

Thrombolytic “clot-busting” therapy for stroke – summary of all trial data in 2012.

What is a stroke?

Most strokes are due to a blood vessel in the brain getting blocked by a clot, and are called “ischaemic” strokes. The other main type of stroke is caused by bleeding into the brain, and is called a haemorrhagic stroke. The outcome for ischaemic stroke is poor, with about a third of patients dying, a third being left dependent on others for basic routine daily care (like feeding and washing) and only a third being able to return to living independently without daily help.

Clot-busting drugs

The thrombolytic or “clot-busting” drug alteplase (rt-PA) has been tested in clinical trials in ischaemic stroke since the 1990s. Early trials were very cautious about which patients were included because of concerns about causing bleeding into the brain while dissolving the clots, but these early trials showed that alteplase improved patient recovery if given within three hours of stroke to highly selected younger patients. Therefore the licence only allowed alteplase to be used in a few patients. However, some trials tested alteplase treatment up to six hours after stroke and, although not conclusive, the results suggested that a much wider range of patients including older people could benefit, maybe even with treatment given as late as six hours after stroke.

The IST-3 trial and previous similar trials

The third International Stroke Trial (IST-3), designed to test alteplase treatment given to a wider range of patients, including those aged over 80, and up to six hours after stroke, published its results in May 2012. Along with this, we have put together the results of all the previous randomised clinical trials, to look at the overall outcomes. There are now 12 completed randomised controlled trials testing intravenous alteplase given up to six hours after stroke, including a total of 7012 patients. Viewed altogether, the results of these 12 trials are very consistent. They show that with alteplase treatment there is an early risk of bleeding into the brain which may cause death, but for the patients that do not suffer bleeding, alteplase increases survival, so that by three or six months after the stroke, there is no overall effect on death. Furthermore, in spite of this early risk of bleeding, alteplase substantially improves the patients’ ability to function independently. We also confirm that bleeding into the brain soon after treatment is the single biggest hazard, and have some more clues as to what might be causing that.

How big is the benefit?

For every 1000 patients who receive alteplase treatment within three hours of stroke, about 100 more will survive alive and independent than for 1000 patients not given alteplase; similarly, for patients treated within six hours of stroke with alteplase, about 50 more will be alive and independent than if they had not

received alteplase, and that is over and above any early increased risk of bleeding.

Who benefits?

IST-3 included many older patients, aged over 80 years, in contrast to previous trials, which excluded these patients. We can say that if treated within three hours with alteplase older people gain as much benefit as younger people, although there is some suggestion that the benefit is less in older people if the treatment is given nearer to six hours. Many of the patients in IST-3 were not eligible to be treated under the current strict licence (which is why they were in the trial; otherwise they would just have been treated conventionally). This analysis of all relevant trials shows that these IST-3 patients who mostly did not meet the current licence approvals got just as much benefit from alteplase as did the carefully selected patients that were included in the original trials in the 1990s and are covered by the current licence.

Act fast

What does this mean? It means that it is really important that any patient (or relative or friend of the patient) of any age who thinks that they might be having a stroke should get to hospital as quickly as possible. Alteplase treatment can only be given safely in a hospital that is set up to deliver it – patients need careful assessment by a stroke team, and they also need a brain scan to make sure that the stroke is not due to a bleed. Ambulance services, GPs, and hospital staff (stroke doctors, radiologists, nurses, pharmacists, i.e. everyone involved in the care pathway) should intensify their efforts to ensure that healthcare systems can deliver the earliest possible treatment with intravenous alteplase, equitably, for all patients that might benefit, no matter what time of day or night they arrive. Treatment should be given as fast as possible to all patients who are suitable, even the very elderly.

More research needed

Not everyone will benefit. Some people suffer the bleeding complication and some people just don't seem to get much benefit. We need to find out more about why some people bleed, and how to reduce this hazard, and increase the effectiveness of clot-busting treatment. So, a group of experts from all 12 completed clinical trials are getting together to share the data and do an analysis to find out which patients may benefit, or be at risk of harm, more precisely. There are also some new trials testing different doses of alteplase, or different clot-busting drugs, or different ways of assessing patients with scanning, to see how much brain tissue might still be alive before they get treatment, or to see if pulling the clot that is blocking the artery out through a small tube passed up through the blood vessel might also help. These trials should move ahead as fast as they possibly can to find out how to improve even more the very powerful benefits of this treatment.