Evidence Synthesis Ireland Fellowship Scheme 2021

Review Identification Form

Review Centre/Group Mentor

Cochrane Stroke/Professor Joanna Wardlaw, University of Edinburgh

Review title

Thrombolysis for acute ischaemic stroke

Review type

Cochrane review of effectiveness

Review details

Background

Stroke remains the second commonest cause of death, and commonest cause of dependency in adults worldwide. The thrombolytic drug *alteplase* was the first licenced treatment for acute ischaemic stroke (1997). The Cochrane Review of 'Thrombolysis for acute ischaemic stroke' has summarised all evidence on thrombolysis since Cochrane's inception, contributed to licencing *alteplase* for stroke treatment, underpinned numerous further trials, and changed guidelines and clinical practice worldwide. *Alteplase* is still the only licensed acute stroke treatment but the licences remain restricted, limiting patient access to an effective treatment. Furthermore, the treatment continues to be criticised by medical commentators in many countries.

The Review was last updated in 2014. Since then at least two further large trials of thrombolysis versus control (≈1200 participants) have been published, adding approximately 20% participants to the review. There is no other comprehensive meta-analysis of thrombolysis for stroke.

The topic is complex and controversial: the Cochrane Review has been closely scrutinised in the past by both critics and proponents of the treatment, and is likely to continue to be closely scrutinised. It is absolutely critical to ensure that the review is as accurate, complete, up to date, and nuanced in its interpretation as possible because clinicians need a balanced view of thrombolysis effectiveness and safety from all available evidence to maximise patient benefit.

Objectives

To determine whether, and in what circumstances, thrombolytic therapy might be an effective and safe treatment for acute ischaemic stroke. We wished to determine whether:

1. thrombolytic therapy increases the risk of death:
    a. within the first two weeks of stroke; or
    b. at long-term follow-up;
2. thrombolytic therapy increases the risk of symptomatic or fatal intracranial haemorrhage, or symptomatic infarct swelling;
3. thrombolysis reduces the proportion of people dead or dependent at long-term follow-up, in spite of any early hazard, so that there is an overall net benefit.

PICO

P: participants with a definite acute ischaemic stroke (CT or magnetic resonance (MR) scanning having excluded intracranial haemorrhage prior to randomisation).

I: all types of thrombolytic drug, given in any dose, by the intravenous or intra-arterial route: urokinase (UK, also known as u-PA), recombinant pro-urokinase (rpro-UK), streptokinase (SK), recombinant tissue plasminogen activator (rt-PA) including duteplase, lumbrokinase (LK), and desmoteplase.
C: placebo/control
O: Primary outcome measures: death or dependency, as defined by modified Rankin score of 3 to 6, and death at the end of follow-up.
Secondary outcome measures:
- Deaths from all causes within the first seven to 10 days after treatment
- Symptomatic intracranial haemorrhage
- Fatal intracranial haemorrhage
- Deaths within the first seven to 10 days not due to intracranial haemorrhage
- Symptomatic infarct swelling (oedema)
- Deaths occurring between the end of the first seven to 10 days and three to six months
- Deaths from all causes during the whole trial follow-up period
- Poor functional outcome at the end of follow-up

Sensitivity analysis of outcomes where there are relevant outcome data such as death, SICH, dependency, and subgroups such as time to treatment, mild vs severe stroke, selection with various imaging parameters (CT vs MR, perfusion vs plain imaging, etc.)

Review current status

Previous version published. Update in planning stage but searches not yet updated

Any specific/desirable requirements for fellow (e.g. clinical expertise, methodological expertise)

The ability to: (1) quickly assimilate large amounts of information and data, (2) learn/apply systematic review methodology and Cochrane-specific software, and (3) work proactively as part of a geographically separated team. An interest in acute stroke would also be desirable.

Estimated start and completion dates

1 April 2021 – 31 May 2022