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Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke

Submission date
24/10/2008

Recruitment status
No longer recruiting

Registration date
23/01/2009

Overall study status
Completed

Last Edited
25/09/2023

Condition category
Circulatory System

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

Plain English Summary
Background and study aims
The current guidelines for treating stroke recommend using a drug called clopidogrel or a combination of two drugs called aspirin and dipyridamole for stroke or a transient ischaemic attack (TIA, mini stroke). They are antiplatelet (blood thinning) medications and work by acting on cells in the blood called platelets and reducing the risk of another stroke by making the platelets less sticky. In this study we want to find out if intensive antiplatelet treatment using all three antiplatelet drugs is better than the current guideline treatment in preventing further strokes.

Who can participate?
Adults aged 50 or over at high risk of recurrent ischaemic stroke.

What does the study involve?
Patients will be randomly allocated to receive either current guideline treatment (clopidogrel alone or combined aspirin and dipyridamole) or to have all three medications (aspirin, dipyridamole and clopidogrel) for 1 month. All other medications will be continued as normal. At the first visit (Day 0) the trial medications are started, questions asked about stroke and medical history, and a medical examination is performed. A small sample of blood will be taken. On Day 7 the trial team will see the patient to see how they are managing with the trial medications. This appointment may be in hospital or at home. A second blood test is also performed. On Day 35 the trial team will see how the patient has recovered from their stroke by doing a neurological examination and also do another blood test. This appointment may be in hospital or at home. On Day 90 patients will complete a questionnaire over the telephone to see how well patients have recovered from their stroke. This involves a short memory test and questions about quality of life and mood. If a telephone call is not possible, a questionnaire will be sent out to the patient in the post.

What are the possible benefits and risks of participating?
The combination of three drugs may reduce the chance of having another stroke soon after the first one. However, this is not guaranteed and there may be no benefit. The information from this study will help in deciding the best treatments for stroke. The main risk is that all three drugs together could cause bleeding. The total amount of time on all three medications will only

be 1 month. The bleeding is usually minor, such as bruising in the skin, but can occasionally be major. In the first part of the study, two patients out of every 100 patients had a major bleeding episode. We expect that the risk will be slightly lower in those patients on guideline treatment and slightly higher in those on intensive antiplatelet treatment. All the antiplatelet drugs used in the TARDIS trial are commonly prescribed in stroke patients and so the side effects are well described. Clopidogrel may cause acid indigestion, diarrhoea or abdominal pains. Dipyridamole may cause headache, dizziness and indigestion. Aspirin may cause indigestion, buzzing or ringing in the ears, stomach ulcers or anaemia. Like all drugs, antiplatelet medications may occasionally cause allergic reactions such as skin rash.

Where is the study run from?
The University of Nottingham (UK)

When is the study starting and how long is it expected to run for?
March 2009 to September 2017

Who is funding the study?
NIHR Health Technology Assessment Programme - HTA (UK)

Who is the main contact?
TARDIS Trial Coordinating Office
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Study website
http://www.tardistrial.org

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2007-006749-42

IRAS number

ClinicalTrials.gov number
NCT01661322

Secondary identifying numbers
1.1

Study information

Scientific Title
Safety and efficacy of intensive versus guideline antiplatelet therapy in high-risk patients with recent ischaemic stroke or transient ischaemic attack: a randomised controlled trial

Acronym
TARDIS

Study hypothesis
To perform a randomised trial assessing the efficacy, safety and tolerability of adding clopidogrel to aspirin and dipyridamole in patients with recent ischaemic stroke or transient ischaemic attack (TIA) and who are at high risk of recurrence. The study will comprise a start-up phase of 350 patients to then expand into a larger trial of 5000 patients assessing the efficacy, safety and health economics of this approach. A secondary hypothesis is that ordinal vascular outcomes will be superior to binary events; the trial is the first to be designed using these outcomes, thus allowing both the frequency and severity of events to be assessed in one measure. Ordinal outcomes include bleeding, adverse events, stroke, myocardial infarction (MI), composite vascular events, and take the form: fatal event/non-fatal severe event/mild event/no event. Conventional binary outcomes will also be measured.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South East MREC approved the protocol (v1.1) on 09/01/2009. Amendments to the protocol (v1.2) were approved on 16/06/2009

Study design
Multicentre parallel-group prospective randomized open-label blinded-endpoint controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Condition
Ischaemic stroke, transient ischaemic attack (TIA)

Interventions
Current interventions as of 19/06/2014:
Intensive versus guideline antiplatelet therapy will be given for 28 to 30 days along with standard best care (including lifestyle advice, BP and lipid lowering). Randomised patients will receive clopidogrel (loading dose 300 mg, then 75 mg daily), aspirin (loading dose 300 mg, then 50-100 mg daily), and dipyridamole (between 225 and 450 mg daily), or guideline antiplatelet therapy (aspirin and dipyridamole or clopidogrel, doses as above).

Previous interventions:
Aspirin (loading dose 300 mg, then 75 mg daily), clopidogrel (loading dose 300 mg, then 75 mg daily) and dipyridamole (modified release 200 mg twice daily) versus dual antiplatelet therapy (aspirin and dypyridamole, doses as above) randomised 1:1. Dysphagic patients with enteral access will take crushed aspirin (or rectal aspirin), crushed or liquid dipyridamole (75 mg three times daily [tds]), and crushed clopidogrel (if so randomised). Patients having a headache on dipyridamole will have the dose weaned up from daily MR 200 mg or standard release 75 mg once daily [od] to MR 200 mg twice daily [bd]. Fixed dose combinations of aspirin and dipyridamole can also be used. Open-label clopidogrel will be given for 30 days on top of routine AD (to cover the period of maximum risk of recurrence) and standard best care (including lifestyle advice, BP and lipid lowering). Patients will be recommended to take gastro-prophylaxis against upper gastrointestinal bleeding (proton pump inhibitor/histamine 2 receptor antagonist + H. pylori eradication), as is standard.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Clopidogrel, aspirin, dipyridamole

Primary outcome measure
The trial will assess ordinal stroke severity at 90 days assessed as a level ordinal outcome: mRS 6 = fatal-5-4-3-2-1-0-TIA-no stroke; this approach allows for smaller sample sizes than for binary outcomes such as stroke/no stroke. The start-up phase will also assess ordinal bleeding (fatal /major/minor/none) at 35 days (end of treatment) as adjudicated by an independent blinded panel.

Secondary outcome measures
1. Secondary outcomes at 35 and 90 days:
1.1. Binary stroke
1.2. Ordinal stroke (fatal stroke/non-fatal stroke/no stroke)
1.3. Binary myocardial infarction
1.4. Ordinal myocardial infarction (fatal MI/non-fatal MI/no MI)

1.5. Binary composite vascular outcome (non fatal MI and stroke, vascular death)
1.6. Ordinal composite vascular outcome
1.7. Composite stroke, TIA, acute coronary syndromes and all cause death
2. Secondary outcomes at 90 days:
2.1. Function (modified Rankin Scale [mRS], Barthel Index)
2.2. Cognition (Telephone Interview for Cognitive Status [TICS]/animal naming)
2.3. Quality of life (EuroQoL/EQ-5D instrument)
2.4. Mood (Zung)
2.5. Disposition (home, institution, dead)
2.6. Days at home
2.7. Economic activity
3. Tolerability: Proportion of patients completing 28 days of randomised treatment
4. Feasibility: Recruitment rate per week
5. Safety measures at 35 and 90 days:
5.1. Death
5.2. Binary major bleeding (fatal, symptomatic, causing fall in haemoglobin of greater than 2 g/l, or leading to transfusion of greater than 2 units of blood/red cells)
5.3. Binary minor bleeding (e.g. bruising)
5.4. Binary all bleeding
5.5. Symptomatic intracerebral haemorrhage
5.6. Major extracranial bleeding
5.7. Binary serious adverse events
5.8. Ordinal adverse events (fatal/serious/other/none)
5.9. Full blood count (at 35 days)
5.10. Thrombotic thrombocytopenic purpura
5.11. Granulocytopenia

Data from two substudies will power substudies within the future main trial:
1. Transcranial Doppler: TCD recordings will be performed from the middle cerebral artery (MCA) at baseline and day 3 ± 1
2. Platelet function: platelet expression of P-selectin will be used to monitor platelet effects in patients. Blood will be taken from all patients at baseline and day 7 ± 1.

Overall study start date
01/03/2009

Overall study end date
30/09/2017

Eligibility

Participant inclusion criteria
Current inclusion criteria as of 19/06/2014:
Adults at high risk of recurrent ischaemic stroke:
1. Age ≥50 years
2. Within 48 hours of ictus (24-48 hours if thrombolysed)
3. TIA with limb weakness and/or dysphasia lasting between 10 minutes and <24 hours with no residual symptoms and presenting with any of the following:
3.1. ABCD2 score >4
3.2. Crescendo TIA
3.3. Already on dual antiplatelet therapy with aspirin and dipyridamole

3.4. Positive neuroimaging evidence to support the new event, ischaemic stroke on MR diffusion imaging

Notes:
1. Patients who are on monotherapy e.g. aspirin alone, or clopidogrel alone, or dipyridamole alone, are eligible for recruitment. Similarly, patients who are on combined therapy aspirin + dipyridamole, are eligible for recruitment if they fulfil the above criteria.
2. Patients with posterior fossa events are eligible if they fulfil the above criteria.
3. Neuroimaging is not necessary for transient ischaemic attack. Crescendo TIA is >1 TIA in 1 week and the onset time of last TIA is taken as time of ictus.
4. Ischaemic non-cardioembolic stroke presenting with any of the following:
4.1. Ongoing limb weakness of more than 1 hour duration; and/or
4.2. Ongoing dysphasia of more than 1 hour duration; and/or
4.3. Resolved limb weakness of more than 1 hour duration with ongoing facial weakness; and/or
4.4. Ongoing isolated hemianopia of more than 1 hour duration with positive neuroimaging evidence to support the new event (e.g. ischaemic stroke in the occipital lobe) and/or
4.5. Limb weakness that resolves between 24-48 hours after onset; and/or
4.6. Dysphasia that resolves between 24-48 hours after onset; and/or
4.7. Positive neuroimaging to support the new ischaemic event with MR diffusion.
4.8. Already on combined dual antiplatelet therapy (aspirin + dipyridamole)
Neuroimaging is essential for ischaemic stroke to exclude intracranial haemorrhage and a non-stroke diagnosis. If the patient received thrombolysis, a post-thrombolysis/pre-TARDIS scan needs to be done to exclude new thrombolysis-associated bleeding prior to enrolment. Typically this is done routinely as standard of care, but if it is not done, then it must be done prior to enrolment.
5. Patients thrombolysed for stroke with full recovery in less than 24 hours from the onset of symptoms are eligible for inclusion providing neuroimaging post thrombolysis excludes intracranial haemorrhage.
6. Informed consent from participant. If the participant is unable to give meaningful consent e.g. due to dysphasia, confusion, or reduced conscious level, proxy consent may be obtained from a relative, carer or legal representative.

Inclusion criteria from 25/03/2010 to 19/06/2014:
Adults at high risk of recurrent ischaemic stroke:
1. Acute non-cardioembolic ischaemic stroke (<48 hours of onset). All strokes must have motor weakness or dysphasia at the time of randomisation.
2. Acute TIA (<48 hours of onset) with one or more of: crescendo TIA (>1 TIA within 1 week), and /or admitted on dual antiplatelet therapy (aspirin/dipyridamole, aspirin/clopidogrel, clopidogrel /dipyridamole), and/or with an ABCD2 score >4. All TIAs must have motor weakness and/or dysphasia lasting at least 10 minutes
3. Meaningful consent, or consent from a relative, carer or legal representative if the patient is unable to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level)

Inclusion criteria at time of registration:
Adults of either sex at high risk of recurrent ischaemic stroke:
1. Acute non-cardioembolic ischaemic stroke (less than 48 hours of onset)
2. Acute TIA (less than 48 hours of onset) with one or more of: crescendo TIA (greater than one TIA within 1 week), and/or admitted on dual antiplatelet therapy (aspirin/dipyridamole, aspirin /clopidogrel, clopidogrel/dipyridamole), and/or with an ABCD2 score greater than 5 (stroke rate at 13 weeks greater than 10%)

Participant type(s)
Patient

Age group
Adult

Lower age limit
50 Years

Sex
Both

Target number of participants
Start-up phase: 350; main phase: 4100

Participant exclusion criteria
Current exclusion criteria as of 19/06/2014:
1. Age <50
2. Isolated sensory symptoms or vertigo/dizziness or facial weakness
3. Isolated hemianopia without positive neuroimaging evidence
4. Intracranial haemorrhage
5. Baseline neuroimaging showing parenchymal haemorrhagic transformation (PH I/II) of infarct, subarachnoid haemorrhage or other non-ischaemic cause for symptoms
6. Presumed cardioembolic stroke (e.g. history or current AF, myocardial infarction within 3 months)
7. Participants with contraindications to, or intolerance of, aspirin, clopidogrel or dipyridamole.
8. Participants with definite need for treatment with aspirin, clopidogrel or dipyridamole individually or in combination (e.g. aspirin and clopidogrel for recent MI/acute coronary syndrome)
9. Definite need for full dose oral (e.g. warfarin, dabigatran) or medium to high-dose parenteral (e.g. heparin) anti-coagulation. NB Low-dose heparin for DVT prophylaxis is allowed
10. Definite need for glycoprotein IIb-IIIa inhibitors
11. Patients who have received thrombolysis within 24 hours
12. No enteral access
13. Pre-morbid dependency (mRS>2).
14. Severe high BP (BP >185/110 mmHg).
15. Haemoglobin less than 10 g/dL
16. Platelet count more than 600 x 109 /L or less than 100 x 109 /L
17. White cell count more than 30 x 109 /L or less than 3.5 x 109 /L
18. Major bleeding within 1 year (e.g. peptic ulcer, intracerebral haemorrhage)
19. Planned surgery during 3-month follow-up (e.g. carotid endarterectomy)
20. Concomitant STEMI or NSTEMI.
21. Stroke secondary to a procedure (e.g. carotid or coronary intervention)
22. Coma (GCS<8)
23. Non-stroke life expectancy <6 months
24. Dementia
25. Participation in another drug or devices trial concurrently or within 30 days (participants may take part in observational studies or non-drug or devices trials)
26. Geographical or other factors that may interfere with follow-up e.g. no fixed address or telephone contact number, not registered with a GP, or overseas visitor.
27. Females of childbearing potential, pregnancy or breastfeeding

28. Patients who have not had post-thrombolysis neuroimaging.
29. Patients on aspirin and clopidogrel prior to the underlying event.

Exclusion criteria from 25/03/2010 to 19/06/2014:
1. Age <50
2. Motor weakness or dysphasia lasting <10 minutes
3. Pure sensory, vertigo or dizziness, speech or visual disturbance symptoms without weakness or dysphasia
4. Patients with contraindications to, or intolerance of, aspirin, clopidogrel or dipyridamole
5. Patients with definite need for treatment with clopidogrel (e.g. recent MI)
6. Pre-morbid dependency (mRS>2)
7. No enteral access
8. Parenchymal haemorrhagic transformation (PH I/II), subarachnoid haemorrhage or other non ischaemic cause for weakness
9. TIA not fulfilling inclusion criteria
10. Definite need for full dose oral (e.g. warfarin) or parental (e.g. heparin or glycoprotein IIb IIIa inhibitors) anti- coagulation. NB Low dose heparin for DVT prophylaxis is allowed.
11. Received thrombolysis within the last 30 hours
12. Presumed cardioembolic stroke (e.g. AF, recent MI, or other conditions need for anticoagulation)
13. Severe high BP (BP>185/110 mmHg)
14. Known haemoglobin less than 10g/dL
15. Known platelet count less than 100 x 109 /L
16. Known white cell count less than 3.5 x 109 /L
17. Bleeding within 1 year (e.g. peptic ulcer, intracerebral haemorrhage)
18. Planned surgery during 3 month follow-up (e.g. carotid endarterectomy)
19. Concomitant acute coronary syndrome
20. Stroke secondary to a procedure (e.g. carotid or coronary intervention)
21. Coma (GCS<8)
22. Non-stroke life expectancy <6 months
23. Dementia
24. Participation in another drug trial concurrently or within 30 days (Patients may be randomised into observational studies or non-drug trials)
25. Not available for follow-up e.g. no fixed address, overseas visitor
26. Females of childbearing potential, pregnancy or breastfeeding

Note: Clopidogrel will be stopped around procedures that become necessary after enrolment

Exclusion criteria at time of registration:
1. Aged less than 40 years
2. Motor weakness lasting less than 30 minutes (pure sensory, vertigo or dizziness, speech or visual disturbance symptoms without weakness are excluded)
3. Patients with contraindications to, or intolerance of, aspirin, clopidogrel or dipyridamole
4. Pre-morbid dependency (modified Rankin Scale [mRS] greater than 3)
5. No enteral access
6. Parenchymal haemorrhagic transformation (PH I/II), subarachnoid haemorrhage or other non-ischaemic cause for weakness
7. TIA not fulfilling inclusion criteria
8. Definite need for, or currently on triple antiplatelet therapy or anticoagulation
9. Indication for, or received (in last week), thrombolysis
10. Presumed cardioembolic stroke (e.g. atrial fibrillation [AF], recent MI, or other conditions need for anticoagulation)

11. Severe high blood pressure (BP) (greater than 185/110 mmHg)
12. Bleeding within 1 year (e.g. peptic ulcer, intracerebral haemorrhage)
13. Planned surgery during 3 month follow-up (e.g. carotid endarterectomy)
14. Concomitant acute coronary syndrome
15. Stroke secondary to a procedure (e.g. carotid or coronary intervention)
16. Planned surgery during first month post stroke (e.g. carotid endarterectomy)
17. Coma (Glasgow Coma Scale [GCS] less than 8)
18. Non-stroke life expectancy less than 6 months
19. Dementia
20. Participation in another drug trial concurrently or within 30 days (patients may be randomised into observational studies or non-drug trials)
21. Not available for follow-up, e.g. no fixed address, overseas visitor
22. Females of childbearing potential, pregnancy or breastfeeding

Note: Clopidogrel will be stopped around procedures that become necessary after enrolment

Recruitment start date
01/03/2009

Recruitment end date
30/09/2017

Locations

Countries of recruitment
Denmark

England

Georgia

New Zealand

United Kingdom

Study participating centre
Institute of Neuroscience
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ROR
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Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (BHF) (UK)

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Statistical Analysis Plan	statistical analysis plan	01/04/2015		No	No
Protocol article	protocol	01/10/2015		Yes	No
Results article	results	03/03/2018		Yes	No
Results article	results	01/08/2018		Yes	No
Basic results			10/09/2019	No	No
Results article		30/07/2023	21/07/2023	Yes	No
Results article	Re-Assessment of the TARDIS trial	05/07/2023	25/09/2023	Yes	No