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Optimal timing of anticoagulation after acute ischaemic stroke

Submission date
04/02/2019

Recruitment status
No longer recruiting

Registration date
25/02/2019

Overall study status
Completed

Last Edited
19/02/2025

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Atrial fibrillation (AF) is a condition in which the heartbeat is irregular. When the heart beats irregularly, blood clots can form within the heart. If a blood clot then breaks off, it can travel along blood vessels to the brain, where it can block a blood vessel and cause a stroke. This type of stroke is called a cardioembolic ischaemic stroke. After a cardioembolic stroke there is a significant risk of a further stroke, and this risk is highest in soon after the stroke. Treatment with blood-thinning drugs called anticoagulants considerably reduces the chance of this. However, we are not sure of the best time to start these anticoagulants after a stroke. On one hand, the sooner an anticoagulant is started, the sooner we can reduce the risk of a further stroke happening by preventing blood clots. On the other hand, there is concern that starting anticoagulation too soon after a stroke could increase the risk of bleeding in the brain, which can be serious and cause symptoms similar to another stroke. At the moment, many doctors delay starting anticoagulants until 7-14 days after stroke. This practice dates back to a time when the only anticoagulant tablet available was warfarin, which has a relatively high risk of causing bleeding. Unfortunately, some patients may have a further stroke while waiting to start an anticoagulant. Now, newer anticoagulant tablets called Direct Oral Anticoagulants (DOACs) are available and are very widely used to prevent stroke in people with atrial fibrillation. Several large studies have shown that these DOACs have a considerably lower risk of causing bleeding in the brain than warfarin. Because DOACs have a lower risk of causing bleeding, it might be possible to safely start them much sooner after a stroke than the current 7 – 14 days. This may prevent further strokes without causing extra bleeding, and evidence from several small studies supports this. The aim of this study is to compare this new approach (starting a DOAC within 4 days of stroke) to the existing usual treatment (starting a DOAC at 7 to 14 days after stroke).

Who can participate?
Patients aged 18 or over admitted to hospital with an ischaemic stroke (a stroke due to a blocked blood vessel in the brain), who have atrial fibrillation and whose doctor recommends starting treatment with a DOAC

What does the study involve?
After deciding to take part in the study, participants complete questionnaires about their medical background and current health and quality of life. They are then randomly allocated to

start treatment with a DOAC early (within 4 days of stroke) or at the standard time of 7-14 days after stroke. The only difference between groups is the time at which the DOAC is started – all other aspects of medical care are the same. Apart from a urine pregnancy test for participants of child-bearing potential, no additional tests are needed as part of the study. Participants are asked to attend one follow-up appointment, 90 days after they join the study. This is usually in person, but can be conducted by phone if needed. Participants are asked to complete questionnaires about their health since joining the study, their medication and healthcare use, and quality of life and ability to perform day-to-day activities.

What are the possible benefits and risks of participating?
Participants in the early treatment group receive a DOAC earlier than is current standard practice. It is hoped that this will be better than the current standard treatment, preventing recurrent strokes without increasing the risk of bleeding. However, this is not certain, which is why we need to perform the study. It is possible that the opposite is true, and that the study treatment will increase the risk of bleeding and/or be no more effective in preventing further strokes. The researchers will be monitoring this throughout the study, and should any evidence arise that early treatment is worse than standard treatment, they will stop the study early. It cannot be guaranteed that participants will benefit from taking part in the study. However, participants will be followed up by a stroke research team which might improve access to advice and information about stroke care. The information from the study will be used to improve treatment for patients with atrial fibrillation who have a stroke in the future.

Where is the study run from?
The trial will be co-ordinated by the Stroke Research Centre and Comprehensive Clinical Trials Unit at University College London, and will take place at hospitals with specialist stroke units throughout the UK.

When is the study starting and how long is it expected to run for?
April 2018 to April 2025

Who is funding the study?
British Heart Foundation (BHF) (UK)

Who is the main contact?
1. Prof. David Werring
d.werring@ucl.ac.uk
2. OPTIMAS trial management team
ctu.optimas@ucl.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2018-003859-38

ClinicalTrials.gov (NCT)
NCT03759938

Protocol serial number
40836

Study information

Scientific Title
OPtimal TIMing of Anticoagulation after acute ischaemic Stroke (OPTIMAS): a randomised controlled trial

Acronym
OPTIMAS

Study objectives
OPTIMAS will investigate whether early initiation of treatment with a direct oral anticoagulant (DOAC), within 4 days (96 hours) of onset, in patients with ischaemic stroke and atrial fibrillation is as effective as, or better than, standard initiation of a DOAC no sooner than day 7 (>144 hours) and no later than day 14 (<336 hours) after onset, in preventing recurrent ischaemic stroke, systemic embolism, and symptomatic intracranial haemorrhage.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central Oxford B REC Committee Bristol HRA Centre Level 3 Block B, Whitefriars, Lewins Mead, BS1 2NT, Tel: +44 (0)207 1048058, Email: nrescommittee.southcentral-oxfordb@nhs.net, 30/01/2019, ref: 19/SC/0021

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute ischaemic stroke with atrial fibrillation

Interventions
Participants in OPTIMAS will be randomised in a 1:1 ratio to intervention (early anticoagulation) or control (standard anticoagulation) groups, using an online randomisation service (Sealed Envelope), with stratification by stroke severity (as assessed by baseline NIHSS) to ensure balance between groups. Randomisation will be carried out in sufficient time (ideally, within 72hrs of stroke onset) for participants to receive a DOAC within 96 hours of stroke onset if allocated to the intervention arm. Participants and treating physicians will not be blinded, but outcomes will be assessed blinded to treatment allocation.

Participants in the study intervention arm will receive a DOAC within 4 days (96hrs) of stroke onset. Participants in the control arm will receive a DOAC no earlier than day 7 (>144hrs) and no later than day 14 (<336hrs) after stroke onset, timing which reflects standard, guideline-based practice in the United Kingdom. The exact timing of anticoagulation within the specified period is at the discretion of the treating physician, as is the choice of DOAC. Any DOAC regimen licensed for stroke prevention in atrial fibrillation may be used, currently:
1. Dabigatran; standard dosage 150 mg BD, reduced dosage (if indicated) 110 mg BD
2. Apixaban; standard dosage 5 mg BD, reduced dosage (if indicated) 2.5 mg BD
3. Edoxaban; standard dosage 60 mg OD, reduced dosage (if indicated) 30 mg OD
4. Rivaroxaban; standard dosage 20 mg OD, reduced dosage (if indicated) 15 mg OD

The four DOACs will be used according to their drug licenses in this trial. The choice of DOAC will be decided by the treating doctor, but the timing of treatment will be allocated to either early or standard. It is expected that 3500 adult patients (> = 18 years) admitted to +100 participating acute stroke units with acute ischaemic stroke and AF will be screened for eligibility, and consented (by patient or legal representative if the patient is too unwell to make their own decisions). They will then be entered into the trial receive early or standard DOAC treatment. Patients who cannot have anticoagulant treatment because of specific conditions such as an increased tendency to bleed or poor liver function will be excluded.

Participants will be followed up at 90 days post-study entry to collect information on how well they have taken DOAC treatment (known as adherence), side effects, and whether they have had specific clinical events such as stroke, bleeding, and systemic embolism. This information will allow the researchers to calculate the rate of newly-occurring stroke, bleeding in the brain (symptomatic intracranial haemorrhage), and systemic embolism in the 90 day treatment period for each of the two groups (early and standard) so they can be compared. The impact of early versus standard treatment on participants' quality of life and cognition will also be investigated by using specific assessments.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)

Dabigatran, apixaban, rivaroxaban, edoxaban

Primary outcome(s)
Composite outcome of the combined incidence (at 90 days from randomisation) of:
1. Recurrent symptomatic ischaemic stroke
2. Symptomatic intracranial haemorrhage (including extradural, subdural, subarachnoid and intracerebral haemorrhage, and haemorrhagic transformation of the qualifying infarct)
3. Systemic embolism

Key secondary outcome(s))
Secondary outcomes will be assessed at 90 days after randomisation. Clinical outcomes will be adjudicated by an independent committee, using case report forms supplemented by participant brain imaging results where applicable.

Secondary efficacy outcomes:
1. All-cause mortality
2. Incidence of vascular death
3. Incidence of recurrent ischaemic stroke
4. Incidence of systemic embolism
5. Incidence of venous thromboembolism (deep vein thrombosis, pulmonary embolism, cerebral venous thrombosis)
6. Functional status (modified Rankin Scale)
7. Cognitive ability (MoCA)
8. Quality of life (EQ-5D-5L)
9. Patient-reported outcomes (PROMIS-10)
10. Ongoing anticoagulation (assessed using study questionnaire)
11. Time to first incidence of a primary outcome component (i.e. recurrent ischaemic stroke, systemic embolism, or symptomatic intracranial haemorrhage)
12. Length of hospital stay for stroke-related care
13. Health and Social Care Resource use (assessed by study-specific HSCR questionnaire)

Safety outcomes:
1. Incidence of symptomatic intracranial haemorrhage (sICH), classified by site: intracerebral, subarachnoid, subdural, extradural and haemorrhagic transformation of a brain infarct
2. Incidence of major extracranial bleeding
3. Incidence of all major bleeding (intracranial and extracranial)
4. Incidence of clinically-relevant non-major bleeding

Completion date
30/04/2025

Eligibility

Key inclusion criteria
1. Aged 18 years or over
2. Clinical diagnosis of acute ischaemic stroke
3. Atrial fibrillation, confirmed by any of:
3.1. 12-lead ECG recording
3.2. Inpatient ECG telemetry
3.3. Other prolonged ECG monitoring technique (e.g. Holter monitor)
3.4. Known diagnosis of atrial fibrillation verified by medical records (e.g. primary care records,

letter from secondary care)
4. Eligibility to commence DOAC in accordance with approved prescribing recommendations confirmed by treating physician
5. Uncertainty on the part of the treating physician regarding early versus standard initiation of DOAC.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
3648

Key exclusion criteria
1. Contraindication to anticoagulation:
1.1. Coagulopathy or current or recent anticoagulation with vitamin K antagonist (VKA) leading to INR > = 1.7 at randomisation.
1.2. Thrombocytopenia (platelets < 75 x 10^9/L)
1.3. Other coagulopathy or bleeding tendency (based on clinical history or laboratory parameters) judged to contraindicate anticoagulation by treating clinician
2. Contraindication to early anticoagulation
2.1. Known presence of haemorrhagic transformation with parenchymal haematoma occupying > 30% of the infarct volume and exerting significant mass effect (i.e. PH2) (NB: HI1, HI2 and PH1 are not considered contraindications)
2.2. Presence of clinically significant intracranial haemorrhage unrelated to qualifying infarct
2.3. Any other contraindication to early anticoagulation as judged by the treating clinician
3. Contraindication to use of DOAC:
3.1. Known allergy or intolerance to both FXa inhibitor and direct thrombin inhibitor
3.2. Definite indication for VKA treatment e.g. mechanical heart valve, valvular AF, antiphospholipid syndrome
3.3. Severe renal impairment with creatinine clearance (Cockcroft & Gault formula) < 15 mL/min (i.e. 14 mL/min or less)
3.4. Liver function tests ALT > 2x ULN
3.5. Cirrhotic patients with Child Pugh score equating to grade B or C
3.6. Patient is taking medication with significant interaction with DOAC, including:
3.6.1. Azole antifungals (e.g. ketoconazole, itraconazole)
3.6.2. HIV protease inhibitors (e.g. ritonavir)
3.6.3. Strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort)
3.6.4. Dronedarone

4. Pregnant or breastfeeding women
5. Presence on acute brain imaging of non-stroke pathology judged likely to explain clinical presentation (e.g. mass lesion, encephalitis)
6. Inability for patient to be followed up within 90 days of trial entry
7. Patient or representative refusal to consent to study procedures, including the site informing GP and healthcare professional responsible for anticoagulation care of participants
8. Any other reason that the PI considers would make the patient unsuitable to enter OPTIMAS

Date of first enrolment
01/04/2019

Date of final enrolment
31/01/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London Hospitals NHS Foundation Trust (lead centre)
250 Euston Road
London
United Kingdom
NW1 2PG

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name

British Heart Foundation; Grant Codes: CS/17/6/33361

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

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		23/10/2024	04/11/2024	Yes	No
Protocol article		12/01/2022	13/01/2022	Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Statistical Analysis Plan		19/02/2025	19/02/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes