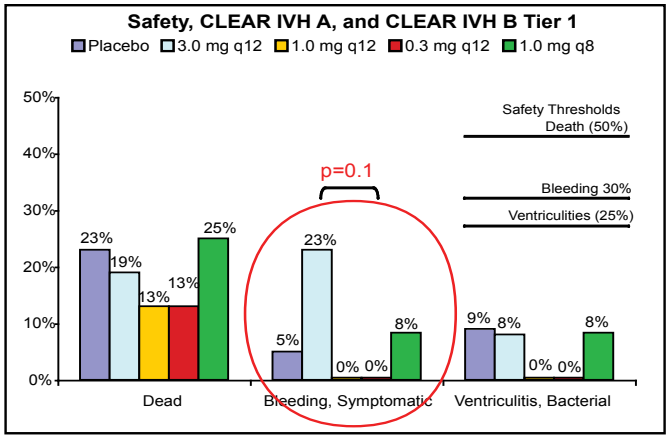
The CLEAR-IVH study enrolled patients aged 18-75 years with IVH within 12 hours of symptom onset who had extraventricular drainage per medical management. Patients with infratentorial intracerebral hemorrhage (ICH), surpratentorial ICH>30 cc, unclipped aneurysm, or active internal bleeding; who were on heparin >10,000 U/day or coumadin; or who had major medical conditions were excluded. Once they were considered stable (ie, after 6 hours and repeat CT that demonstrated no clot enlargement), patients gave informed consent and were assigned in a 1:1 ratio to either recombinant tissue plasminogen activator (rt-PA) or placebo. Dose escalation was subsequently performed in three other tiers: 0.3 mg Q12h, 1.0 mg Q12h, and 1.0 mg Q8h. If the investigator believed it was necessary, a second external ventricular drain (EVD) was allowed in cases of a trapped ventricle or intractable intracranial pressure.

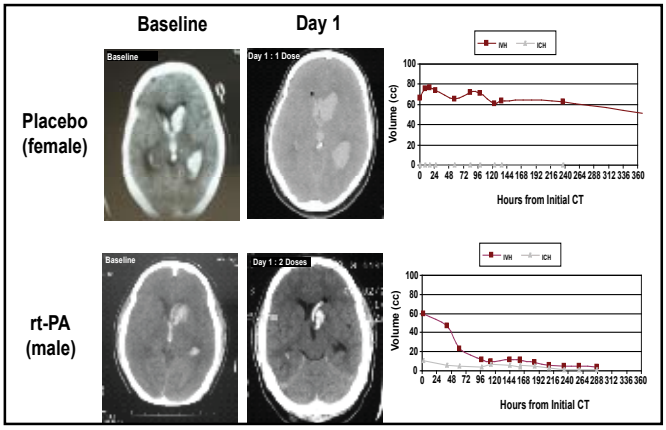
Twenty-two patients were treated with placebo and 88 with rt-PA. The bleeding threshold of 30% was never approached in any tier (Figure 1). "Cases treated with rt-PA had very dramatic clearance of the ventricles," said Dr. Awad (Figure 2). The entire cohort demonstrated a significantly faster clearance when treated with rt-PA compared with placebo ($p<0.05$). There was no relationship between dose group and overall clearance; however, there was a significant relationship between dose and clearance of the third and fourth ventricles ($p=0.01$). Modified Rankin scale data displayed a trend toward better outcomes in the treated group at 30, 90, and 180 days post-injury. Patients with rt-PA treatment had a lower number of treatment days (7.5 vs 12). For the safety phase (initial 48 subjects), only one rt-PA patient needed three EVDs, as opposed to seven patients in the placebo group.

Figure 1. 1^0 Endpoint Comparison: Safety, CLEAR A & B –IVH Trials.



CLEAR-IVH Investigators

Figure 2. Comparison Treatments: Baseline and Day 1.



CLEAR-IVH Investigators

When examining data from large clots in trapped ventricles, placement of a second catheter led to better clearance. "This clotbuster works, but you have to put the catheter in the right place," commented Dr. Awad. Based on the second catheter data, the surgeon's committee suggested that dual catheters be considered for large IVH, and that image-guided placement of the second catheters be utilized. A large phase 3 randomized, placebo-controlled trial of 500 subjects has been planned and will hopefully start later this year. For more information regarding this clinical program, visit www.clearivh.com.

Results of EPITHET

Intravenous recombinant tissue plasminogen activator (tPA) is recommended for the treatment of acute ischemic stroke within the first 3 hours of stroke onset. However, some randomized controlled trials have suggested that tPA might improve clinical outcome beyond the established 3 hour time limit. The objective of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was to evaluate the effect of the administration of tPA 3-6 hours after stroke onset as measured by echoplanar magnetic resonance imaging (MRI), diffusion-weighted MRI (DWI), and perfusion-weighted MRI (PWI). Because the probability of infarction depends on the severity and duration of hypoperfusion in the ischemic penumbra (the salvageable area around the irreversibly damaged infarct core), measurement of the mismatch between the larger PWI and smaller DWI lesion area can be used to estimate the salvageable tissue in the penumbra.

Prof. Stephen M. Davis, Royal Melbourne Hospital, Melbourne, Australia, presented data from the EPITHET study, which examined the effects of tPA on lesion growth and reperfusion as well as clinical outcomes in patients with acute hemispheric ischemic stroke. Mismatch was defined as PWI (T_{max} delay ~2 seconds) >20% and over 10 mL greater than the DWI lesion volume. The primary endpoint was infarct growth between baseline DWI and the Day 90 T2 lesion in mismatch patients. Other endpoints included reperfusion, recanalization, symptomatic intracranial hemorrhage, good neurological outcome, and good functional outcome.

Mismatch was present in 86% of patients. Arterial occlusion was present in 62% (54/87) of those with an adequate baseline MRI. The study did not meet its primary endpoint, which was to show that tPA could significantly reduce infarct growth in the area of the brain affected by the stroke as shown by MRI. The geometric mean infarct growth was 1.24 with tPA and 1.78 with placebo (p=0.24). Reperfusion, which was more common with tPA than with placebo, occurred in 39% of mismatch patients, and was associated with less infarct growth (p=0.001) and improved neurological (63% vs 32%; p=0.00l) and functional outcomes (73% vs 28%; p<0.0l).

Reperfusion was associated with improved clinical outcomes. tPA was associated with increased reperfusion and attenuated infarct size in stroke patients with mismatch. Recanalization was not increased by tPA. Although the study was too small to draw definitive conclusions on the effect of tPA, Prof. Davis suggested that the results provide support for further studies on extending the time window for thrombolysis treatment beyond 3 hours in some patients.

Control of Hypertension and Hypotension Immediately Post-Stroke Pilot Study

Elevated blood pressure (BP) levels are important in predicting primary and secondary prevention of stroke, but not much is known about the role of elevated BP in the acute stroke situation. The most recent American Heart Association guidelines recommend that emergency administration of antihypertensive agents be withheld unless the diastolic blood pressure is >120 mm Hg or the systolic blood pressure (SBP) is >220 mm Hg.

Prof. John Potter, University of East Anglia, Norwich, UK, presented data from the Control of Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) pilot study, which assessed the safety and effectiveness of lowering BP following acute stroke in patients aged >18 years with symptom onset <36 hours lasting more than 60 minutes, a clinical diagnosis of suspected stroke (neuroimaging required within 72 hours of randomization), and SBP >160 mm Hg. Subjects were randomly assigned to receive lisinopril (n=57; dose range 5-15 mg), labetalol (n=56; dose range 50-150 mg BID) or matching placebo (n=59) for 14 days. BP was measured at 30-minute intervals for 8 hours, then at 24 hours and 2 weeks. Treatment dose was administered orally and titrated at 4 and 8 hours in non-dysphagic patients, while dysphagic patients received sublingual lisinopril or intravenous labetalol during the first 3 days, then either orally or via NG/PEG tube. The primary study endpoint was the proportion of dead/dependent patients (defined as a modified Rankin Scale [mRS] of >3 at 2 weeks post-stroke). Secondary endpoints included casual BP changes (at 24 hours and 2 weeks), treatment discontinuations and withdrawals, serious adverse events (SAEs), early (<72 hours) neurological deterioration (NIHSS increase ≥4/death), fatal and non-fatal stroke recurrence, and mortality at 3 months.

The active treatment group had a greater decline in SBP within the first 24 hours compared with placebo (21 mm Hg, 95% CI 17-25 vs 11 mm Hg, 95% CI 5-17, respectively; p=0.004). Significant differences in SBP declines between patients on active treatment versus those receiving placebo continued at 2 weeks (31 mm Hg vs 24 mm Hg, respectively; p<0.05). Neither active treatment was associated with deterioration in neurological status at 72 hours. Discontinuations, withdrawals, and adverse events were similar in the active and placebo treatment groups. There was no difference in death/dependency at 2 weeks between the active treatment group (61%) and the placebo group (59%; p=0.82). There were borderline reductions in 90-day mortality in favor of active treatment (p=0.05; Hazard Ratio 2.2; 95% CI 1.0-5.0), but the small number of events precluded firm conclusions.

The CHHIPS pilot data suggest that early use of anti-hypertensives following acute strokes significantly lowers BP compared with placebo without causing serious adverse effects or an early increase in stroke severity and may reduce long-term mortality. These results need to be confirmed in larger trials.