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Optimal Timing of Anticoagulation after Acute Ischaemic Stroke with Atrial Fibrillation (OPTIMAS): Protocol for a Randomised Controlled Trial

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Abstract

Rationale Atrial fibrillation (AF) causes one-fifth of ischaemic strokes, with a high risk of early recurrence. Although long-term anticoagulation is highly effective for stroke prevention in AF, initiation after stroke is usually delayed by concerns over intracranial haemorrhage (ICH) risk. Direct oral anticoagulants (DOACs) offer a significantly lower risk of ICH than other anticoagulants, potentially allowing earlier anticoagulation and prevention of recurrence, but the safety and efficacy of this approach has not been established.

Aim OPTIMAS will investigate whether early treatment with a DOAC, within 4 days of stroke onset, is as effective or better than delayed initiation, 7 to 14 days from onset, in AF patients with acute ischaemic stroke.

Methods and design OPTIMAS is a multicentre randomised controlled trial with blinded outcome adjudication. Participants with acute ischaemic stroke and AF eligible for anticoagulation with a DOAC are randomised 1:1 to early or delayed initiation. As of July 2021, 80 centres in the United Kingdom have opened.

Study outcomes The primary outcome is a composite of recurrent stroke (ischaemic stroke or symptomatic ICH) and systemic arterial embolism within 90 days. Secondary outcomes include major bleeding, functional status, anticoagulant adherence, quality of life, health and social care resource use, and length of hospital stay.

Sample size target 3478 participants assuming event rates of 11.5% in the control arm and 8% in the intervention arm, 90% power and 5% alpha. We will follow a non-inferiority gatekeeper analysis approach with a non-inferiority margin of 2 percentage points.

Discussion OPTIMAS aims to provide high-quality evidence on the safety and efficacy of early DOAC initiation after AF-associated ischaemic stroke.

Trial registrations: ISRCTN: 17896007; ClinicalTrials.gov: NCT03759938

Introduction and rationale

Atrial fibrillation (AF) causes at least 20% of all ischaemic strokes (1). Oral anticoagulation reduces the risk of stroke in AF by around two-thirds (2,3), but its safety and benefit in acute ischaemic stroke is unclear. Current practice - based on limited observational data and expert opinion - is to delay anticoagulation by up to two weeks, during which the daily risk of recurrence is 0.4-1.3% (4–7). Earlier anticoagulation might prevent many recurrent ischaemic strokes, but might cause intracranial haemorrhage (ICH), including intracerebral haemorrhage due to haemorrhagic transformation of the infarct (*Supplementary Figure 1*), which is associated with poor outcome if severe (8). The optimal timing of anticoagulation after AF-associated ischaemic stroke is thus a frequent dilemma in stroke medicine.

Historical evidence suggests that anticoagulation within 48 hours of stroke onset with vitamin K antagonists (VKAs) or heparins is not beneficial because an increased risk of symptomatic ICH outweighs any reduction in ischaemic stroke (9). However, direct oral anticoagulants (DOACs) are as effective in ischaemic stroke prevention, but with half the risk of ICH of vitamin K antagonists (3). Although the large randomised trials of DOACs excluded participants with acute ischaemic stroke (10), increasing observational data suggest they might be used safely in acute AF-associated stroke (*Supplementary Table 1)*. However, this evidence is limited by selection bias and may not generalise beyond mild-moderate stroke (10). Randomised controlled trials (RCTs) are therefore needed, are supported by stroke physicians, who report clinical uncertainty regarding optimal anticoagulation timing (11), and have been called for by international guidelines (12,13).

The OPtimal TIMing of Anticoagulation after acute ischaemic Stroke trial (OPTIMAS) aims to establish the safety and efficacy of early anticoagulation with a DOAC after AF-associated stroke.

Methods and design

OPTIMAS is a phase IV multicentre RCT with an open-label intervention, blinded end-point adjudication, and hierarchical non-inferiority/superiority gatekeeper design, comparing a policy of early DOAC initiation, within 4 days of stroke onset, to delayed initiation, 7 to 14 days from onset, in patients with AF and acute ischaemic stroke.

Patient population

OPTIMAS will recruit 3478 participants within 4 days of stroke onset, from UK stroke units. Sites are listed at https://optimas.org.uk.

Inclusion criteria

- ≥18 years old
- AF (confirmed by ECG recording or medical records)
- Clinical diagnosis of acute ischaemic stroke
- Eligible for anticoagulation with DOAC
- Treating physician is uncertain regarding the potential participant's optimal time to start DOAC

Exclusion criteria

- Coagulopathy or current anticoagulation with INR ≥1.7 at randomisation (anticoagulant-treated patients not excluded if INR < 1.7); clinically-significant thrombocytopenia (platelets < 75 x 10^9/L)
- Severe haemorrhagic transformation of the infarct (ECASS PH2) (14) or acute ICH unrelated to infarct
- DOAC use contraindicated: severe renal impairment (creatinine clearance <15ml/min); cirrhosis (Child Pugh B or C) or ALT >2x upper limit of normal; concurrent medication with significant interaction (e.g. strong CYP3A4 inducers); definite indication for VKA use
- Pregnancy or breastfeeding

Randomisation

Participants will be randomised in a 1:1 ratio using an independent online randomisation service with random permuted blocks and randomly varying block lengths, stratified by NIHSS at randomisation (0-4, 5-10, 11-15, 16-21, >21). The participant and treating clinicians will not be blinded to allocation, but outcomes will be adjudicated blind.

Intervention

The intervention group will initiate a DOAC within 4 days of stroke onset (or the time symptoms were first noted, if the onset time cannot be determined). The control group will initiate a DOAC 7 to 14 days after onset, an interval selected based on a 2018 survey of UK

practice (11). The treating clinician determines the exact timing of anticoagulation in each group. Any DOAC licensed for stroke prevention in AF (i.e. apixaban, dabigatran, edoxaban, rivaroxaban) may be used. The dose may be reduced if recommended by the relevant Summary of Product Characteristics (15–18). All other clinical care follows current UK best practice (19).

Primary outcome

The primary outcome is a composite of recurrent ischaemic stroke, symptomatic ICH (including haemorrhagic transformation), unclassifiable stroke syndromes, and systemic arterial embolism incidence at 90 days post-randomisation. Primary outcome events will be adjudicated centrally by independent expert clinicians blinded to treatment allocation.

Secondary outcomes

Secondary efficacy outcomes include all-cause and cardiovascular mortality, recurrent ischaemic stroke, systemic embolism, and venous thromboembolism. Safety outcomes include symptomatic ICH, its anatomical subtypes, major extracranial bleeding (20), and clinically-relevant non-major bleeding (21). We will record functional (modified Rankin Scale), cognitive (MoCA), and patient-reported (EQ-5D-5L, PROMIS-10) outcomes, length of hospital stay, medication adherence, and health and social care resource use.

Data collection

Trial data are collected via a secure online electronic data capture system, and pseudonymised clinical imaging data via a secure file transfer portal. *Table 1* shows the schedule of study assessments and interventions, and *Figure 1* the study flowchart.

Sample size estimates

Our planned sample size assumed a reduction in the primary outcome event rate from 11.5% in the control group to 8% in the intervention group (a relative risk reduction of 30%). We judged this to be a clinically meaningful benefit likely to influence guidelines and practice. The assumed composite event rate and hypothesised effect size were derived from the Virtual International Stroke Trials Archive of trials in patients with ischaemic stroke and AF (22). The sample size calculation used 90% power for superiority, significance level 5%, and was inflated by 10% for loss to follow-up or other challenges; we anticipate a much lower rate than this. Based on the expected event rate and a non-inferiority margin of 3%, a sample size of 3478 evaluable participants would have had 80% power for non-inferiority.

We re-evaluated study power in November 2021 at the request of our Independent Data Monitoring Committee, due to a lower-than-expected interim adjudicated primary outcome rate of 4.3%. Given this event rate, our planned sample size has 80% power to show non-inferiority based on a non-inferiority margin of 2%, and 80% power for superiority assuming an odds ratio reduction of 38%.

Statistical analyses

Our main analysis will follow the intention-to-treat principle. Outcome data will be collected from all participants enrolled, unless consent is specifically withdrawn (in which case data will be included up to the point of withdrawal). We will first test for non-inferiority of the intervention, using a non-inferiority margin of 2 percentage points identified as clinically acceptable. If non-inferiority is established, we will test for superiority. For our primary outcome, we will use mixed-effects logistic regression including an independent variable indicating treatment allocation, with adjustment for stroke severity (NIHSS) at randomisation. Sites will be included as random intercept terms.

The health economic evaluation will calculate the mean incremental cost per quality adjusted life year (QALY) gained by early initiation of a DOAC. Cost-effectiveness will primarily be evaluated using cost-effectiveness acceptability curves generated from bootstrapped results to calculate the probability that early initiation of DOAC is cost-effective compared to late initiation for a range of values of willingness to pay for a QALY gained.

Further details of our statistical and health economic analyses are presented in the *Appendix.* A full statistical and health economic analysis plan will be published before the end of recruitment. Prespecified secondary statistical analyses will include: a per-protocol analysis; a mediation analysis; and analyses by stroke severity (NIHSS) and neuroimaging features including infarct location, volume, haemorrhagic transformation (including subtypes of haemorrhagic infarction and parenchymal haematoma (14)), and cerebral small vessel disease markers.

Study organisation and funding

The study is funded by the British Heart Foundation (CS/17/6/333561) and sponsored by University College London. The *Appendix* describes study approvals and governance, key study committees (*Supplementary Tables 2 – 7*), and arrangements for data monitoring, safety reporting, and quality assurance. Study results will be presented at scientific meetings and published in peer-reviewed journals.

Discussion

OPTIMAS is a prospective RCT based in routine clinical practice throughout the UK, addressing the important clinical uncertainty of the optimal timing of anticoagulation for secondary prevention of cardioembolic stroke, with broad eligibility criteria intended to give a representative study sample and results readily applicable to clinical practice.

We decided against imaging-based eligibility criteria. Although infarct size is a risk factor for haemorrhagic transformation (8), to our knowledge, it has not been shown that anticoagulation timing and infarct size interact with respect to the risks of clinically-significant haemorrhagic transformation and adverse clinical outcomes, although these considerations often feature in expert guidance (23). Furthermore, larger infarct size is also a risk factor for recurrent ischaemic stroke in AF patients (24,25). Visual classifications of infarct size are based mainly on vascular anatomy and expert opinion (8), and accurate measurement requires diffusion-weighted MRI (or a delayed CT) and trained raters, increasing the time and complexity of establishing eligibility, an important consideration in a time-sensitive trial. Our approach concurs with that of the Swedish TIMING trial (ClinicalTrials.gov NCT02961348) (26), facilitating pooled individual patient data (IPD) analyses, and will complement the international imaging-based ELAN trial (which varies anticoagulation timing according to infarct size; NCT03148457) and the United States' START trial (which excludes participants

with large infarct volumes; NCT03021928) (27), with the possibility of aligning imaging-based subgroup analyses.

We chose a hierarchical non-inferiority then superiority gatekeeper design because: (1) a finding of non-inferiority but not superiority at our chosen margin of 3 percentage points would give confidence that early anticoagulation with a DOAC is of similar clinical benefit to delayed anticoagulation, so could reasonably be chosen for its practical advantages; and (2) early anticoagulation might have advantages beyond prevention of stroke and systemic arterial embolism, such as improved adherence and reduced length of stay.

No participants in OPTIMAS will be randomised to start anticoagulation between four and seven days after onset per protocol. This separation between treatment groups aims to minimise crossovers and ensure that the two groups receive different timings of treatment onset. Our best judgement was that these advantages would outweigh the possibility that the optimal timing of anticoagulation might be within this period. A large-scale pooled analysis with other anticoagulation timing trials is planned, giving full coverage of the first two weeks after stroke onset and power to explore this issue in detail.

Summary and conclusions

OPTIMAS will determine the efficacy and safety of early anticoagulation with a DOAC in patients with acute ischaemic stroke and AF, a strategy with the potential to prevent early recurrent ischaemic strokes, shorten hospital stays, and improve quality of life.

Declaration of competing interests

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All other authors declare no competing interests.

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Tables

Table 1: schedule of study assessments and interventions

Assessment	**Screening and enrolment**	**Acute stroke unit treatment**	**Discharge from ASU**	**Follow-up**
Time	*Within 96 hours of stroke onset*			*90 days from randomisation*
Informed consent	X			
Documentation of AF diagnosis [a]	X			
Blood tests (creatine, ALT, platelets, INR) [b]	X			
Documentation of admission NIHSS [b]	X			
NIHSS at randomisation	X			
Baseline BP and weight	X			
Baseline scales and scores (premorbid mRS, IQCODE, EQ-5D-5L)	X			
First administration of DOAC		X[c]		
SAE/outcome event reporting		X	X	X
Collection of participant brain and vascular imaging [d]			X	X
Follow-up scales and scores (mRS, MoCA, PROMIS-10, EQ-5D-5L,				X

health and social care resource use questionnaire)				

[a] Current or previous ECG recording or report, or documentation in medical care records

[b] Generally part of routine clinical care

[c] During hospitalisation in most cases, but initiation after discharge also permitted

[d] Imaging performed as part of clinical care only

Figure titles and legends

Figure 1: Study flowchart