Cynics may consider that review of emergent stroke therapies in 2007 is likely to make for quick reading—it is certainly true that many high profile trials reported unexpected neutral outcomes. However, although these disappointments made for headline medical news, there were still a number of encouraging results of novel acute therapies.

The first “casualty” of the year was neuroprotection. The free radical trapping agent NXY-059 had been consistently shown to reduce infarct size and improve functional outcomes in published reports of animal models. The first phase III study in humans (SAINT) was positive, reporting a statistically significant improvement in global disability (Figure). Unfortunately, the follow up SAINT II trial did not confirm this result (Figure). This randomized placebo-controlled study of 3306 ischemic stroke patients up to 6 hours from ictus demonstrated no significant improvement in the primary end point of day 90 modified Rankin score (mRS). Subgroup analyses also failed to replicate the previous finding of reduced hemorrhagic transformation rate in patients treated with thrombolytic.

Although the result was disappointing, the trial itself was rigorous and it optimized statistical analyses to describe functional outcomes across the treatment groups. A clear message from the SAINT trials is that even large-scale meticulously planned trials are subject to the play of chance, and that initial positive results require verification with a second adequately powered study. These themes have been echoed in other acute stroke trials throughout the year.

As the European Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) confirmed safety and efficacy of intravenous thrombolysis in routine practice, the stroke community were already advancing knowledge on novel approaches to reperfusion. The second Desmoteplase in Ischemic Acute Stroke (DIAS II) study sought to build on the success of previous studies using the fibrin specific plasminogen activator desmoteplase. The aim was to target therapy to those most likely to benefit by including only patients with perfusion-diffusion mismatch of at least 20% total infarct volume or equivalent CT-perfusion findings. In a cohort of patients 3 to 9 hours after event, placebo was tested against intravenous boluses of 90 μg/kg and 125 μg/kg desmoteplase. In contrast to previous results, no benefit was found from desmoteplase; in fact patients treated at highest dose showed a trend toward excess mortality.

The reasons for this neutral result remain unclear and may relate to the active agent, to the imaging based protocol, or to statistical underpowering—at 186 patients this was still a small trial. It seems unlikely that patients selected for persistence of penumbra 3 to 9 hours after stroke will show a greater response to thrombolysis than we achieve with rapid alteplase use. Groups of 60 patients are too small to confirm treatment effects comparable to those of alteplase when used under optimal conditions. The excess mortality in the higher desmoteplase dosage group seems unlikely to relate directly to desmoteplase as, of the 14 deaths, 9 were considered nonneurological and 9 occurred 1 week or later after treatment. Were the DIAS trialists simply victims of “significant” bad luck?

At present the future of desmoteplase is unclear. However, the evidence base for using penumbral imaging to target acute therapies continues to grow. The DEFUSE study successfully used MRI imaging to predict patients likely to benefit from tPA in the 3- to 6-hour time period, a result confirmed in a recent analysis of pooled data from 5 European centers.

Intraarterial delivery of thrombolytic has theoretical advantages over intravenous administration, including local delivery of agent and reduced systemic effects. It is almost a decade since the PROACT-II study first suggested efficacy of intraarterial thrombolysis. A confirmatory trial was never completed, although many centers continued to use intraarterial lytics for patients ineligible for standard intravenous therapy. The MELT study (MCA Embolism Local fibrinolytic intervention Trial) helps reassure us that the intraarterial approach represents a viable treatment option. This prospective trial randomized 114 patients, with confirmed occlusion of the M1 or M2 MCA segment and within 6 hours of event, to intraarterial urokinase or medical therapy. The trial was terminated early when intravenous tPA was licensed for clinical use in Japan. Although no difference was seen on primary end point (mRS 0 to 2; P=0.345; Figure), on prespecified secondary end point analysis an increase in patients showing excellent recovery was demonstrated (mRS 0 to 1; P=0.045; Figure) with no significant difference in mortality or hemorrhage.

Primary intracerebral hemorrhage (ICH) is a frustrating entity, with higher levels of mortality and disability than ischemic stroke and few proven therapies. Pilot results using the hemostatic agent recombinant factor VII (rFVII) had...
suggested efficacy, therefore results of the phase III FAST trial were eagerly awaited. In FAST, 821 patients diagnosed within 3 hours of onset were randomized to rFVII 20 μg/kg; 80 μg/kg or placebo. Despite a significant dose-dependent reduction in hematoma growth, no significant difference was seen in the main end point of the trial of death or severe disability at 90 days. These data seem counterintuitive: hematoma growth is known to be independently associated with poor outcome. Although this could represent further play of chance, analysis of trial subpopulations may offer explanation. According to baseline characteristics presented at the European Stroke Conference in 2007 (http://www.eurostroke.org/esc_gla_highlights.htm#oral%20presentation, accessed 24/10/07), more patients in the treatment arms had low conscious level, had evidence of left ventricular hypertrophy, and had intraventricular extension of hemorrhage—all powerful predictors of outcome. It should also be noted that unlike most acute stroke trials, FAST did not specify an upper age limit. It seems plausible that rFVII may only impact on outcomes in a younger, fitter cohort. We await publication of the full results so that we can consider all likely confounding influences.

The disappointing result of FAST must be balanced by promising work in other areas of ICH intervention. The INTERACT pilot study of blood pressure reduction has completed initial work demonstrating that rapid reduction of blood pressure to a target of 140/90 mm Hg is feasible and well tolerated. In recognition of the grave prognosis associated with intraventricular hemorrhage—i.e., one of the most refractory neurological complications of acute ischemic stroke, with mortality approaching 80%—decompressive hemicraniectomy has been practiced for many years. How to optimize hemicraniectomy has been a common theme in major recent European trials. However, only three adequately powered randomized controlled trials have compared hemicraniectomy to conservative management. Individually the trials provided a strong suggestion of benefit; however, it took this year’s pooled analysis to finally prove efficacy. Compared with best medical treatment, numbers needed to treat to prevent death, severe disability, or moderate disability are 2, 2, and 4, respectively. It is remarkable that in a complication of stroke previously considered fatal, intervention can leave a significant number of patients with a much higher degree of survival and function, as has been seen in the main endpoint of the trial of death or severe disability at 90 days. These data seem counterintuitive: hematoma growth is known to be independently associated with poor outcome. Although this could represent further play of chance, analysis of trial subpopulations may offer explanation. According to baseline characteristics presented at the European Stroke Conference in 2007 (http://www.eurostroke.org/esc_gla_highlights.htm#oral%20presentation, accessed 24/10/07), more patients in the treatment arms had low conscious level, had evidence of left ventricular hypertrophy, and had intraventricular extension of hemorrhage—all powerful predictors of outcome. It should also be noted that unlike most acute stroke trials, FAST did not specify an upper age limit. It seems plausible that rFVII may only impact on outcomes in a younger, fitter cohort. We await publication of the full results so that we can consider all likely confounding influences.

The disappointing result of FAST must be balanced by promising work in other areas of ICH intervention. The INTERACT pilot study of blood pressure reduction has completed initial work demonstrating that rapid reduction of blood pressure to a target of 140/90 mm Hg is feasible and well tolerated. In recognition of the grave prognosis associated with intraventricular hemorrhage—the CLEAR trials are testing local thrombolysis to aid clot resolution. Results to date are promising with a suggestion of markedly improved outcomes, and a definitive trial is being planned.

Physiological monitoring is an important component of acute stroke unit care. However, there is little evidence to guide treatment when parameters become deranged. The Glucose in Stroke Trial (GIST) was the first multicenter study of acute glycaemic intervention. Patients were randomized to treatment with a glucose-potassium-insulin infusion (GKI) to maintain euglycemia (capillary blood glucose 4 to 7 mmol/L) or placebo. Treatment conferred no benefit either in terms of 90-day mortality or functional outcome measures (Figure). This neutral result does not necessarily signal the end of glycaemic control in acute stroke; at 933 patients the study population fell well short of the planned 2355 and although statistically significant, the mean difference in glucose between GKI and control (0.57 mmol/L) was clinically modest, probably less than can be achieved with insulin infusion. Further trials targeting insulin therapy to patients with higher baseline sugars are ongoing.

Last year may have been disappointing for acute pharmacotherapy but was less so for nondrug intervention. The Wingspan stenting device was approved by the US Food and Drug administration in 2005 for use in intracranial stenosis. An NIH funded registry of 131 stenting outcomes reported a high degree of technical success (97%) and a low rate of early complications (4.6%). Observational data have also been reported for the mechanical embolectomy device—the MERCI retriever. The Multi-MERCI study of 164 patient outcomes again reported high rates of successful recanalization (57.8%) with few periprocedural complications (6.9%). Although new tools for use in acute stroke are welcome, these results should be treated with some caution. Voluntary registries and single arm studies are likely to overestimate benefits from treatment. There is now an ethical and scientific need to build on these observational data with prospective randomized controlled trials comparing intervention with best medical therapy.

Malignant MCA infarction is a feared complication of ischemic stroke, with mortality approaching 80%. Decompressive hemicraniectomy has been practiced for many years with case-series suggesting potential for good outcomes but no adequately powered randomized controlled trials. Three recent European trials have compared hemicraniectomy to conservative management. Individually the trials provided a strong suggestion of benefit; however, it took this year’s pooled analysis to finally prove efficacy. Compared with best medical treatment, numbers needed to treat to prevent death, severe disability, or moderate disability are 2, 2, and 4, respectively. It is remarkable that in a complication of stroke previously considered fatal, intervention can leave a substantial proportion with slight disability only (Figure). Having now proven benefit, we must better define optimal timing and patient characteristics. In these studies the population were relatively young (mean age 43 years, maximal age 60 years) and intervention was rapid (less than 48 hours from stroke).

So perhaps there were fewer successful emergent therapies in 2007 than we dared to hope. Regardless, we have still strengthened the evidence base for acute stroke care. Trials would not be performed if we were already certain of the outcome, and the major trials of last year, both positive and neutral, have greatly added to our knowledge of stroke care and reconfirmed that large scale well conducted clinical trials are possible in acute stroke. Medicine advances incrementally; we should celebrate the opportunities that await as much as the successes we have achieved.

Disclosures

K.R.L. was international principal investigator for the SAINT I trial and chaired the steering committee for the CHANT and SAINT I & II trials (AstraZeneca). He chaired the data monitoring committee for
DIAS, DEDAS, and DIAS-II trials (Forest, Paion). Both authors have participated in locally funded projects examining acute glycaemic control in stroke. Neither author has any specific conflict of interest in relation to the content of this article.

References


Keywords: acute care ■ acute stroke ■ clinical trials ■ hyperglycaemia ■ interventional neuroradiology ■ intracranial hemorrhage ■ neuroprotectant ■ thrombolysis