Antithrombotic treatment after intracerebral haemorrhage (Protocol)

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A B S T R A C T

This is the protocol for a review and there is no abstract. The objectives are as follows:

Primary objective

To determine the effectiveness and safety of antithrombotic treatment in survivors of intracerebral haemorrhage (ICH).

Secondary objective

To determine whether the effectiveness and safety of antithrombotic treatment differs in pre-specified subgroups (see Subgroup analysis and investigation of heterogeneity).

B A C K G R O U N D

Description of the condition

Intracerebral haemorrhage

Intracerebral haemorrhage (ICH) is the extravasation of blood into brain parenchyma (bleeding within the brain) following rupture of a cerebral artery or arteriole. The Global Burden of Disease (GBD) Study estimated that in 2010 there were 5.32 million incident (first ever) haemorrhagic stroke events globally, resulting in an incidence of 81.52 (95% confidence interval (CI) 72.27 to 92.82) per 100 000 person-years (Krishnamurthi 2010). Hypertension is the most common cause of non-traumatic, spontaneous ICH, and is responsible for approximately half of cases (MacKenzie 1996). Other aetiologies include amyloid angiopathy (deposits of abnormal proteins within blood vessels), arteriovenous malformations (abnormal vascular architecture), haemorrhagic transformation of ischaemic infarcts (ischaemic strokes that subsequently bleed), and

bleeding diatheses (predispositions), particularly from complications of antiplatelet, anticoagulant, and thrombolytic therapy.

Outcome of intracerebral haemorrhage

Survivors of ICH are at risk of recurrent ICH, particularly if the underlying cause of the incident ICH is not treated (e.g. hypertension, arteriovenous malformation). They are also at risk of ischaemic events of the brain (ischaemic stroke, i.e. stroke due to blocked blood vessel), heart (myocardial infarction) and other organs, due to associated co-morbidities (e.g. ischaemic and hypertensive heart disease, intracranial small vessel disease) and treatments (e.g. atrial fibrillation requiring prophylactic anticoagulation).

A review of observational studies found that the annual risk of recurrent ICH was 2.0% to 2.4%, with the risk of recurrence in the first year being between 1.8% and 7.4% (Poon 2014). The Poon 2014 review included three studies that compared outcomes after ICH in different locations within the brain (lobar and deep). Two of these three studies demonstrated that lobar ICH carries a recurrence rate per patient-year of 4.3% compared with 2.1% for deep haemorrhage (Poon 2014). Furthermore, no statistically significant difference was found between the risks of recurrent ICH and ischaemic stroke after ICH (Poon 2014). The presence of cerebral microbleeds on magnetic resonance imaging (MRI) or computed tomography (CT) at the time of ICH is associated with poor prognosis and an increased risk of recurrence; these microbleeds are also associated with prior antithrombotic use (Yates 2013).

Description of the intervention

Anticoagulants and antiplatelets are used to prevent thromboembolism (clots) in the brain, heart, limbs and lungs of individuals at risk. These anti-clotting benefits must be balanced against the increased risk of recurrent ICH and haemorrhagic complications associated with their use.

The practice of administering antithrombotics after ICH varies from 11% to 45% in different samples (Pasquini 2014). Population-based case-control studies report that, among those with ICH, about 20% were taking anticoagulants and 30% were taking antiplatelet agents at the onset of symptoms, whereas among populations free of ICH, about 6% were taking anticoagulants and about 23% were taking antiplatelet agents (Lauer 2013).

The indications (reasons) for continuing antithrombotic therapy after ICH may include the presence of prevalent risk factors for thromboembolism (e.g. atrial fibrillation, valvular heart disease, atherosclerosis (i.e. deposits of fat within arteries), pulmonary embolism or deep vein thrombosis (i.e. clots in the lungs or major leg veins)) and the indication for starting antithrombotic therapy after ICH may include new risk factors for thromboembolism (e.g. a

reduction in mobility predisposing to venous thromboembolism, or new atrial fibrillation).

Why it is important to do this review

The GBD 2010 study found an increase in incidence and a decrease in the mortality-to-incidence ratio (i.e. a reduction in the death rate) for haemorrhagic stroke during the period 1990 to 2010, reflecting the large and growing number of ICH survivors (Krishnamurthi 2010). Survivors face a high risk of death and clinical events, which may include future ischaemic and haemorrhagic vascular events. Antithrombotic therapy may reduce the risk of these ischaemic events, but could increase the risk of recurrent ICH and other haemorrhagic complications.

Little is known about the balance of the risks of taking antithrombotic therapy after ICH. While there are many observational studies that have addressed the use of antiplatelet and anticoagulant agents after ICH, most are not large enough. Two recent exceptions assessed anticoagulant resumption after ICH in people with atrial fibrillation (AF) (Kuramatsu 2015; Nielsen 2015). Kuramatsu 2015 and Nielsen 2015 had similar findings and found that anticoagulant resumption was associated with a statistically significant reduction in ischaemic complications, a survival benefit, and no statistically significant difference in haemorrhagic complications. Nielsen 2015 also included data on antiplatelet resumption, which was associated with higher rates of ischaemic complications and mortality, and a non-significant reduction in recurrent ICH when compared to anticoagulant resumption.

One systematic review conducted in 2002 identified three randomised controlled trials (RCTs) that included a subset of people who received antithrombotic treatment after ICH (Keir 2002). Due to scant outcome data and poor generalisability of the included studies, it was unable to draw any reliable conclusions. The important issue of whether and when to use antithrombotic treatment after intracerebral haemorrhage was identified as a dilemma in the European Stroke Organisation's guideline (Steiner 2014). This review aims to inform the current uncertainty about the risks and benefits of starting, re-starting, or avoiding antithrombotic treatment after ICH.

O B J E C T I V E S

Primary objective

To determine the effectiveness and safety of antithrombotic treatment in survivors of intracerebral haemorrhage (ICH).

Secondary objective

To determine whether the effectiveness and safety of antithrombotic treatment differs in pre-specified subgroups (see Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

We will include all RCTs that make unconfounded comparisons of antithrombotic treatment with no antithrombotic treatment for preventing thrombotic events after ICH, as well as those that make direct comparisons of different antithrombotic agents. We will include studies published in all languages and arrange translation where the language of publication is not English.

Types of participants

We will include studies whose participants survived a spontaneous ICH as diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI). We will include studies in which the participants were on antithrombotic treatment prior to ICH, as well as those in which participants were not taking these treatments at the time of ICH.

Types of interventions

We will include studies that compare the use of any antithrombotic treatment (e.g. anticoagulant or antiplatelet drugs) against no antithrombotic treatment for preventing thrombotic events after ICH, as well as studies that compare different antithrombotic agents. We will place no constraints on dosage, route of administration, or duration of administration.

Where a trial is confounded by the administration of an active therapy to participants, and this additional treatment is not accounted for by the randomisation process (i.e. this additional treatment is not spread equally across the two groups by the randomisation process), we will explore this in our risk of bias assessment and with sensitivity analyses.

Types of outcome measures

Primary outcomes

- Composite vascular endpoint (non-fatal or fatal ischaemic stroke, myocardial infarction, other major ischaemic event, intracerebral haemorrhage, major extracerebral haemorrhage, and vascular death from other cause) during the scheduled follow-up period.

Secondary outcomes

- Death and rate of death from all causes during the scheduled follow-up period.
- The individual components of the composite vascular endpoint: non-fatal or fatal ischaemic stroke, myocardial infarction, other major ischaemic event, intracerebral haemorrhage, major extracerebral haemorrhage, and vascular death from other causes).
- Functional status (modified Rankin scale) at the end of the scheduled follow-up period.
- Cognitive status at the end of the scheduled follow-up period.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We will search for trials in all languages and arrange for the translation of relevant articles where necessary.

Electronic searches

We will search the Cochrane Stroke Group trials register and the following electronic databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library, latest issue).
- MEDLINE (from 1948) (Appendix 1).
- EMBASE (from 1980).

We developed the MEDLINE search strategy (Appendix 1) with the help of the Cochrane Stroke Group Trials Search Co-ordinator and will adapt it for the other databases.

We will also search the following ongoing trials registers.

- ClinicalTrials.gov (www.clinicaltrials.gov/).
- Stroke Trials Registry (www.strokecenter.org/trials/).
- Current Controlled Trials (www.controlled-trials.com).

Searching other resources

We will screen the reference lists of relevant studies to identify further studies for potential inclusion in the review. We will also use Science Citation Index Cited Reference Search for forward tracking of relevant articles.

Data collection and analysis

Selection of studies

Independently, three review authors (LAP, JB, EF) will screen the titles and abstracts of the references obtained as a result of our searching activities and will exclude reports that are obviously irrelevant. We will retrieve full-text articles for the remaining references, and, independently, the same three review authors will screen these full-text articles to identify studies for inclusion, and identify and record reasons for the exclusion of ineligible studies. We will resolve any disagreements through discussion or, if required, we will consult a fourth review author (EB). We will collate multiple reports of the same study so that each study, not each reference, is the unit of interest in the review. We will record the selection process and complete a PRISMA flow diagram.

Data extraction and management

Independently, three review authors (LAP, JB, EF) will extract data from included studies using a pre-formulated data collection form.

Assessment of risk of bias in included studies

Independently, three review authors (LAP, JB, EF) will assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (EB). We will assess the risk of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

We will grade the risk of bias for each domain as high, low or unclear and provide information from the study report, together with a justification for our judgment, in the 'Risk of bias' tables.

Measures of treatment effect

We will convert categorical estimates of effect to the risk ratio (RR) or odds ratio (OR), as appropriate. We will express measures of survival as a hazard ratio (HR). We will use summary measures obtained from univariable or, where there are common covariates analysed between studies, from multivariable analyses.

Unit of analysis issues

Repeated observations on participants

We will analyse functional and cognitive status at end of follow-up, and not use repeat observations during follow-up. If one trial (or only a few trials) has a much longer period of follow-up than the majority of trials (for example, two years compared with six months in the majority of trials) we will perform a sensitivity analysis using the six-month observations from all trials.

Events that may reoccur

We will analyse the first event in all participants, and not later events.

Multiple intervention groups

Where a trial contains multiple treatment groups that are all compared with just one placebo group, we will ensure that the placebo group is shared between the multiple treatment groups by dividing it into the appropriate number of subgroups and conducting separate, independent comparisons.

Dealing with missing data

We will contact trial authors for unpublished data where relevant data are missing. Where only a minority of data are missing, we may ignore the missing data and perform a 'complete set analysis'. Where more substantial amounts of data are missing, and there is a chance that data are not missing at random, we will perform sensitivity analyses assuming both a best-case and a worst-case scenario, or apply statistical imputation or models, or both, to account for the missing data. A best-case scenario means that we will assume that all missing data in the intervention group represent good outcomes and all missing data in the control group represent poor outcomes. A worst-case scenario means that we will assume that all missing data in the intervention group represent poor outcomes and all missing data in the control group represent good outcomes.

Assessment of heterogeneity

We will investigate heterogeneity of the studies included using the I^2 statistic. We plan to interpret this value using the guide provided in Chapter 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: represents considerable heterogeneity.

If we observe substantial heterogeneity in our data, we will then use sensitivity analysis to elucidate which factors may be causing this effect.

Assessment of reporting biases

We will include all published and unpublished data and secondary publications from trials. If we included a sufficient number of trials (greater than 10), we will assess the likelihood of reporting biases through the use of a funnel plot.

Data synthesis

Where we consider studies to be sufficiently similar, we will conduct a meta-analysis by pooling the appropriate data using RevMan 5.3 (RevMan 2014). We will calculate the risk ratios (RR), odds ratios (OR) or hazard ratios (HR) for each outcome from data extracted from included trials using the Peto fixed-effect method, and where there is significant heterogeneity between trials we will use the random-effects method. Significant heterogeneity is defined as substantial clinical or methodological diversity between trials such that the true effect measure is no longer uniform.

'Summary of findings' table

We will create a 'Summary of findings' table using the GRADE-pro Guideline Development Tool for the following outcomes (GRADEpro GDT): composite vascular endpoint, all-cause death, functional outcome, and cognitive status. Independently, two review authors (LAP, JB) will classify the quality of the evidence as being either 'high', 'moderate', 'low', or 'very low', based on the presence and extent of the following five criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- Limitations in the design and implementation of the contributing trials
- Indirectness of evidence
- Unexplained heterogeneity or inconsistency of results
- Imprecision of results
- High probability of publication bias

We will provide justification in the footnotes when we downgrade the quality from 'high'.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses, if possible.
- Different classes of antithrombotic agents
- Different intensities of antithrombotic treatment
- Different times of start of treatment (e.g. within one month of ICH versus later, or within 10 to 30 weeks or later)
- Participants that were on antithrombotic treatment prior to ICH (possible re-starters) versus participants who were not receiving these treatments (possible starters)
- Different levels of risk for future ischaemic events (for example, because of differences in age, sex, history of hypertension, history of atrial fibrillation (with further stratification by the CHADS2Vasc score))
- Different levels of risk for future ICH; many are similar to risk factors for ischaemic events: age, blood pressure, etc (e.g. PANWARDS score) or ECH (e.g. HASBLED scores)
- Different findings on CT or MRI (in particular microbleeds on MRI)

Sensitivity analysis

If the results are heterogeneous, we will use sensitivity analysis to investigate how the results differ when we exclude trials that were found to have a high risk of bias. We will also perform other sensitivity analyses to explore reasons for heterogeneity, for example, where there is an active therapy other than an antithrombotic drug that is not balanced by the randomisation process.

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Kuramatsu 2015
Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres

M, Sobesky J, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA* 2015;**313**(8):824–36.

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antithrombotic drugs at hospital discharge after ICH. *Stroke* 2014;**45**:2643–8.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

Antithrombotic treatment after intracerebral haemorrhage
MEDLINE (Ovid)
1. exp basal ganglia hemorrhage/ or intracranial hemorrhages/ or cerebral hemorrhage/ or intracranial hemorrhage, hypertensive/
2. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.
3. ((h?emorrhag$ or bleed$) adj5 (stroke or apoplex$)).tw.
4. (ICH or ICHs).tw.
5. 1 or 2 or 3 or 4
6. exp anticoagulants/
7. exp Vitamin K/ai or thrombin/ai or factor Xa/ai or exp Blood coagulation factors/ai
8. exp antithrombins/ or hirudin therapy/
9. (anticoagul$ or antithromb$).tw.
10. (Vitamin K antagonist$ or VKA or VKAs).tw.
11. (direct$ adj3 thrombin adj3 inhib$).tw.
12. DTI$1.tw.
13. ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj3 inhib$).tw.
14. (activated adj3 (factor X or factor 10) adj3 inhib$).tw.
15. (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ or warfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or esculi$ or ochratoxin$ or umbelliferone$ or dermatan sulfate$ or dextran$ or edetic acid$ or

enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosan sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin$).tw,nm.

16. (tinzaparin or parnaparin or dalteparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw,nm.

17. (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw,nm.

18. (argatroban or MD805 or MD-805 or dabigatran or ximelagatran or melagatran or efegatran or flovagatran or inogatran or napsagatran or bivalirudin or lepirudin or hirudin$ or desirudin or desulfatohirudin or hirugen or hirulog or AZD0837 or bothrojaracin or odiparcil).tw,nm.

19. (xabans or antistasin or apixaban or betrixaban or du 176b or eribaxaban or fondaparinux or idraparinux or otamixaban or razaxaban or rivaroxaban or yagin or ym 150 or ym150 or LY517717).tw,nm.

20. exp platelet aggregation inhibitors/ or exp platelet glycoprotein gpiib-iiia complex/ai

21. (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj3 inhibit$) or (thrombocyt$ adj3 inhibit$)).tw.

22. (alprostadil$ or aspirin$ or acetylsalicylic acid or acetyl salicylic acid$ or acetyl?salicylic acid or epoprostenol$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or procainamide$ or thiophen$ or trapidil$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or ((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or triflusal).tw,nm.

23. (Beraprost or Cicaprost or Cilostazol or Clopidogrel or Dipyridamole or Iloprost or Indobufen or Lepirudin or Pentosan Polysulfate or Pentoxifylline or Piracetam or Prostacyclin or Sulfinpyrazone or Sulphinpyrazone or Ticlopidine or Triflusal or Abciximab or Disintegrin or Echistatin or Eptifibatide or Lamifiban or Orbofiban or Roxifiban or Sibrafiban or Tirofiban or Xemilofiban or terutroban or picotamide or prasugrel).tw,nm.

24. (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix or ReoPro or Integrilin$ or Aggrastat).tw,nm.

25. or/6-24

26. Randomized Controlled Trials as Topic/

27. random allocation/

28. Controlled Clinical Trials as Topic/

29. control groups/

30. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/

31. double-blind method/

32. single-blind method/

33. Placebos/

34. placebo effect/

35. randomized controlled trial.pt.

36. controlled clinical trial.pt.

37. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.

38. (random$ or RCT or RCTs).tw.

39. (controlled adj5 (trial$ or stud$)).tw.

40. (clinical$ adj5 trial$).tw.

41. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

42. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

43. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

44. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

45. (placebo$ or sham).tw.

46. trial.ti.

47. (assign$ or allocat$).tw.

48. or/26-47

49. 5 and 25 and 48

50. exp animals/ not humans/

51. 49 not 50

CONTRIBUTIONS OF AUTHORS

All authors, Luke A Perry, Eivind Berge, Joshua Bowditch, Elisabeth Forfang, Ole Morten Rønning, Graeme J Hankey, Elmer Villanueva, Rustam Al-Shahi Salman, contributed to planning, writing, and editing the protocol.

DECLARATIONS OF INTEREST

Luke A Perry: none known

Eivind Berge: none known

Joshua Bowditch: none known

Elisabeth Forfang: none known

Ole Morten Rønning: none known

Graeme J Hankey: in the past three years, GJH has received honoraria from AC Immune for chairing the data safety monitoring committee of two clinical trials of vaccines for Alzheimer's disease, from Bayer for lecturing about stroke prevention in atrial fibrillation at sponsored scientific symposia, and from Medscape, Web MD for participating in a discussion about stroke prevention in atrial fibrillation for theheart.org.

Elmer Villanueva: none known

Rustam Al-Shahi Salman: Chief investigator of the UK REstart or STop Antithrombotics Randomised Trial (RESTART, www.RESTARTtrial.org, ISRCTN71907627), which is funded by a special project grant from the British Heart Foundation. His salary is paid by the UK Medical Research Council.