ISRCTN25765518 https://doi.org/10.1186/ISRCTN25765518

Imaging perfusion deficits and thrombolysis safety and efficacy in acute ischaemic stroke: the Third International Stroke Trial

Submission date
29/04/2004

Recruitment status
No longer recruiting

Registration date
02/07/2004

Overall study status
Completed

Last Edited
23/07/2021

Condition category
Circulatory System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
About 85% of strokes are ischemic strokes. Ischemic strokes happen when the arteries that supply the brain with oxygen become narrowed or blocked, causing severely reduced blood flow (ischemia). As we age, a gradual build-up of a sticky substance called plaque can occur in our arteries. When there is a lot of plaque, particularly with a rough or irregular surface, blood clots can develop, depriving the brain of oxygen and leading to an acute ischemic stroke (AIS). Fast diagnosis and treatment are essential in the treatment of AIS. Thrombolysis, also known as “clot busting”, is a drug treatment that breaks down clots, helping to restore the blood supply to the brain. Recombinant tissue plasminogen activator (rt-PA) is a thrombolytic agent which, when approved for use in Europe, was restricted for use in patients under 80 years old within three hours of stroke onset. The aim of this study is to find out whether treatment with rt-PA is still effective within six hours of stroke onset, and whether it is still effective in older patients.

Who can participate?
Adults who have had an ischaemic stroke within the past six hours.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive rt-PA at a dose of 0.9 mg per kg of body weight (up to a maximum dose of 90mg) intravenously (through a drip). Those in the second group do not receive any rt-PA treatment, but are treated in the same clinical environment as participants in group one. Participants in both groups are carefully monitored for seven days and the numbers of people who die or have further strokes are recorded. Participants are also followed up for 6 months in order to record to number who are alive and independent.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
This study is run from 156 hospitals in 12 countries across Europe, North America and Australia

When is the study starting and how long is it expected to run for?
April 2008 to December 2012

Who is funding the study?
1. The Health Foundation (UK)
2. Medical Research Council (UK)
3. Stroke Association (UK)
4. AFA Insurances (Sweden)
5. The Norwegian Research Council (Norway)
6. The Heart Foundation (Australia)
7. The Government of Poland (Poland)

Who is the main contact?
Professor Peter A. G. Sandercock

Contact information

Type(s)
Scientific

Contact name
Prof Peter A. G. Sandercock

Contact details
Department of Clinical Neurosciences
University of Edinburgh
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh
United Kingdom
EH4 2XU

Additional identifiers

Clinical Trials Information System (CTIS)
2004-000238-36

Protocol serial number
EME 08/43/52; IST399

Study information

Scientific Title
The Third International Stroke Trial (IST-3) of thrombolysis for acute ischaemic stroke: an international multicentre, randomised, controlled trial to investigate the safety and efficacy of treatment with intravenous recombinant tissue plasminogen activator (rt-PA) within six hours of onset of acute ischaemic stroke

Acronym

IST-3

Study objectives
The principal research questions to be addressed are:
1. Does thrombolysis with intravenous (iv) recombinant tissue plasminogen activator (rt-PA) up to six hours increase the number of independent survivors?
2. Does early treatment with iv rt-PA benefit a wider variety of patients than that defined by the current restricted licence (especially older people, who contribute the greatest proportion of the burden of stroke)?
3. What is the effect on deaths from all causes?

Link to EME project website: http://www.eme.ac.uk/projectfiles/084352info.pdf
Link to protocol: www.eme.ac.uk/projectfiles/084352protocol.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute ischaemic stroke

Interventions
In each collaborating hospital, the hospital co-ordinator will implement a written protocol for the immediate assessment of patients with suspected acute stroke. Patients will be 'fast-tracked' to the computerised tomography (CT) scanner in order to exclude intracranial haemorrhage as a cause of the stroke.

Consent will be sought from those patients with definite ischaemic stroke who can be treated within six hours of onset of stroke symptoms. After appropriate consent has been granted, patients will be entered in the trial by means of a telephone call to a central computer randomisation system. At the end of the call, once the patients details have been entered on the randomisation computer, the system will allocate the treatment.

Patients allocated active treatment will receive rt-PA in a dose of 0.9 mg per kg of estimated body weight up to a maximum of 90 mg. 10% will be given as an intravenous bolus over 1 - 2 minutes and the rest of the infusion will be given over the following 60 minutes.

Patients allocated control will be managed in the same clinical environment and as carefully monitored as those allocated rt-PA.

Patients will be closely monitored to detect any adverse events. Patients will have a repeat brain scan 24 hours after randomisation. Hospital events occurring within the first week will be recorded on a seven-day form.

The main follow-up will be at six months. The six month follow-up will be performed by postal administration of a questionnaire to measure functional status and health related quality of life. If a patient, who is known to be alive, does not respond to two requests to complete a postal questionnaire, disability status will be obtained by other appropriate means, usually a telephone interview but sometimes from the patients' general practitioner.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Recombinant tissue plasminogen activator (rt-PA)

Primary outcome(s)
Proportion of patients alive and independent at six months (Modified Rankin Scale score of 0, 1, or 2).

Key secondary outcome(s))
1. Events within seven days:
1.1. Deaths from any cause
1.2. Symptomatic intracranial haemorrhage (fatal or non-fatal)
1.3. Any intracranial haemorrhage (including asymptomatic bleeds on repeat computed tomography [CT])
1.4. Severe extracranial haemorrhage (i.e. fatal, severe enough to require transfusion or operation, or an absolute decrease in haemoglobin greater than 5 g/dl, or a decrease in haematocrit of greater than 15%, or bleeding associated with persistent or serious disability)
2. Status at six months:
2.1. Number of patients dead from any cause within six months
2.2. Number of patients making a complete recovery, and those who are alive but dependent (defined by the questions used in IST), Health Related Quality of Life (HRQoL), measured with the postal questionnaire version of the European quality of life (EuroQol)

Completion date
31/03/2010

Eligibility

Key inclusion criteria
Patients with mild, moderate or severe strokes are potentially eligible if the following criteria are met:
1. Symptoms and signs of clinically definite acute stroke
2. Time of stroke onset is known and treatment can be started within six hours of this onset
3. Computerised tomography (CT) or magnetic resonance imaging (MRI) brain scanning has reliably excluded both intracranial haemorrhage and structural brain lesions which can mimic stroke (e.g. cerebral tumour)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
3035

Key exclusion criteria
1. The patient has previously been randomised in IST-3
2. Major surgery, trauma (e.g. major fall at time of stroke) or gastrointestinal or urinary tract haemorrhage within the previous 21 days
3. Any known defect in coagulation, e.g.:
3.1. Currently on oral anticoagulants with an International normalised ratio (INR) greater than 1.3, or
3.2. Current treatment with heparin (unless activated partial thromboplastin time [APPT] within normal laboratory limits), or
3.3. Treatment with low molecular weight heparin or heparinoid, or
3.4. Treatment with Ximelagatran
4. Known defect of clotting or plaelet function (but patients on antiplatelet agents can be randomised)
5. The patient is female and of childbearing potential (unless it is certain that pregnancy is not possible) or breastfeeding
6. Hypo- or hyperglycaemia sufficient to account for the neurological symptoms; the patient should be excluded if their blood glucose is less than 3.0 or greater than 20.0 mmol/L ('stick testing' is a sufficiently accurate test for this purpose)
7. Symptoms considered likely to resolve completely within the next few hours (i.e., a transient ischaemic attack [TIA])
8. Patient has had a stroke within the previous 14 days or has had a treatment for acute ischaemic stroke with thrombolytic therapy within the past 14 days
9. Patient was already dependent in activities of daily living before the present acute stroke
10. Patient has other life threatening illness (e.g. advanced cancer) likely to lead to death within a few months
11. Likely to be unavailable for follow-up, e.g., no fixed home address
12. Patient has blood pressure less than 90 mmHg or greater than 220 mmHg or diastolic blood pressure less than 40 mmHg or greater than 130 mmHg

Date of first enrolment
01/04/2005

Date of final enrolment
31/03/2010

Locations

Countries of recruitment
United Kingdom

Scotland

Australia

Austria

Belgium

Canada

Italy

Norway

Poland

Sweden

Study participating centre
University of Edinburgh
Edinburgh
United Kingdom
EH4 2XU

Sponsor information

Organisation
University of Edinburgh (UK)

ROR
https://ror.org/01nrxwf90

Funder(s)

Funder type
Government

Funder Name
The Health Foundation (UK) (ref: 2268/1282)

Funder Name
Medical Research Council (MRC)/National Institutes of Health Research (NIHR) (UK) - Efficacy and Mechanism Evaluation (EME) Programme (ref: EME 08/43/52)

Funder Name
Stroke Association

Alternative Name(s)
TheStrokeAssociation, TheStrokeAssoc

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Funder Name
AFA Försäkring

Alternative Name(s)
AFA Insurance, AFA Insurance (Sweden)

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Sweden

Funder Name
Norges Forskningsråd

Alternative Name(s)

Forskningsrådet, Norwegian Research Council, Research Council of Norway, The Research Council of Norway

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Norway

Funder Name
The Heart Foundation (Australia)

Alternative Name(s)
The Heart Foundation, Steven S. Cohen Heart Fund, The Steven S. Cohen Heart Fund, THF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Funder Name
The Government of Poland (Poland)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	23/06/2012	Yes	No	
Results article	follow-up results	01/08/2013	Yes	No	
Results article	results	01/04/2014	Yes	No	

Results article	results	01/07/2014		Yes	No
Results article	results	01/12/2014		Yes	No
Results article	results	01/01/2015		Yes	No
Results article	results	01/01/2015		Yes	No
Results article	results	01/03/2015		Yes	No
Results article	results	01/05/2015		Yes	No
Results article	results	01/08/2015		Yes	No
Results article	results	01/09/2016		Yes	No
Results article	results	01/12/2016		Yes	No
Results article	results	01/02/2017		Yes	No
Results article	consent method results	22/07/2021	23/07/2021	Yes	No
Protocol article	protocol	17/06/2008		Yes	No
Other publications	validation of a prognostic model	01/04/2008		Yes	No
Other publications	update	30/11/2011		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes