Statistical Analysis Plan for STudy of Antithrombotic Treatment after Intracerebral Haemorrhage (STATICH)

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Contents

Abbreviations:

CI: confidence interval

HR: hazard ratio

ICrH: intracranial haemorrhage

ITT: intention-to-treat

mRS: modified Rankin scale

OR: odds ratio

SAE: Serious adverse event

SAP: statistical analysis plan

SD: standard deviation

sICH: spontaneous intracerebral haemorrhage

STATICH: Study of Antithrombotic Treatment after Intracerebral Haemorrhage

TIA: transient ischaemic attack

1 Introduction

Spontaneous (non-traumatic) intracerebral haemorrhage (sICH) constitutes about 28% of all strokes worldwide (1). The prognosis is poor, with about 40% one-month case fatality (2). About 50% of people suffering a sICH are using an antithrombotic (antiplatelet or anticoagulant) drug at symptom onset (3). The most common indication for antiplatelet drugs is secondary prevention of ischaemic events and for anticoagulant drugs it is stroke prevention in atrial fibrillation. People who suffer a sICH have an increased risk of ischaemic events, but also an increased risk of a new sICH (4-6). To date, there are no clear guidelines on whether people with sICH and an indication for an antithrombotic drug should (re)start them after sICH or not (7, 8). Both policies occur in clinical practice.

The STATICH protocol has been published (9). Some elements of the protocol are repeated below.

1.1 Aims of the study

The primary aim of Study of Antithrombotic Treatment after IntraCerebral Haemorrhage (STATICH) is to assess the effects of antithrombotic drugs on the risk of recurrent sICH.

The secondary aim is to assess whether brain imaging findings, such as cerebral microbleeds, modify the effects of antithrombotic drugs after sICH (9).

2 Study methods

2.1 Trial design

STATICH is a Scandinavian investigator-led, multicentre, randomised controlled open trial of antithrombotic drugs for prevention of ischaemic events in people with prior sICH. Originally, the study was designed as one trial, investigating the safety of antithrombotic drugs in people with prior sICH and an indication for antithrombotic drugs. From the time the study was planned and until the end of follow-up, the clinical question has changed. The scientific issue is now to investigate the safety and efficacy of antiplatelet drugs for people with an indication for antiplatelets, and the safety and efficacy of anticoagulants for people with atrial fibrillation and an indication for anticoagulants.

2.2 Ethical approvals

STATICH is conducted according to Good Clinical Practice and The Declaration of Helsinki. Regulatory agencies and research ethics committees in the three participating countries have approved the trial.

2.3 Randomisation

All participants eligible for inclusion were randomised using a central, web-based randomisation system. Participants with an indication of antiplatelet drugs were randomised in the antiplatelet part of the trial, whereas participants with atrial fibrillation and an indication for anticoagulant drugs were randomised in the anticoagulant part of the trial. For each of these trial parts, participants were randomised to either intervention (treatment with antithrombotic drugs) or open control using a minimisation algorithm without a pre-determined sequence. The first participant was randomly allocated with a probability of 0.5 to one of the arms. Adaptive minimisation was used to allocate each subsequent participant with a probability of 0.8 to the arm that minimises the difference between the arms, with respect to baseline characteristics (see below) in the previously randomised participants. The minimisation criteria are listed below.

2.3.1 Minimisation criteria in randomisation algorithm

- Age
  - < 70 versus ≥ 70 years
- Index sICH location
  - Only supratentorial lobar regions are affected; yes versus no
- Probability of a good outcome at six months (10)
  - < 0.15 versus ≥ 0.15
- Days from index sICH to randomisation
  - 0 to 6 days versus 7 to 30 days versus > 30 days
- Antiplatelet drug the patient's physician would use if allocated (this criterion only applies to the antiplatelet trial)
  - Aspirin only; yes versus no

2.4 Sample size

The sample size estimation was made before the initiation of the study. A fourfold increase in the annual rate of recurrent sICH on antithrombotic drugs (from 2% to 8%) was considered unacceptable and higher than any plausible beneficial effect antithrombotic drugs would have on ischaemic events.

With power of 80% and a 5% significance level to detect an increase of the annual rate of recurrent sICH from 2% to 8% with antithrombotic therapy, the sample size was estimated to 500 participants randomised to intervention versus control. The sample size estimation was made for the trial as a whole, and not as two separate trials investigating the effect and safety of antiplatelets and effect and safety of anticoagulants as two separate trials. No sample size estimation for the two separate trials was performed. Regardless of this, analyses will be made for antiplatelet treatment versus control and anticoagulant treatment versus control separately.

2.5 Timing of outcome assessments

Outcomes will be assessed by study-personnel who are blinded to treatment allocation. Outcome assessment will take place by telephone interview with participants, participants relatives or health professionals every six months. Participants will be followed up for a minimum of two years. The inclusion period run longer than initially planned due to slow recruitment. The last participant was included December 2022 and per protocol the follow-up should continue until December 2024. Due to lack of resources the Trial Steering Committee decided in February 2024 to end follow-up in August 2024, leaving four participants not reaching two-year follow-up.

2.6 Timing of final analysis

Final analysis will take place after the follow-up period ends August 31st 2024. We will perform primary analysis on all patients who reached two-year follow-up. We will also

perform secondary analysis for total follow-up time for patients followed up for longer than two years.

3 Statistical principles

3.1 General considerations

This analysis plan will apply for the primary aim of the STATICH study.

3.2 Confidence intervals and p-values

The results with p-values below 0.05 will be considered statistically significant, unless otherwise specified. The differences between the groups will be presented with 95% confidence intervals (CIs). All statistical tests will be two-sided.

3.3 Adherence and protocol deviations

3.3.1 Adherence to allocated treatment

Adherence to the intervention will be assessed by open follow-up from unblinded study-personnel every six months during the follow-up period. Adherence will be described for each treatment group, but no statistical tests will be performed.

3.3.2 Protocol deviations

Important protocol deviations are deviations that may significantly impact the completeness, accuracy, and reliability of the study data or that may significantly affect a participant's rights, safety or well-being. The following are considered important protocol deviations in this study:

- Participants randomised despite not meeting the entry criteria.
- Participants who received the wrong treatment or incorrect dose.
- Participants who received an excluded concomitant treatment.
- Absence of source documents.
- Failure to collect data on the primary or secondary endpoints.

We will list all important protocol deviations, but no formal statistical testing will be performed.

3.4 Analysis populations

To preserve the benefit of randomisation, we will include all randomised participants in the analysis (irrespective of whether they adhere to the allocated treatment), all retained in the group to which they were allocated (i.e. "intention-to-treat" analysis). We will also consider conducting per-protocol analysis including randomised participants without major protocol deviations.

4 Trial population

4.1 Eligibility criteria

4.1.1 Inclusion criteria

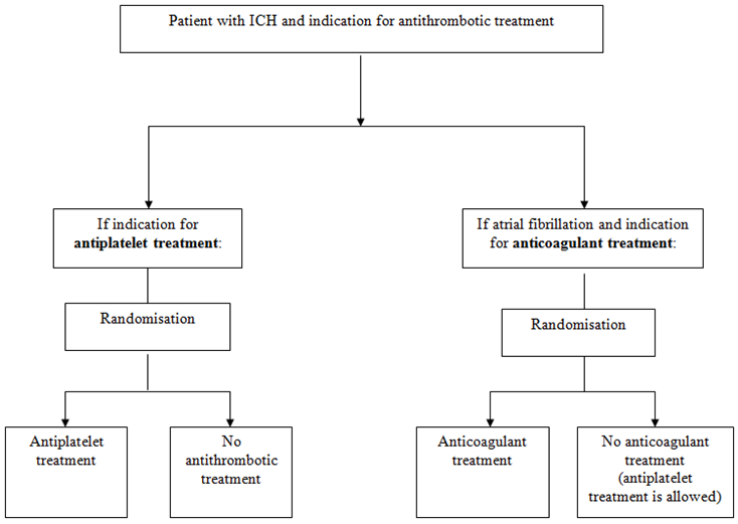
1. People aged ≥ 18 years of age
2. Non-traumatic, sICH at least 24 hours ago without a preceding traumatic brain injury, based on history from the patient/witness of spontaneous symptom onset and brain imaging appearance consistent of sICH.
3. No underlying structural cause (e.g. aneurysm, tumour, arteriovenous malformation, intracerebral venous thrombosis, or haemorrhagic transformation of an ischaemic stroke)
4. Indication for antithrombotic (i.e. anticoagulant or antiplatelet) drug for the prevention of ischaemic events, either antiplatelet drugs for patients with vascular disease, or anticoagulant drug for patients with atrial fibrillation
    a. Indication for antiplatelet drugs can be previous ischaemic stroke, myocardial infarction, other occlusive arterial disease, or arterial stents or other arterial implants (secondary prevention), or patients with known significant atherosclerotic arterial disease, such as carotid or coronary artery stenosis or mobile aortic atheroma (primary prevention)
5. Consent to randomisation from the patient (or personal/legal/professional representative, if the patient does not have mental capacity to give consent, and waiver of consent is acceptable in the patient's country)
6. CT and/or MRI is performed before randomisation

4.1.2. Exclusion criteria:

1. Clear indication for antiplatelet or anticoagulant treatment (e.g. recent coronary artery stenting, or prosthetic metallic heart valves)
2. Contraindications to the antithrombotic drug that will be administered
3. Patient is pregnant, breastfeeding or of childbearing potential and not using contraception
    a. A woman of childbearing potential must undergo a pregnancy test before randomisation and the result must be recorded in the case report form.
    b. Women of childbearing potential randomised to active treatment must use effective methods of contraception and undergo regular pregnancy testing during follow-up, and the results must be recorded in the case report forms.
4. Malignancy with life expectancy less than two years
5. For MRI examination: Contraindication to the brain MRI

4.2 Recruitment

Participants may be recruited during their hospital admission for the qualifying sICH or at a later stage in an outpatient clinic.



Trial flow chart

4.3 Withdrawal/loss-to-follow-up

Follow-up will be censored at death (unrelated to an outcome event), last available follow-up (if less than two years), or voluntary withdrawal from the trial.

4.4 Baseline patient characteristics

4.4.1 Baselines variables

The following baseline variables will be reported: Age, sex, comorbidities, living arrangements, functional status at randomisation, medications used before randomisation, physiological parameters, time from sICH to randomisation, location (non-lobar versus lobar) and volume (< 30 ml versus ≥ 30 ml) of sICH on CT or MRI before randomisation.

4.4.2 Descriptive statistics of baseline characteristics

Continuous variables will be presented using means and standard deviations (SDs), medians and minimum and maximum value, and quartiles. Categorical data will be presented using frequencies and percentages.

5 Analysis

5.1 Outcome definitions

5.1.1. Primary outcome:

The primary outcome is new symptomatic sICH (fatal or non-fatal) found on CT scan, MRI scan or by autopsy over at least two years follow-up. We will perform analysis of time to first event after two years follow-up as primary analysis and after total follow-up time as

secondary analysis. Those not experiencing the event will be censored at last available follow-up, death unrelated to a primary outcome or voluntary withdrawal from the trial (whichever occurs soonest).

5.1.2. Secondary outcomes:

Secondary outcomes will be analysed as composite endpoints except for functional outcome at two years (according to modified Rankin Scale) and death of any cause. The secondary endpoints will also be reported individually. Secondary outcomes will be analysed as reported by investigator.

5.1.2.1 Composite secondary outcomes:

The following composite endpoints will be analysed:

- ***Major ischaemic events***: Ischaemic stroke, myocardial infarction, mesenteric ischaemia, peripheral arterial occlusion, deep vein thrombosis, pulmonary embolism, revascularisation procedures (carotid, coronary or peripheral)
- ***Major haemorrhagic events***: symptomatic intracerebral haemorrhage, other symptomatic intracranial haemorrhages (epidural, subdural or subarachnoid haemorrhages both spontaneous and traumatic), symptomatic major extracranial haemorrhage requiring transfusion with more than 2 units of whole blood or red cells, a fall in > 2.0 g/L haemoglobin, bleeding in a critical area or organ (intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) or haemorrhage leading to death.
- ***Major adverse cardiovascular events (MACE)*** defined as ischaemic stroke, myocardial infarction, other major ischaemic events, intracerebral haemorrhage, other intracranial haemorrhage, major extracranial haemorrhage or vascular death.

Time to event for secondary outcomes except for functional outcome according to modified Rankin Scale will be defined in the same way as for primary outcome. Modified Rankin Scale is not subject to survival analysis and thus time to event is irrelevant for this outcome.

As for the primary outcome, secondary outcomes will be analysed as time to first event after two-years follow-up and after total follow-up time.

5.2 Analysis methods

Analyses will be performed separately for participants included in the antiplatelet trial and participants included in the anticoagulant trial.

5.2.1 Primary analysis

Primary analysis is a comparison between groups of time-to-first event of new symptomatic sICH during two-year follow-up. This will be assessed by generating life tables, Kaplan-Meier curves and applying log-rank test.

The sample size calculation, performed before the study was started, is based on comparisons of proportions. However, in the protocol (latest protocol version v210421), time-to-event-analysis is defined as primary analysis. We will follow the protocol.

To adjust the differences between the groups, Cox proportional hazards (PH) regression model will be used. The results will be presented as an adjusted hazard ratio with the corresponding 95% CI.

All regression analyses will be adjusted for the variables being part of the minimisation criteria. If adjustment for all these variables is not possible due to few events (and consequently low power), age (< 70 versus ≥ 70) and ICH location will be prioritized.

If the PH assumption is violated, time-dependent covariates will be included.

Since death is a competing risk, we will perform competing risk model as a sensitivity analysis.

5.2.2. Secondary analyses

Secondary dichotomous composite outcomes will be analysed using the same statistical approach as primary outcome, i.e. by Kaplan-Meier curves, log-rank test, and Cox PH model. Ordinal outcome of function (modified Rankin Scale) will be analysed by an ordinal logistic regression model if the proportional odds assumption is confirmed. Adjustments for covariates will be performed in the same manner as for primary analysis.

5.2.3 Exploratory analyses

If appropriate, primary and secondary outcomes will be compared between subgroups of patients defined by median age, timing of treatment initiation (0 to 6 days, 7 to 30 days and ≥ 31 days) and haemorrhage location (lobar versus non-lobar). For participants randomised to anticoagulants versus control, relevant subgroups also include CHA^2DS^2VASc score (median score as cut-off) and HAS-BLED score (median score as cut-off). The same statistical analyses as described above will be applied.

If low power, we will only present descriptive numbers and not statistical tests.

5.2.4 Hierarchical structure:

Since the study is multicentre, data might exhibit a hierarchical structure with some degree of cluster effect within study centres. The intra-class correlation coefficient (ICC) will be estimated to assess the possible cluster effect in all outcome variables. If ICC will show to be non-negligible suitable adjustment of statistical methods specified above will be applied through inclusion of random effects on study centre into the considered models. In such a

case, frailty models (Cox PH model with fixed and random effects) and generalized linear mixed models will be estimated instead of Cox PH model and ordinal regression model, respectively.

5.2.5 Quality control

Prior to statistical analysis a thorough quality check of the data base will be performed and obvious mistakes properly handled.

5.3 Missing data

During the study period, comprehensive efforts will be made to obtain complete outcome data. In case of missing values, different approaches will be considered to handle them, such as complete case analysis, multiple imputation or inverse probability weighting. Thorough sensitivity analyses will be performed in the case of imputation.

5.4 Statistical software

We plan to use the statistical software STATA version 17 or a more recent version.

5.5 References in Trial Master File

Data Management Plan

Protocol Deviation Handling Plan

Other Standard operating procedures to be adhered to

6 References

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