Protocol

Study of Antithrombotic Treatment after Intracerebral Haemorrhage (STATICH)

A randomised-controlled trial of antithrombotic treatment for prevention of ischaemic events after intracerebral haemorrhage

EudraCT number: 2014-002636-13

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Signature page

Sponsor

_____

Director of research (signature and date)
Oslo University Hospital

_____

Trial co-ordinating investigator (signature and date)
Oslo University Hospital

Principal investigator

I have read this protocol and agree that it contains all the necessary details for carrying out the study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention and the conduct of the study.

_____

Principal investigator (signature and date)

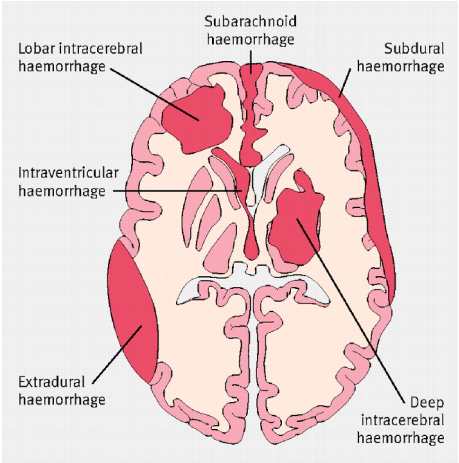
_____

Name of institution

1 Background

1.1 Rationale for the study

Intracerebral haemorrhage (ICH) refers to bleeding within the brain parenchyma or into the ventricular system, i.e. bleedings that are not extradural, subdural or subarachnoid (1). This trial is restricted to adults with stroke due to spontaneous ICH, which affects ~1,500 adults in Norway and almost 3000 adults in Sweden each year. Within one month of ICH ~40% of patients die and more than half the survivors are dependent on help from others(2).



Intracranial haemorrhage types (1)

Patients with spontaneous ICH have an increased risk of recurrent ICH. However, they also have an increased risk of ischaemic diseases, and many patients with ICH have also had ischaemic stroke (14%) or ischaemic heart disease (8-21%)(3, 4), or have risk factors for ischaemic disease, for example hypertension (47- 66%), smoking (41%), atrial fibrillation (11-14%) and diabetes mellitus (11-14%) (3, 4). These risk factors and diseases may also cause ischaemic events after ICH, which – overall – appear to occur with a similar frequency to recurrent ICH (5-21).

Annual absolute risk estimates of vascular events for all patients with intracerebral or intracranial haemorrhage who survive for at least one month

Vascular death	Myocardial infarction	Ischaemic stroke	ICH
0,7 % to 3,2%	1,3%	1.3% to 3%	1.8% to 7.4%

However, little is known about the benefits and harms of using antithrombotic drugs for prevention of ischaemic events in patients who have had an ICH. Among individuals at high risk because of a prior ischaemic event, but without an ICH, aspirin provides absolute reductions in serious vascular events from 8.2% to 6.7% per year, in stroke from 2.5% to 2.1% per year, and in coronary events from 5.3% to 4.3% per year, despite a non-significant increase in the risk of ICH (22). Likewise, among patients with atrial fibrillation, who are at risk of stroke due to cardio-embolism, treatment with vitamin K antagonist (VKA) leads to a relative risk reduction for ischaemic stroke of 67% (23). Non-vitamin K antagonist Oral Anticoagulants (NOACs) have been shown to provide protection that is similar to this (24). The risk of ICH while on VKA is 0,3 to 3% per year, and increases with increasing age (25-28), and the risk is reduced by half in patients treated with NOACs compared to VKA (24). Importantly, patients with ICH have not been included in trials of antiplatelet or anticoagulant agents for secondary prevention. However, it is possible that the benefits of secondary prevention with antithrombotic drugs will apply after ICH, among patients who have clear indication for such agents.

1.2 Risks and benefits of antithrombotic treatment after intracerebral haemorrhage

Around 40-50% of patients use, or have an indication for antithrombotic drugs, at the time of ICH (20, 29). The proportion of anticoagulant treatment at the time of ICH is increasing: 8.1 % in 2006 and 14.6 % in 2012 (30). It has long been unclear whether patients who develop spontaneous ICH while taking antithrombotic drugs for the prevention of ischaemic disease (for example, patients taking antiplatelet drugs after myocardial infarction or patients taking an anticoagulant for atrial fibrillation), should receive antithrombotic drugs for continued secondary prevention of ischaemic disease (31). There are three observational studies addressing the safety of long-term antiplatelet drugs for secondary prevention after spontaneous ICH (32-34). There are also a few observational studies addressing whether, when and in whom to restart anticoagulation after intracranial or intracerebral haemorrhage (20, 30, 35-42). Most of the observational studies are small, and the results are not conclusive. Overall, these observational studies of antiplatelet or anticoagulant treatment after ICH suggest that there is no increased risk of haemorrhagic complications (including new ICH), and that there might be a reduction in ischaemic complications.

It is also uncertain whether findings on brain CT or MRI has an impact on the effect of antithrombotic drugs after ICH: Brain microbleeds on magnetic resonance imaging (MRI) seem to indicate vascular pathological states, e.g. hypertensive vasculopathy or cerebral amyloid angiopathy (CAA) and appear to be associated with an increased risk of both ischaemic and haemorrhagic strokes in the general population (43). Brain microbleeds restricted to lobar locations indicate CAA, while deep hemispheric or infratentorial locations indicate hypertensive vasculopathy (44). In patients with CAA, lobar microbleeds are a predictor of recurrent ICH (45). One study found that the hazard- ratio for lobar ICH recurrence associated with aspirin increases with increasing numbers of brain microbleeds (32). The sample sizes of these studies were not large and allocation to aspirin was not randomised, so chance, bias and confounding might have influenced their results.

Because of the lack of randomised-controlled trials and the findings of the observational studies discussed above, guidelines have variably endorsed both starting and avoiding antithrombotic drugs after ICH (46, 47). Consequently, either starting or avoiding antithrombotic drugs for the prevention of ischaemic disease after spontaneous ICH are forms of standard clinical care (48), and clinical equipoise between these two treatment policies are confirmed in surveys in the UK and Norway (49).

Because the benefits of antithrombotic drugs for the prevention of ischaemic disease are likely to continue to apply after ICH, because observational studies indicate that there is no increase in the risk of recurrent ICH, and because starting antithrombotic drugs after ICH occurs in standard clinical practice (20, 30, 48), we believe that a randomised-controlled trial is warranted. *A randomised-controlled trial like STATICH is needed to address the uncertainty about whether to give or avoid antithrombotic drugs after ICH*. Furthermore, since findings on MRI can be biomarkers for subsequent bleeding, *we will also perform MRI scanning to assess the association between such findings on MRI and risk of recurrent ICH during treatment with antithrombotic drugs*.

2 Study questions

2.1 Primary study question

What are the effects of antithrombotic drugs on the risk of recurrent symptomatic ICH associated with a policy of starting antithrombotic drugs after the acute phase of spontaneous ICH?

2.2 Secondary study question

Is there an interaction between the presence of brain microbleeds on MRI and the effect of antithrombotic drugs on the risk of recurrent ICH?

3 Aims

The aims of the study are to answer the primary and secondary study questions:

3.1 Primary aim

To estimate the effects of antithrombotic drugs on the risk of recurrent symptomatic ICH associated with a policy of starting antithrombotic drugs after the acute phase of spontaneous ICH.

3.2 Secondary aim

To assess whether there is an interaction between the presence of brain microbleeds on MRI and the effect of antithrombotic drugs on the risk of recurrent ICH.

4 Study design, material and methods

STATICH is an investigator-led, multicentre randomised-controlled, open, blinded end-point (PROBE) clinical trial comparing two forms of standard care at multiple hospitals in Norway, Sweden and Denmark.

4.1 Patient population

Inclusion criteria

- Patient age ≥18 years.
- Spontaneous, primary ICH of ≥1 day after onset of qualifying ICH, i.e.:
    - No *preceding* traumatic brain injury, based on history from the patient/witness of spontaneous symptom onset, and brain imaging appearances consistent of spontaneous ICH (i.e. any brain/bone/soft tissue appearances of trauma must have occurred secondary to a spontaneous ICH)
    - No 'secondary' or underlying structural cause (e.g. haemorrhagic transformation of an ischaemic stroke, aneurysm, tumour, arteriovenous malformation, or intracerebral venous thrombosis)
- Patient has 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. 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 atheromas (primary prevention).
- Consent to randomisation from the patient (or personal/legal/professional representative if the patient does not have mental capacity, and waiver of consent is acceptable in the patient's country).
- CT and MRI (if possible) is performed before randomisation.

Exclusion criteria

- Clear indication for antiplatelet or anticoagulant treatment (e.g. prosthetic heart valves).
- Contraindications to the antithrombotic drug that will be administered.
- Patient is pregnant, breastfeeding, or of childbearing potential and not using contraception methods. A woman of childbearing potential must undergo a pregnancy test before randomisation and the result must be recorded in the CRF. Women of childbearing potential randomised to active treatment must use an effective method of contraception and undergo regular pregnancy testing during follow-up, and the results must be recorded in the CRF. Accepted methods of contraception are defined in the appendix.
- For patients in MRI substudy: Contraindication for the brain MRI
- Malignancy with life expectancy less than 2 years

4.2 Collection of baseline data, and randomisation

The eligibility criteria identify adults with stroke due to spontaneous, primary ICH who have indication for antithrombotic drugs for the prevention of ischaemic disease. Participants may be recruited during their hospital admission for the qualifying ICH or at a later stage in an outpatient clinic.

Cerebral CT and, if possible, , a MRI shall be performed before randomisation. We will want gradient recalled echo (GRE) T2*, T1, T2, FLAIR and DWI sequences to be performed, with susceptibility-weighted imaging if it is available, but routine MRI can also be used. All brain scans (CT or MRI) shall be sent to the Trial Co-ordinating Centre in DICOM format once the patient has been included.

At inclusion, the investigator enters the participant's baseline data into our computerised central randomisation service that allocates the patient a unique study identification number and informs the investigator about the participant's allocation to starting or avoiding antithrombotic drugs. The randomisation service will dynamically allocate treatment according to the minimisation algorithm, without a pre-determined allocation sequence, and only reveals treatment allocation for an individual participant after the investigator has submitted the baseline data. To avoid predictable alternation of treatment allocation (and consequent loss of allocation concealment) the minimisation algorithm will randomly allocate the first participant with a probability of 0.5 to one of the treatment groups. The randomisation algorithm for each

subsequent participant involves adaptive stratification (i.e. minimisation) and allocates them with a probability of 0.8 to the group which minimises differences between the two groups with respect to variables collected by the investigator before randomisation.

4.3 Treatment in the intervention and control groups

Patients will be randomly allocated to intervention or control. The *intervention* is a policy of giving antithrombotic drugs (antiplatelet drugs or anticoagulant drugs) after ICH. The *control* is a policy of avoiding antithrombotic drugs (Figure 1). Patients with an indication for *antiplatelet drugs* will be randomised to an antiplatelet drug or to avoid antithrombotic agents. Patients with atrial fibrillation, for whom there is an indication for *anticoagulant drugs*, will be randomised to anticoagulant drug or to avoid anticoagulant drugs (which means that antiplatelet drugs and left atrial appendage occlusion can be allowed in the control group, at the treating physician's discretion).

If a patient is randomised to intervention, the investigator is responsible for the choice and prescription of antithrombotic treatment and for the use of this treatment during the follow-up period. The prescribed antithrombotic drugs will be dispensed at the patient's local pharmacy. The use of antithrombotic treatment (mode of administration, dose, etc.) will be in accordance with the label for marketing authorisation. The following drugs have a marketing authorisation for prevention of ischaemic events, and will be used in the trial: aspirin, dipyridamole, clopidogrel, warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban.

The treatment allocation is open to participants, the clinicians caring for them in secondary and primary care, and local research staff. However, the Trial Co-ordinating Centre carrying out the patient follow-up and the Event Adjudication Committee will be blinded to participants' treatment allocation.

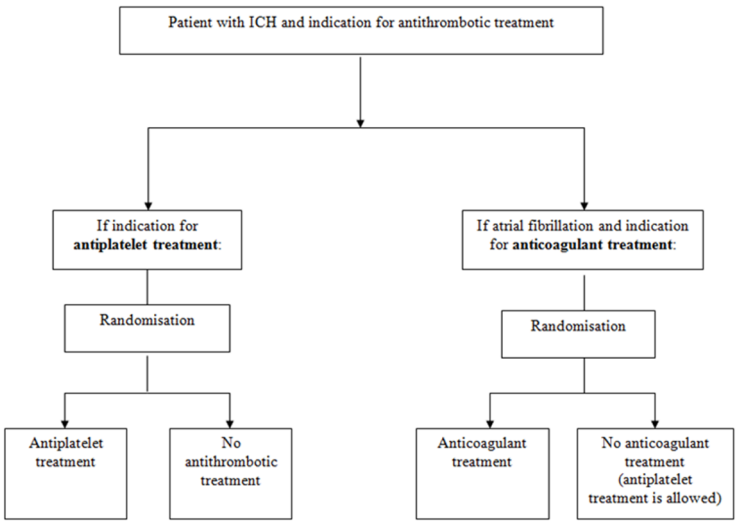


Figure 1: Trial flow chart

4.4 Follow-up

Trial participants will receive a Patient Card containing the study code, the name of the Sponsor, and the telephone number to the Trial Co-ordinating Centre. When the Trial Co-ordinating Centre is notified that a patient is included, and thereafter at 6 month's intervals, a letter will also be sent to the participant and to the GP to remind them of the treatment allocation. The letter will also contain information about the correct and safe use of the allocated treatment.

Participants will be visited every 6 months by the national Co-ordinating Investigator for at least two years after randomisation, normally by telephone and, in addition, by collection of data from the patient's medical records. The main focus of follow-up is patient's safety, and the national Co-ordinating Investigator will at each visit record patient's compliance with allocated treatment and any adverse events. Recording of compliance will be done by structured interviews with the patient (including checks of consistency of answers), his/her nearest relative and the GP, and by recording of batch numbers.

Antithrombotic treatment should be discontinued in case of an ICH or symptomatic major extracranial haemorrhage, in case of any serious adverse reaction (SAR) or if other serious adverse events occur, which, in the clinician's opinion, are likely to be caused by the trial treatment (suspected unexpected serious adverse reactions, SUSARs). Participants can also at any time decide if they want to discontinue treatment, follow-up, or both. The trial treatment should not be discontinued routinely if an event occurs, which is not likely to be caused by the trial treatment, such as ischaemic events.

Long-term follow-up at 5 and 10 years will occur by contact (normally telephone) and, in addition, by collection of data from the patient's medical records and by performing linkage with patients' data in national registries (national hospital patient registries, death registries, drug prescription registries and stroke registries) to determine long-term survival and risk of vascular events. During follow-up, patients are allowed to be included in other trials if they wish, as long as no interaction between trial interventions can be expected, and as long as co-enrolment does not interfere with follow-up in STATICH.

For participants in the MRI-sub study we will perform a MRI of the brain 2 years after randomisation.

4.5 Effect variables

Primary effect variable
Fatal or non-fatal symptomatic ICH.

Secondary effect variables
- Functional outcome at two years (according to the modified Rankin Scale)
- Death of any cause
- Vascular death
- Symptomatic epidural, subdural, or subarachnoid haemorrhage
- Symptomatic major extracranial haemorrhage
- Clinically relevant non-major bleeding
- Ischaemic events: transient ischaemic attack, ischaemic stroke, unstable angina, acute myocardial infarction (type 1), peripheral arterial occlusion, mesenteric ischaemia, retinal arterial occlusion, revascularisation procedures, deep vein thrombosis or pulmonary embolism.

4.6 Statistical considerations

There is uncertainty about the absolute risks of recurrent ICH among survivors who are taking antithrombotic drugs after an ICH. A review of the literature suggests that the risk for recurrent ICH lies in the range of about 1-2% per year among patients not taking antithrombotic drugs after an ICH. The risk is about 1.8 to 7.4% per year among patients taking antiplatelet drugs (15), and about the same among patients taking anticoagulant drugs (35, 37, 40, 41, 50). Similarly, there is uncertainty about the relative increase in the risk of recurrent ICH on antiplatelet or anticoagulant drugs, but observational studies addressing the safety of long-term antiplatelet (32-34) or anticoagulant drugs(29, 35-42) indicate that there is no increased risk of recurrent ICH or other haemorrhagic complications. We would consider a four-fold increase (from 2% to 8%) to be unacceptable, and higher than any plausible effect on ischaemic events, in which case it may be inappropriate to consider a larger trial designed to demonstrate net benefit. With 500 participants randomised to antiplatelet drugs vs. control, or to anticoagulant drugs vs. control, STATICH will have more than 80% power at the 5% significance level to detect such a difference. The aim of the trial is to randomise 500 participants to antiplatelet drugs vs. control, and over 50 patients to anticoagulant drugs vs. control. This information will be used to assess the plausibility of a net benefit emerging in a larger main study.

Information from STATICH will also be used in a pre-planned individual patient data (IPD) meta-analysis together with its on-going sister trials in other European countries: The REstart or Stop Antithrombotics Randomised Trial (RESTART) and the Start or Stop Anticoagulants Randomised Trial (SoSTART) in the UK, RESTART Nord de France and the A3ICH trial in France and the Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation (APACHE-AF) trial in the Netherlands (51, 52), which means that, overall around 1500 patients will be included in a pre-planned statistical analysis (around 1,000 patients randomised to antiplatelet drugs

vs. control, and around 500 to anticoagulant drugs vs. control). Together, the six trials will have the possibility to answer whether antithrombotic treatment is beneficial after ICH. If no clear answer can be given, the meta-analysis will be used to plan a larger, definite study. Previous meta-analyses of randomised-controlled trials of antithrombotic drugs have provided reliable information on the relative effects of antithrombotic drugs in the sorts of people with ischaemic disease who will be recruited into STATICH(53)(22)(23)(24), and information about the overall rates of ischaemic events will be used together with reasonable assumptions about the effects of antithrombotic drugs on such events in order to assess the plausibility of a net benefit emerging in a larger main study.

The Trial Steering Committee will review the target sample size and adjust this based on accruing data on: the number of primary outcome events, completeness of follow up, and the enrolment into specific pre-specified subgroups (e.g. lobar ICH location).

The primary analysis will be performed separately among patients with an indication for antiplatelet agents and patients with indication for anticoagulant drugs, and will be restricted to the primary effect variable of symptomatic ICH. Secondary analyses will be performed for the secondary effect variables listed above. We will also perform sub-group analyses of the primary effect variable, and test for sub-group interactions, if appropriate. Relevant subgroups are those defined by age, type of antithrombotic treatment (type of antiplatelet or anticoagulant drug), time of start of treatment, CHA_2DS_2VASc score and HAS-BLED score (and the individual components within these scores). The MRI scans we will be able to assess the effects in subgroup of patients with microangiopathies, and explore whether there is a statistical interaction between the presence, number, or location of brain microbleeds and the effect of antithrombotic drugs on the primary effect variable.

In order 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). This will comprise a Kaplan Meier survival analysis of time to first event during at least two years of follow-up from randomisation. 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. We will compare the survival function in the two trial arms over two years using a Cox proportional hazards regression model, adjusting for all the covariates included in the minimisation algorithm, and presenting the result as an estimated adjusted hazard ratio with its corresponding 95% confidence interval.

5 Conduct of the trial, and practices/procedures

We aim to enrol 500 participants in STATICH. Based on the annual number of patients with ICH, the proportion of patients that will be eligible for the trial, and the number of centres that have expressed an interest for the trial, we have estimated that 500 patients can be included. The formal approvals, the case report forms (CRF), the randomisation system, and the patient data database will be in place during 2017, so that patient recruitment can start during the first half of 2018. The following is the time schedule for the trial:

	2018		**2019**		**2020**		**2021**		**2022**		**2023**		**2024**		**2025**	
	1	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
Collaborators’ meeting	x															
Initiation visits to centres	x	x	x	x	x	x										
Patient recruitment	x	x	x	x	x	x	x	x	x	x	x					
2-years’ follow-up					x	x	x	x	x	x	x	x	x	x	x	
Study close-down																x

Data analysis																x
Presentation of results																x

5.1 Compliance with regulations and guidelines

The trial will conform to the EU Clinical Trials Directive (2001/20/EC) and national applicable regulatory requirements. EudraCT number: 2014-002636-13. The trial is registered: ClinicalTrials.gov ID number NCT03186729.

5.2 Data protection

Personal identifiers will not be stored together with clinical information about the patient, but will be stored on a separate, password-protected computer with access only for persons in the Trial Co-ordinating Centre who are responsible for central follow-up. The code linking personal identifiers with clinical data will be destroyed 15 years after the publication of the primary report, of the trial. The procedures for protection of personal information will be approved by the Research Ethics Committee, and the Norwegian Data Inspectorate.

5.3 Ethical conduct

The trial will be conducted in accordance with the MRC Guidelines for Good Clinical Practice in Clinical Trials, the Council of Europe's Convention on Human rights and Biomedicine (CETS No.: 164), the ICH Harmonized Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) and the Declaration of Helsinki (Edinburgh, October 2000).

We will seek informed consent from all patients, and approval from the ethics committees, according to local or national regulations. All patients will be monitored carefully during treatment and follow-up, and procedures for management of adverse drug reactions and reporting of adverse events are given in the protocol. All events will be evaluated, and the trial will be monitored, audited, and inspected according to applicable regulatory requirements.

5.4 Liability

Patients are indemnified by insurance specific for patients participating in trials of an Investigational Medicinal Product (IMP). Patients are also covered for non-negligent liability by the product indemnity provided by the supplier.

5.5 Recording and reporting of adverse events

All adverse events will be recorded in the case report forms. Definitions of adverse events and serious adverse events are given in the appendix. In case of unexpected serious adverse events, the Trial Co-ordinating Centre should be notified immediately and within 24 hours at the latest, in accordance with the EC guidance document 2011/C 172/01 ("CT-3"). The report of the SAE must include an assessment of whether there is a reasonable possibility that the IMP caused the event.

The Sponsor has the responsibility for assessing whether there is a possible causality between IMP and the event. Reports of suspected unexpected serious adverse reactions (SUSARs), with all relevant information, will be reported in an expedited manner by the Sponsor, to the competent authority, the ethics committee, and the Data Monitoring Committee, according to the EU Clinical Trials Directive (2001/20/EC) and applicable regulatory requirements. Copies of such reports will be sent to the principal investigators and the Sponsor.

Serious adverse events that are expected will not be reported in an expedited manner by the Sponsor, for example ischaemic stroke, intracranial haemorrhage, myocardial infarction, or death. These are events that are expected, and that will be reported as end-points in the case report forms. The Summaries of Product Characteristics (SmPCs) are defined as reference safety information for the trial. Expected adverse reactions listed in the safety sections of SmPCs will therefore not be regarded as SUSARs, and will not be reported in an expedited manner.

5.6 Event adjudication

A central Event Adjudication Committee will evaluate all events, blinded to treatment allocation.

5.7 Monitoring of data quality

The central computer randomisation system will check eligibility for all patients entered in the trial. Data entered over the Internet (at trial entry) and data in case report forms will be checked for validity and internal consistency, to ensure high data quality and completeness, and coherence with the protocol. Centres with poor standards will be contacted and appropriate measures will be taken. During the course of the study the Sponsor will visit all centres at start-up and at least once for monitoring purposes, with review of the CRF, comparison with source documents, and observation of the conduct of the trial and adherence to the protocol. It will be particularly important to check that each patient exists, that a valid consent form is present, to confirm patient information and adherence to the protocol. There will also be frequent telephone contacts, with the purpose of facilitating the work and fulfilling the objectives of the study.

5.8 Handling of protocol violations and protocol amendments

The nature and reasons for the protocol violation shall be recorded in the CRF, in the source documents and in the monitoring visit report. Corrective and/or preventive actions will be undertaken and documented, including any retraining of the investigator and site staff. All patients who have been included in the trial will be followed up, irrespective of whether treatment was discontinued prematurely, or whether the protocol was violated. If treatment discontinuations or protocol violations become frequent the Data Monitoring Committee will consider whether there is a need to increase the number of patients to be included in the trial.

All important changes to the trial will be specified in protocol amendments. Amendments must be approved by the Steering Committee, and the Sponsor has the responsibility to seek approval from the competent authorities and the ethics committees. Completed and signed protocol amendments will be circulated to all those who were on the circulation list for the original protocol.

5.9 Monitoring of effectiveness and safety

The overall responsibility for the safety of trial participants lies with the Sponsor. During the course of the trial the Data Monitoring Committee (DMC) will every 12 months perform an unblinded review of SAEs, in all patients, and in the pre-specified subgroups. The DMC will also perform an unblinded interim analysis of the primary effect variables when half of the patients have been included. If, in their view, there is credible evidence of harm, or overwhelming evidence of efficacy, the committee will advise the chairman of the Steering Committee. Unless this happens, the Steering Committee will remain ignorant of the interim results.

The exact terms of reference for the DMC, including the criteria for "proof beyond reasonable doubt" and the criteria for premature modification or stopping of the trial, will be specified in the DMC Charter. The criteria will not be based solely on statistical considerations, and the criteria for benefit or harm may not be symmetrical: A much weaker signal might be needed for claiming harm than for claiming benefit. However, as a general rule, the DMC will work along the principle that a difference of at least 3 standard errors of a major effect variable will be needed to justify modifying the study prematurely.

5.10 Audit and inspection

All source data and all trial data and material will be made directly available for audit and inspection. Source data is all information in original records and certified copies of original records that is necessary for the reconstruction and evaluation of the trial.

5.11 Handling of patient data

All patients will be assigned a unique code number. The patient data will be linked to this number, and the patients' names or other personal identifiers will not be included in the database. The patient database will be kept on a separate, secure computer. The code will be stored on another, secure computer, and will be deleted 15 years after the results of the trial have been published. The trial's procedures for data protection will conform to the Norwegian applicable regulatory requirements, and to the conditions set by the Norwegian Data Inspectorate.

5.12 Handling of the list of treatment codes

The lists of random treatment codes will be produced by the Statistical Centre at the University of Edinburgh. Copies of the list will be kept by the person setting up the central randomisation system, and the Trial Statistical Centre. The list will be kept secret for all other people involved in the trial until the closure of the patient database.

5.13 Screening logs

Selected centres will be asked to make records of all patients considered for inclusion in the trial (screening logs).

5.14 Financial conduct

Contracts will be agreed between the Sponsor and each of the investigators/institutions. The Co-ordinating Investigator or other people centrally involved in the trial will not have any financial or other conflicts of interest in connection to the trial. Patients participating in the trial will be reimbursed for their travel expenses.

5.15 Publication and data sharing policy

The trial will be published in accordance with the CONSORT guidelines and will be presented by a writing committee on behalf of the investigators. All participating centres and collaborators will be acknowledged in the main publication. The primary results and results of any substudies will be presented at international meetings and in public media.

5.16 User involvement

Representatives of national stroke patient organisations will participate in the Steering Committee, and will be consulted in all phases of the study.

6 Organisation

6.1 Sponsor and funding bodies

The Oslo University Hospital will be the Sponsor of the trial. The Director of research will act as the Sponsor's legal representative.

The trial has received basic funding from Oslo University Hospital, Umeå University, and Västerbottens läns landsting, and will seek additional funding from Northern Norway Regional Health Authority and Research Council of Norway.

6.2 Trial Co-ordinating Centre

The Trial Co-ordinating Centre will be hosted within the Stroke Research Group at Oslo University Hospital (Ullevål). Members of the research group responsible for the trial are Torgeir Bruun Wyller (Trial Co-ordinating Investigator), Ole Morten Rønning (Trial Co-ordinating Investigator), Kristin Tveitan Larsen (Trial Manager), and a Trial Secretary. The Trial Co-ordinating Centre will work in close collaboration with National Co-ordinating Investigators in Sweden and Denmark.

6.3 Steering Committee

Ole Morten Rønning, Rustam Al-Shahi Salman, Christina R. Kruuse, Eva-Lotta Glader, Johanna Pennlert, Per Wester, Elisabeth Forfang, Kristin Tveitan Larsen, Hege Ihle-Hansen, Torgeir Bruun Wyller, others (to be appointed)

6.4 Data Monitoring Committee and Event Adjudication Committee

An independent Event Adjudication Committee and Data Monitoring Committee will be established before the start of the trial. The members will be listed in the final trial protocol.

6.5 MRI Review Committee

Ole Morten Rønning (chair), Maria Carlsson, Kristin Tveitan Larsen

6.6 STATICH Study Group

The study group consists of all centres that participate in the trial, and will meet regularly at regional and national collaborators' meetings.

7 Scientific relevance

The incidence of stroke is increasing, partly due to an ageing population. At the same time, case fatality after stroke is decreasing, and this means that the number of stroke survivors will increase substantially during the coming years. In Norway, the average cost of a stroke is 600.000 NOK, and the annual costs of stroke is estimated to a total of 7-8 billion NOK, mainly because of high costs related to long-term care and rehabiliation of survivors (54). This is particularly true for spontaneous ICH, which affects ~1,500 adults in Norway each year, because a large proportion of survivors after ICH are dependent of help from others. Among long time survivors after ICH, a large proportion live functionally independent lives in their private homes (55).

Many patients with ICH are at risk for ischaemic disease, and there is uncertainty about the net benefit of giving antithrombotic therapy after ICH. The proposed study has the potential to clarify whether such treatment should be given or whether it should be avoided, and to cause cost-savings to society. The study will also tell us whether the presence of findings on cerebral MRI increases the risk of recurrent ICH in patients treated with antithrombotic agents, so that treatment can be tailored to patients with most chance of benefit and least risk of harm.

The results will be published in international peer reviewed journals, and presented at international scientific meetings. In addition we will communicate the results as popular science articles in newspapers and other public media.

8 Ethical considerations

Surveys in the UK and in the Scandinavian countries have shown that there is equipoise between giving or avoiding antithrombotic drugs for the prevention of ischaemic disease after spontaneous ICH (49). Both treatments are forms of standard clinical care (48), and to investigate which of the two options has the most beneficial effect on outcome should not rise an ethical conflict. The study will be conducted in accordance with the principles of GCP. A favourable ethical opinion will be obtained from the Regional Ethics Committee. If a patient lacks capacity to consent for themselves, a legal representative may provide consent on the patient's behalf. If a participant regains capacity, the participant should be informed about their enrolment in the trial and fully informed consent should be obtained from the participant. Linkage with national registers will be anonymous and all results will be presented on a group level. The Principal Investigator at each centre is responsible for the overall conduct of the study at the site and ensuring any person delegated responsibilities is fully informed, understands and is fully compliant with the protocol and any protocol amendments

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10 Appendix

10.1 Definition of adverse events

Adverse event
An adverse event (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an IMP.

Adverse reaction
All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Serious adverse event
A serious adverse event (SAE) is any adverse event that at any dose:
- results in death
- is life threatening
- requires hospitalisation or prolongation of an existing hospitalization
- results in persistent or significant disability or incapacity
- consists of a congenital abnormality / birth defect
- results in any other significant medical event not meeting the criteria above

10.2 Definition of effect variables

Symptomatic ICH
Neurological deterioration or death associated with intracerebral haemorrhage found on CT scan, MRI, or autopsy

Symptomatic major extracranial haemorrhage
Clinically overt bleeding associated with one or more of:
- Transfusion of >2 red cell units of blood
- A fall in haemoglobin of 2 g/dL, (1.24 mmol/L)
- Bleeding into retroperitoneum, intraocular space or major joint
- Bleeding leading to permanent treatment cessation

Myocardial infarction (type 1)
Typical rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit, and at least one of the following:
- Symptoms of ischaemia
- Typical changes in the electrocardiogram
- Identification of an intracoronary thrombus by angiography or autopsy

- Imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality
-

Deep vein thrombosis
The clinical suspicion of deep vein thrombosis will need confirmation by either venography or ultrasound examination

Pulmonary embolism
The clinical suspicion of pulmonary embolism will need confirmation by either: ventilation-perfusion lung scintigraphy, pulmonary angiography, inconclusive lung scintigraphy and diagnosed deep vein thrombosis, or autopsy.

10.3 Accepted methods of contraception

Methods with a failure rate of <1% per year when used consistently and correctly:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation 1 (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence