despite continuous EVD drainage; the proportion of CPP compromise was 2% less in the alteplase arm (see Table 1). Permanent ventriculo-peritoneal shunts were placed in 18% of subjects.

Primary Efficacy Outcomes: Retention to day 180 was 98%. The primary ITT analysis comparing arms by mRS ≤ 3 outcome was 48% for alteplase and 45% for saline (RR (95% CI)=1.06 (0.88, 1.28), $p = 0.554$) (Fig. 2 and Table 2). The difference in good outcome (alteplase – saline) adjusted for IVH size and thalamic ICH was 3.5% (RR (95% CI)=1.08 (0.90, 1.29), $p=0.420$), not significantly different from zero. A single subject received alteplase after completion of 12 doses of saline (crossover). A subsequent sensitivity analysis was performed with this subject moved to the active treatment arm. The primary results did not change.

Secondary Outcomes and Safety: The mRS 6 (death) category showed a 50% decrease in the odds of being dead (mRS 6) for alteplase versus saline (Adjusted OR (95% CI) = 0.49 (0.37, 0.81), $p = 0.001$) (Table 3). No effect of hospital site was demonstrated for the primary mRS 0-3 outcome. (See Supplemental Table S1.) Estimated Kaplan-Meier survival probabilities were greater throughout 180 days of follow-up for the alteplase group (cumulative case fatality: 18% vs. 29%; $p=0.006$) (Fig. 3). Safety parameters favoured alteplase: bacterial ventriculitis (7% vs. 12%; RR (95% CI)=0.55 (0.31, 0.97), $p=0.048$) and SAEs (49% vs. 63%; RR (95% CI)=0.77 (0.66, 0.91), $p=0.002$). The frequency of symptomatic bleeding was similar between groups (2% in both arms; RR (95% CI)=1.21 (0.37, 3.91), $p = 0.771$). Table S1 in the supplemental appendix shows the primary, secondary and safety outcomes. Table 4 shows the safety profile by group and by the Medical Dictionary for Regulatory Activities (MedDRA) body system classifications.

A post-hoc analysis of the mRS 5 (i.e., bedbound) category shows a greater proportion in the alteplase group (17% vs. 9%; RR (95% CI)=1.99 (1.22, 3.26), $p=0.005$). Other post-hoc analyses demonstrated no difference in the proportion of subjects in a vegetative state, measured by the eGOS scale (3% in both groups; RR (95% CI)=1.33 (0.47, 3.78), $p=0.787$) nor for subjects surviving in long-term care facilities (alteplase 14% vs. saline 12%; RR (95% CI)=1.18 (0.74, 1.88), $p=0.479$) (see Fig. 2 and Table S2). Neither Barthel index nor EuroQol Visual Analog Scale (EQ-VAS; self-reported, quality of life scale with scores ranging from 0-worst to 100-best imaginable health state) was different between groups (see Table S1).

Clot Removal: Removal of clot varied widely, dependent on number and location of EVDs and number of alteplase doses. Thirty percent (30%) of the alteplase group and 10% of the saline group achieved the 80% removal endpoint. The planned secondary analysis relating mRS to the amount and timing of clot removal in all subjects demonstrated a significant relation between clot removal (per clot remaining (mL), as measured by normalised AUC) and both mRS ≤ 3 (AOR (95% CI)=0.96 (0.94, 0.97); $p < 0.0001$) and case fatality (AHR (95% CI) of death per mL of time-weighted clot volume remaining = 1.03 (1.02, 1.04); $p < 0.0001$), adjusted for age, thalamic ICH location, stability ICH volume, and randomised GCS (see Supplemental Table S3). The results of the subgroup analyses pre-specified in the protocol are shown in Supplemental Figure S1. No p values for interaction were significant.

Discussion

In the CLEAR III trial, irrigation of the ventricles with alteplase via a routine EVD did not improve functional outcomes in patients with IVH. Analyses of our secondary outcome measures, 180 day case fatality was significantly lower in the alteplase group, but the majority of these survivors ended up with severe disability (i.e., mRS4,5 or eGOS lower and upper significant disability). Clot removal analyses showed a correlation between amount of removal and improved mRS ≤ 3 . Alteplase appears safe when compared to saline. These findings suggest possible value to the concept of removing greater amounts of IVH volume. On the face of the

current evidence, however, alteplase at the dose of 1 mg every 8 hours cannot be recommended as an intervention to improve functional outcome in patients with IVH.

There are limitations to this trial. This was the first Phase III IVH thrombolysis trial and evidence-based standards for subject selection and treatment endpoint did not exist. Current guidelines do not mandate the use, number, or location of EVD catheters, which are important factors influencing the amount of IVH removed. Routine practice produced good adherence to EVD safety, and opening of the midline ventricles occurred; but, poor adherence to removal of >80% IVH. This lack of adherence may have limited the stringency of the test of our hypothesis. Not all severity factors are known, so imbalances in severity could have existed. For example, nonspecific factors (e.g., type and extent of ICU care) could have been different between the treatment arms and influenced outcomes. For ICU care this does not seem likely, as subject severity, “withdrawal of care,” and ICU care were similar between groups. CLEAR III was a small sample of current clinical practice taken from the most aggressive end of the treatment spectrum: those subjects whose physicians utilised EVDs. The control intervention represents an aggressive level of care not always offered to every subject with IVH. The baseline mortality and good functional outcomes observed in the CLEAR III controls was greater than in our prior study⁶ or in the expected levels from the general population (where low frequencies of EVD use are coupled with very high reliance on medical care as the sole supportive intervention for IVH).^{2,3,6,7,9} Only convenience sample data exists for outcomes of medically managed subjects thus our knowledge about risk and benefit for the intervention in the general population is limited. Another possible limitation is that the CLEAR III sample might not represent a true general IVH population, rather a milder or more severe population. Evaluations of the general population of IVH, concurrently performed, have demographics and severity factors matching CLEAR III. They show full population estimates of mortality (40%-60%) and low good functional outcome (10%-30%) suggesting less intense therapies may not produce as many benefits.^{2,5} Finally, the main outcome measure: mRS 0-3 vs. 4-6 proportion is only one measure of disability. Further research will be needed to clarify the divergent picture within the more severe disability segments of mRS and eGOS.²¹ If survival comes at the cost of living with unacceptable impairment, this or any treatment could be seen as limited in value.

Potential to improve practice is evident with the findings that CPP/ICP are not always controlled by a single EVD routinely placed into the anatomically largest pool of cerebrospinal fluid or least bloody site. This is a starting point for investigating multiple catheters where clot is large, bilateral, trapping the ventricle, or creating a local mass effect. Placing a second catheter near or into the largest portion of the clot leads to greater and more rapid removal²² and possibly greater clinical benefit. The precise clinical definitions for the at-risk population will need to be tested in a surgically-standardised trial setting.²³ The signal of benefit from greater clot removal and the low percentage of subjects achieving 80% removal raise the possibility that benefit of alteplase may be possible if greater clot removal could be achieved and, if it is achieved, more rapidly. As CLEAR III did not demonstrate improved rates of good functional recovery with alteplase rather than saline, future investigation will need improved surgical placement of catheters to achieve effective clot reduction more frequently and more rapidly. A possible solution is an adaptively-designed, efficacy-to-effectiveness trial²⁴ that demonstrates a better clot removal protocol can be integrated into routine stroke care and tests for influence on function, disability and case fatality.

Panel: Research in Context

Evidence before this study: A literature search was done from January 1, 1950 until November 1, 2015 on PubMed with the terms: IVH, IVH AND ICH, IVH AND TPA, IVH AND thrombolytic, IVH AND cross sectional, and IVH AND treatment. Search filters for "adult" and "human subjects" publications were applied. Meta-analysis of case series, one small multisite trial, and single-site convenience samples suggest mortality and perhaps functional impairment can be mitigated via enhanced clearance of the IVH through thrombolysis. Prior to and after the Clot Lysis: Evaluating Accelerated Resolution of IVH Phase III (CLEAR III) trial, when caring for patients with a small ICH and large IVH, clinicians have no class 1 evidence regarding the safety and effectiveness of IVH thrombolysis.

Added value of this study: CLEAR III is a randomised, double-blinded study designed to provide a test of the combination of extraventricular drainage (EVD) and low dose thrombolytic as a method of removing IVH and improving functional outcomes. This multisite study is the first to prospectively collect several objective

functional performance (modified Rankin Scale [mRS] and extended Glasgow Outcome Scale [eGOS]) as well as patient-based (Euro –QoL [EQ], Stroke Impact Scale [SIS]) measures of satisfaction. Medical care in the intensive care unit (ICU) was standardised and assessed rigorously. Data were prospectively defined and collected in a uniform manner and monitored thoroughly providing evidence of type, intensity and duration of ICU care required. Precise measurement of IVH size occurred in this trial possibly improving estimates of severity and treatment performance. The results of CLEAR III provide a robust estimate of the proportion of mRS 0-3 (approximately 45% to 48%) that occurs, if subjects are supported until the EVD is no longer needed. This led to an adjusted (IVH size and thalamic location) estimate of treatment effect of 3.5% (95% CI -4%, 12%). This effect size was not different between alteplase and saline treatment plans, though case fatality did differ. The absolute proportion of mRS 0-3 found in all CLEAR III subjects compares favourably to the untreated subjects in the literature. The study provides detailed evidence that a protocolled approach to remove IVH with alteplase is safe and that the 3rd and 4th ventricles open sooner if alteplase is utilized. A legitimate concern could be raised about greater infection rates due to frequent injections of alteplase or saline in the EVD, however a comparison of infection rate in CLEAR is in the same range as that reported in a meta-analysis of infections from published EVD series where injections were not performed. The data presented characterise substantial variations in current EVD-related neurosurgical practice. They demonstrate usefulness of the measures of initial severity (Glasgow Coma Scale [GCS], location, and ICH/IVH size) and the elements of treatment needed for precise characterization of prognosis in the aggressively treated IVH patient. The subgroup analysis suggests increased focus on larger IVH and earlier treatment times is appropriate.

Implications of all the available evidence: The trial was neutral on primary outcome of functional improvement. Therefore we do not think practice should change. Other post hoc results are consistent with the hypothesis that removal saves lives and possibly improves function. The issue of survival with disability is now well defined by our primary results and other measures of disability. The secondary results leave open a possible role of IVH volume reduction as a biomarker for treatment, with better outcomes more likely achieved with enhanced IVH clearance, particularly in subjects with larger initial IVH volume. The results are consistent with prior convenience reports and meta-analyses that good functional outcome can occur in up to 50% of treated subjects. The data provide a sound basis to critically redefine short-term neurosurgical and ICU management

around the task of volume removal. A trial testing these more objective goals is needed, if we are to be assured that aggressive removal of IVH is safe and can predictably produce increased independent function and decreased case fatality. Current information suggests as many as 25% of ICHs have large IVH. How many of these patients receive care and would be eligible for treatment is not known. An estimate of the full benefit of intervention will require a combined epidemiological and RCT intervention approach that randomises available subjects and collects information about usual care controls. A novel trial would provide a standardised surgical task, treat subjects more rapidly and require greater care team adherence to the removal of large amounts of the IVH, not just removal of enough blood clot to open the 3rd and 4th ventricles. Sharing the full results of CLEAR III is likely to stimulate further investigations of a worldwide problem that is serious, growing, and could be treatable.

Contributions. DFH and IAA organised the trial hypotheses, designed the trial, and provided guidance about the data analysis and interpretation/presentation of the data. DFH drafted most of the sections of the manuscript. KL, NMcB, WZ, ST, ADM, BG, KB, PV, DWW, PMK, MDW, SJo, SH, GL, EFA, MRH, SA, JJ, JLC, DL, OA, MZ, and HPA were involved in the design of the study and provided contributions to the writing and revising of the manuscript. KL, NMcB, and SWM organised and managed the trial including trial start-up, data collection, quality assurance, and trial close-out. KRL and JD provided the independent review and central adjudication of the modified Rankin Scale scores. DG, NU, and WAM provided the region of interest calculations for all volumetric measurement results. WZ, CSK, and JRC provided independent review and adjudication of all safety events. MR and RET generated the random allocation method. RET, JM, JFB, MR, CBT, EAS, and GY were involved in the statistical analysis, data interpretation, and contributed to the development and revisions to the manuscript. SJa provided critical review of the manuscript. The CLEAR III investigators contributed equally to the identification and, when eligible, randomization of trial participants.

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References

1. Hanley DF. Intraventricular hemorrhage severity factor and treatment target in spontaneous intracerebral hemorrhage. *Stroke* 2009; **40**(4): 1533-8.
2. Hansen BM, Morgan TC, Betz J, et al. Intraventricular Extension of Supratentorial Intracerebral Hemorrhage: The Modified Graeb Scale Improves Outcome Prediction in Lund Stroke Register. *Neuroepidemiology* 2015; **46**(1): 43-50.
3. Tuhim S, Horowitz DR, Sacher M, Godbold JH. Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage. *Critical Care Medicine* 1999; **27**(3): 617-21.
4. Qureshi AI, Tuhim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *New England Journal of Medicine* 2001; **344**(19): 1450-60.
5. Moradiya Y, Murthy SB, Newman-Toker DE, Hanley DF, Ziai WC. Intraventricular Thrombolysis in Intracerebral Hemorrhage Requiring Ventriculostomy A Decade-Long Real-World Experience. *Stroke* 2014; **45**(9): 2629-35.
6. Naff N, Williams MA, Keyl PM, et al. Low-Dose Recombinant Tissue-Type Plasminogen Activator Enhances Clot Resolution in Brain Hemorrhage The Intraventricular Hemorrhage Thrombolysis Trial. *Stroke* 2011; **42**(11): 3009-16.
7. Gaberel T, Magheru C, Parienti J-J, Huttner HB, Vivien D, Emery E. Intraventricular Fibrinolysis Versus External Ventricular Drainage Alone in Intraventricular Hemorrhage A Meta-Analysis. *Stroke* 2011; **42**(10): 2776-81.
8. Nieuwkamp DJ, de Gans K, Rinkel GJ, Algra A. Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature. *Journal of Neurology* 2000; **247**(2): 117-21.
9. Staykov D, Bardutzky J, Huttner HB, Schwab S. Intraventricular fibrinolysis for intracerebral hemorrhage with severe ventricular involvement. *Neurocritical Care* 2011; **15**(1): 194-209.
10. Ziai WC, Muschelli J, Thompson CB, et al. Factors affecting clot lysis rates in patients with spontaneous intraventricular hemorrhage. *Stroke* 2012; **43**(5): 1234-9.
11. MIS+rtPA for ICH Evacuation (MISTIE).
12. Josephson CB, White PM, Krishan A, Al-Shahi Salman R. Computed tomography angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral haemorrhage. *The Cochrane Library* 2014.
13. Ziai WC, Tuhim S, Lane K, et al. A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III). *International Journal of Stroke* 2014; **9**(4): 536-42.
14. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975: 103-15.
15. Weir CJ, Lees KR. Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. *Statistics in Medicine* 2003; **22**(5): 705-26.
16. Morgenstern L, Hemphill 3rd J, Anderson C, et al. American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010; **41**(9): 2108-29.

17. Broderick J, Connolly S, Feldmann E, et al. American Stroke Association Stroke Council; American Heart Association/American Stroke Association High Blood Pressure Research Council; Quality of Care and Outcomes in Research Interdisciplinary Working Group. 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. *Circulation* 2007; **116**(16): e391-413.
18. Mould WA, Carhuapoma JR, Muschelli J, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. *Stroke* 2013; **44**(3): 627-34.
19. Morgan TC, Dawson J, Spengler D, et al. The modified Graeb score an enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. *Stroke* 2013; **44**(3): 635-41.
20. Mattle HP, Raabe A. CLEAR Intraventricular Hemorrhage More Than a Glimmer of Hope. *Stroke* 2011; **42**(11): 2999-3000.
21. TEASDALE GM, PETTIGREW LE, Wilson JL, MURRAY G, JENNETT B. Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. *Journal of Neurotrauma* 1998; **15**(8): 587-97.
22. Hinson HE, Melnychuk E, Muschelli J, Hanley DF, Awad IA, Ziai WC. Drainage efficiency with dual versus single catheters in severe intraventricular hemorrhage. *Neurocritical Care* 2012; **16**(3): 399-405.
23. Vespa PM, Martin N, Zuccarello M, Awad I, Hanley DF. Surgical trials in intracerebral hemorrhage. *Stroke* 2013; **44**(6 suppl 1): S79-S82.
24. Selker HP, Oye KA, Eichler HG, et al. A proposal for integrated efficacy-to-effectiveness (E2E) clinical trials. *Clinical Pharmacology and Therapeutics* 2014; **95**(2): 147-53.

Table Notes and Figure Legends

Table Notes

Table 1. Demographic and Baseline Subject Characteristics by Group.

Table 2. Treatment Variables by Group. Additional Outcome Variable Data are Included as Table S4 in the Supplementary Materials.

Table 3. mRS Score Frequencies for the 30, 180, and 365 Day Time Points. The 180-Day Data Represent the Primary, Unadjusted Outcome. Corresponding eGOS Data for the Same Time Points Can Be Seen in Supplemental Table S3. In the alteplase group, one subject who was initially thought to be lost to follow-up at day 30 was located and evaluated at day 180.

Table 4. SAEs by treatment group. This listing shows fewer neurologic, respiratory, and sudden deaths (found in the MedDRA general disorders classification) in the alteplase group. This is consistent with the hypothesis that early removal of blood corrects a severe life threatening cerebral anatomic defect and possibly limits the structural brain injury as well as limits the effects of immobility on cardiorespiratory risks inherent with structural brain injury.

Figures Legends

Figure 1. CONSORT diagram. The CONSORT diagram summarizes the number of subjects that progressed through the enrollment, allocation, and follow-up periods of the trial. In the alteplase group, one subject who was initially thought to be lost to follow-up at day 30 was located and evaluated at day 180.

Figure 2. Outcome dichotomies of mRS (left panel; scores range from 0 [no disability] to 6 [death]) and eGOS (right panel; scores range from 8-upper good recovery to 1-death) scores at 30 and 180 days by treatment.

The left panel blue lines indicate the differences in proportion of 180-day mRS ≤ 3 (45% in saline vs. 48% in alteplase; $p=0.477$) and deceased subjects (30% in saline vs. 19% in alteplase; $p=0.09$).

Figure 3. Kaplan-Meier survival estimates with truncation at 193 days for late and missed 180-day visits ($n=36$), which corresponds to the longest “in-window” 180-day visit. Estimated survival probabilities were higher throughout 180 days of follow-up with alteplase compared to the saline group ($p=0.006$).

Table 1

	Alteplase (N=249)	Saline (N=251)
Demographic variables		
Age in Years: Median [IQR]	59 [51, 66]	59 [51, 67]
Gender: Female: no. (%)	105 (42)	117 (47)
Race		
White: no. (%)	144 (58)	161 (64)
African American: no. (%)	92 (37)	78 (31)
American Indian or Alaskan Native: no. (%)	0 (0)	1 (<1)
Other: no. (%)	13 (5)	11 (4)
Ethnicity: Hispanic/Latino: no. (%)	28 (11)	32 (13)
Baseline variables		
Tobacco Use: no. (%)	73 (29)	59 (24)
Cocaine Use: no. (%)	12 (5)	18 (7)
Anticoagulated at Registration: no. (%)	20 (8)	29 (12)
Antihypertensive Med Compliant (self-report): no. (%)	168 (67)	202 (80)
Hyperlipidemia Med Compliant (self-report): no. (%)	240 (96)	245 (98)
On Antiplatelet at Registration: no. (%)	56 (22)	72 (29)
Randomization MAP: Median [IQR]	96 [86, 106]	94 [86, 104]
Randomization GCS [†] Total: Median [IQR]	10 [7, 13]	9 [7, 12]
Randomization NIHSS: Median [IQR]	(N=231) 19 [11, 32]	(N=232) 20 [11, 35]
Stability CT (last CT prior to enrollment)		
IVH Volume (mL): Median [IQR]	21.2 [12.6, 36.1]	22.4 [12.7, 39.1]
ICH Volume (mL): Median [IQR]	8.2 [2.8, 15.2]	7.2 [2.3, 14.7]
Index Clot Location		
Thalamus: no. (%)	149 (60)	144 (57)
Primary IVH: no. (%)	18 (7)	27 (11)
Ictus to Hospital Arrival (hrs.): Median [IQR]	1.5 [0.8, 3.4]	1.5 [0.8, 3.6]
Ictus to 1 st CT (hrs.): Median [IQR]	2.3 [1.3, 4.6]	2.3 [1.4, 5.2]
Ictus to 1 st EVD (hrs.): Median [IQR]	7.0 [4.5, 11.8]	7.9 [5.0, 12.0]
Ictus to Stability CT (hrs.): Median [IQR]	43.0 [25.4, 58.9]	44.0 [28.2, 57.0]
Ictus to Randomization (hrs): Median [IQR]	51.8 [36.4, 65.8]	52.2 [41.2, 66.8]

Table 2

	Alteplase (N=249)	Saline (N=251)	p-value
Treatment Variables			
Randomization to 1 st Dose (hrs.): Median [IQR]	3.0 [1.7, 5.3]	3.1 [1.7, 5.7]	0.62
Total number of Doses: Median [IQR]	5 [3, 8]	12 [9, 12]	<0.001
Duration of Dosing (days): Median [IQR]	1 [1, 2]	4 [3, 4]	<0.001
Randomization to EOT (days): Median [IQR]	2.5 [1.8, 3.7]	4.7 [4.0, 5.1]	<0.001
EOT IVH Volume (mL): Median [IQR]	5.9 [1.9, 13.0]	11.5 [5.8, 23.1]	<0.001
Time to Open Ventricles (days): Median [IQR]	2 [2,3]	5 [3,7]	<0.001
ICP ≥20 mmHg: Mean proportion of events (mean of patient-specific proportions)	9.8	10.2	0.45
CPP <70 mmHg was lower with alteplase: no. (%)	644(7)	867(9)	<0.001
One or more ICP Therapy(ies): no. (%)	67 (27)	77 (31)	0.35
Dual EVD Placed: no. (%)	66 (27)	71 (28)	0.66
Day 0-180 Bacterial Ventriculitis: no. (%)	17 (7)	31 (12)	0.05
Symptomatic Bleeding ≤72 hr. post Last Dose: no. (%)	6 (2)	5 (2)	0.77
SAEs: no. (%)	121 (49)	158 (63)	0.002
Days in ICU: Median [IQR]	14 [11, 21]	15 [12, 22]	0.10
Withdrawal of Care: no. (%)	27 (11)	30 (12)	0.70
Ventilator Support: no. (%)	184 (74)	192 (76)	0.50
Pressor/Inotrope use: no. (%)	60 (24)	63 (25)	0.79
Ventriculoperitoneal Shunt: no. (%)	46 (18)	44 (18)	0.78

†Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma)

Table 3

mRS	Visit and Treatment							
	30 days				180 days			
	Saline (n=249)		Alteplase (n=245)		Saline (n=245)		Alteplase (n=246)	
0	4	1.61%	2	0.82%	11	4.49%	6	2.44%
1	2	0.80%	4	1.63%	13	5.31%	19	7.72%
2	7	2.81%	17	6.94%	31	12.65%	34	13.82%
3	28	11.24%	27	11.02%	55	22.45%	58	23.58%
4	46	18.47%	51	20.82%	41	16.73%	41	16.67%
5	126	50.60%	122	49.80%	21	8.57%	42	17.07%
6	36	14.46%	22	8.98%	73	29.80%	46	18.70%
Total	249	100.00%	245	100.00%	245	100.00%	246	100.00%

Table 4

Body System	Alteplase	Saline
Blood and lymphatic disorders	0	1
Cardiac disorders	7	14
Gastrointestinal disorders	4	1
General disorders and admin site conditions	22	34
Hepatobiliary disorders	1	0
Infections, non-neurologic	12	6
Injury, poisoning and procedural complication	5	3
Investigations (laboratory)	0	1
Metabolism and nutrition disorders	0	1
Musculoskeletal & connective tissue disorders	0	2
Nervous system disorders	40	53
Psychiatric disorders	1	2
Renal and urinary disorders	2	2
Respiratory, thoracic & mediastinal disorders	22	33
Surgical and medical procedures	1	1
Vascular disorders	4	4
Total	121	158
Percentage	48.6%	62.9%

p=0.0016