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Antithrombotic therapy to prevent cognitive decline in people with small vessel disease on neuroimaging but without dementia (Protocol)

Kwan JSK, Myint PK, Wong A, Mok V, Lau GKK, Mak KFH

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[Intervention Protocol]

Antithrombotic therapy to prevent cognitive decline in people with small vessel disease on neuroimaging but without dementia

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ABSTRACT

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

To assess the effects of antithrombotic therapy in preventing cognitive decline in people with small vessel disease on neuroimaging but without dementia.

BACKGROUND

Description of the condition

Significance of dementia

Dementia is of huge international concern. Worldwide, over 35 million people have dementia (Prince 2013), with almost half of all people aged 85+ years living with dementia. The worldwide annual cost of dementia is over US $600 billion (Wimo 2013). By 2050, it is estimated that the impact of dementia will exceed that of heart disease, cancer and stroke combined (World Alzheimer Report 2015). The currently approved treatments for Alzheimer's disease only have mild and short-term delaying effects on cognitive decline, and no drug can effectively halt or reverse disease progression.

Cerebrovascular contribution to Alzheimer's pathology

Alzheimer's disease is the commonest form of dementia, characterised by clinical progression with cognitive and physical decline. Despite decades of scientific research, the pathogenesis of Alzheimer's disease remains unclear. The "amyloid cascade hypothesis" of Alzheimer's disease suggests that amyloid-beta accumulation leads to neurofibrillary tangles, which are made up of hyperphosphorylated tau aggregation (Jack 2010). More recently, there is support for a "vascular hypothesis" in Alzheimer's pathogenesis (Grammas 2011). Autopsy studies have demonstrated significant interactions between cerebral aging, cerebrovascular damage and Alzheimer's pathology (Iadecola 2010). Vascular risk factors such

as diabetes, hypertension and adiposity are independent predictors of Alzheimer's disease (Akinyemi 2013). Markers of thrombosis, haemostasis and chronic inflammation are also linked to cognitive decline (Quinn 2011). Cerebrovascular damage can lead to blood-brain barrier disruption, impaired cerebral blood flow regulation, hypoxic injury, diminished amyloid-beta clearance, and neurotoxicity (Janota 2015). Amyloid-beta aggregation, in turn, can cause further cerebrovascular damage, thus perpetuating the cycle of neurodegeneration (Chiarini 2015).

Small vessel disease in stroke-free population

Cerebral small vessel disease can be visualised using magnetic resonance imaging (MRI) studies as lacunar infarcts, white matter hyperintensities, and cerebral microbleeds (Boutet 2016; Mok 2015). Positive MRI findings of small vessel disease frequently occur in patients without a prior history of symptomatic focal neurological deficit such as stroke or transient ischaemic attack (TIA). Computed tomography (CT) scanning is another clinical tool, but its diagnostic precision is inferior to that of MRI (Norrving 2015). In one systematic review, 5% to 62% of the population has MRI evidence of asymptomatic lacunar infarction, especially in patients with hypertension, carotid stenosis, chronic kidney disease, metabolic syndrome, heart failure, coronary artery disease, hyperhomocysteinaemia and obstructive sleep apnoea (Fanning 2014). The overall prevalence of asymptomatic small vessel ischaemia (white matter hyperintensities + lacunar infarcts) is much higher, at 67% in one community-based study (Del Brutto 2015).

Association between white matter lesions and cognitive decline

White matter lesions can be an early predictor of all types of dementia, with an overall hazard ratio of 2.9 (1.3 to 6.3) in one large meta-analysis (Montamais 2013), However, this association is heterogenous, modulated by cognitive reserve, age and spatial distribution (e.g. periventricular vs. subcortical) of the white matter lesions. There are no clear associations between the presence of white matter lesions and the development of dementia in patients with mild cognitive impairment, or in the general population (Montamais 2013). Whilst white matter lesions can impact upon specific cognitive domains such as executive dysfunction (Prins 2005), their effects on other domains such as processing speed and verbal fluency remain unclear (Montamais 2013). The estimated proportion of dementia with contribution from small vessel disease ranges from 36% to 67% (Grau-Olivares 2009). The traditional dichotomisation between Alzheimer's disease and vascular dementia subtypes is therefore outmoded and no longer valid.

Clinical question to be answered

The important clinically-relevant question is this: does this patient with small vessel disease on neuroimaging, but no prior history of cardiovascular or cerebrovascular disease, benefit from treatment with antithrombotic therapy, and if so, which regimen? Many experts are already calling for improved vascular risk management for the primary prevention of dementia including Alzheimer's disease (Safouris 2015), yet there is little understanding of the effectiveness of these strategies in altering the trajectory of pathogenesis and cognitive decline. One of the most widely adopted strategies for vascular disease prevention is the use of antithrombotic therapy.

Description of the intervention

Antithrombotic therapy consists of antiplatelet agents, oral anticoagulants, and a combination of these two modalities. Antiplatelet agents include: inhibition of cyclooxygenase (e.g. aspirin); inhibition of phosphodiesterases III and V and uptake by red cells of adenosine (e.g. cilostazol, dipyridamole); blockade of the platelet ADP P2Y12 receptor (e.g. clopidogrel, prasugrel); blockade of glycoprotein IIb/IIIa receptors (e.g. abciximab); and increasing nitric oxide levels (e.g. triflusal) (Geeganage 2010). Oral anticoagulants include traditional vitamin K antagonists (e.g. warfarin) and non-vitamin K oral anticoagulants (NOACs). NOACs include agents that inhibit activated factor Xa (e.g. apixaban and rivaroxaban) or thrombin (e.g. dabigatran) (Lip 2015).

How the intervention might work

Antiplatelet agents are the usual treatment for secondary stroke prevention (ATC 2002), including lacunar (subcortical) stroke (Kwok 2015). Different regimens have been evaluated in this setting, both as single and combination agents (Ishida 2014). For certain high-risk patients, such as those with existing cardiovascular disease (with or without cerebrovascular disease), trials of different antiplatelet agents regimens have demonstrated the potential benefit of dual antiplatelet therapy of aspirin plus clopidogrel over aspirin monotherapy to prevent stroke (Gouya 2014). However, the overall effects on stroke prevention (balancing with harm) of long-term use of dual antiplatelet therapy has not been proven in patients with ischaemic stroke or TIA (Lee 2013). The use of antiplatelet agents in patients with small vessel disease needs to balance the potential benefit against the risk of haemorrhage (Mok 2015).

Oral anticoagulants are the standard treatment for the primary and secondary prevention of stroke in high-risk patients with non-valvular atrial fibrillation (Cameron 2014), but not those with ischaemic attack or minor ischaemic stroke of presumed arterial origin (De Schryver 2012). NOACs have been shown to be at least as efficacious and safe as vitamin K antagonists for stroke prevention in patients with non-valvular atrial fibrillation (Bruins Slot 2013; Senoo 2015). Combination of antiplatelet agents and oral anticoagulants has also been investigated for high-risk patients with atrial fibrillation, and one systematic review concluded that there was insufficient evidence of its effects in terms of reducing vascular events (Lane 2013).

Antithrombotic therapy has already been established as the standard treatment for stroke prevention. We therefore hypothesise

that antithrombotic therapy might also be effective in preventing cognitive decline in people with small vessel disease on neuroimaging but without dementia.

Why it is important to do this review

Dementia is a huge public health concern, and currently no intervention can effectively halt or reverse cognitive decline. There is a clear need to identify effective interventions to alter the trajectory of cognitive decline and prevent dementia, especially for high-risk groups such as those with small vessel disease on neuroimaging. It is unclear whether antithrombotic therapy may be effective in preventing cognitive decline in people with small vessel disease on neuroimaging but without dementia.

OBJECTIVES

To assess the effects of antithrombotic therapy in preventing cognitive decline in people with small vessel disease on neuroimaging but without dementia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

We will consider all studies that have recruited people with evidence of small vessel disease on neuroimaging but without dementia:

1. Presence of small vessel disease on neuroimaging - CT or MRI - including white matter hyperintensities and lacunes of presumed vascular origin. We will use the definitions of the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) (Wardlaw 2013) as a standard reference and guidance in this review, but a degree of flexibility of interpretation will be employed and noted. The presence or absence of cerebral microbleeds will also be noted.
2. Absence of dementia of any cause as defined by internationally-accepted diagnostic criteria.

We are also making an assumption that people with recent small subcortical infarcts would routinely be offered antithrombotic therapy, and those with visible perivascular spaces, cerebral microbleeds and brain atrophy would not be routinely be considered for antithrombotic therapy (Wardlaw 2013).

Types of interventions

Antithrombotic therapy can include the following three treatment regimens involving two classes of pharmaceutical agents:

1. Antiplatelet agents (e.g. aspirin, dipyridamole, and clopidogrel - as mono- or combination therapy)
2. Oral anticoagulants (e.g. vitamin K antagonist, direct thrombin inhibitor, and factor Xa inhibitor)
3. Antiplatelet agent(s) + oral anticoagulant(s).

We will consider all studies that have compared anti-thrombotic treatment (administered for at least 6 months (180 days)) to no anti-thrombotic treatment (which may be placebo or treatment as usual), or that have compared different anti-thrombotic treatment regimes.

Types of outcome measures

Primary outcomes

1. Change in cognitive function between baseline and final follow-up using recognised and validated cognitive assessment measures.
2. Incident dementia of any cause as defined by internationally-accepted diagnostic criteria.
3. New intracranial haemorrhagic events (including intracerebral, subdural, subarachnoid and extradural) and extracranial haemorrhagic events.

Secondary outcomes

1. Functional/vital outcome, e.g. dependency or disability (using recognised and validated functional assessment measures).
2. Ischaemic stroke or TIA
3. Death
4. Any adverse events
5. Withdrawal from the allocated treatment within the scheduled follow-up period. This is a composite outcome which takes into account several factors including adverse events, compliance and perceived effectiveness.
6. New cerebral microbleeds on neuroimaging.

Search methods for identification of studies

Electronic searches

We will search ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Review Group's Specialised Register, and the Cochrane Stroke Group's Specialised Register.

ALOIS is maintained by the Review Group's Information Specialist and contains dementia and cognitive improvement studies identified from:

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and Lilacs
2. Monthly searches of a number of trial registers: meta Register of Controlled Trials; Umin: Japanese Trial Register; WHO portal (which covers ClinicalTrials.gov; ISRCTN; Chinese Clinical Trials Register; German Clinical Trials Register; Iranian Regsitry of Clinical Trials and the Netherlands National Trials Register, plus others)
3. Quarterly search of the *Cochrane Library's* Central Register of Controlled Trials (CENTRAL)
4. Six-monthly searches of a number of grey literature sources: ISI Web of Science Conference Proceedings; Index to Theses; Australasian Digital Theses

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS web site.

Additional separate searches will be run in many of the above sources to ensure that the most up-to-date results are retrieved. The search strategy that will be used for the retrieval of reports of trials from MEDLINE (via the Ovid SP platform) is presented in Appendix 1.

Searching other resources

We will check the reference lists of articles retrieved from the above searches and, where clarification of information is needed, we will attempt to contact the investigators of the relevant studies. Importantly, we anticipate that there may be unpublished cognitive data of relevance to this review which have been collected in studies with the primary aim of stroke prevention using antithrombotic therapy. We will approach experts in the field in order to identify such data.

Data collection and analysis

Selection of studies

Two review authors will independently screen all of the titles, abstracts, and keywords of publications identified by the searches to assess their eligibility. Publications that clearly do not meet the inclusion criteria will be excluded at this stage. We will retrieve the full-text versions of every study that might possibly be relevant. Two review authors will independently assess each study according to pre-specified selection criteria. Any disagreement will be resolved by discussion.

Data extraction and management

If studies are included, two review authors will independently extract the data onto a data extraction form. Any disagreement will be resolved by discussion. Data reported by the published sources will be used for the analyses in this review. Where additional outcome data are needed, we will attempt to contact the investigators of the studies. In studies that have included a mixed population of participants with and without dementia, we will attempt to extract the data from the published sources for those participants without dementia. If this is not possible, then we will attempt to contact the investigators of the studies for additional data and clarification. If this remains not possible, the study will be excluded.

In additional to the important study methodology and outcome data, we will also extract demographic data (e.g. age and sex distribution, level of cognitive reserve) and possible confounding factors (e.g. neuroimaging modalities, cognitive assessment methods, method and duration of treatment, number of participants who withdraw or are lost during follow-up). Any disagreement will be resolved by discussion and a consensus decision made.

Assessment of risk of bias in included studies

Risk of bias in included studies will be assessed according to the guidance in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (http://handbook.cochrane.org/).

Measures of treatment effect

For trials with comparable primary and secondary outcomes, mean differences and standardised mean differences, with 95% confidence intervals, will be calculated using a random-effects model. The differences between treatment groups at final follow-up will be analysed and the results will be converted into a format suitable for meta-analysis. Drug safety and adherence results will be summarised.

Unit of analysis issues

The participant will be the unit of analysis.

Dealing with missing data

We will contact the investigators of the relevant studies to request missing data as required. We will use "available case analysis" by including the data only from those whose results are known, using as a denominator the total number of people who had data recorded for the particular outcome in question. Variation in the degree of missing data across studies will be used as a potential source of heterogeneity.

Assessment of heterogeneity

We anticipate a degree of clinical heterogeneity resulting from differences in participant demographics and baseline cognitive function. Statistical heterogeneity may also result from differences in antithrombotic regimens involving different pharmaceutical agents or classes of agents. Statistical heterogeneity will be assessed according to the guidance in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (http://handbook.cochrane.org/).

Assessment of reporting biases

Reporting bias will be assessed according to the guidance in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (http://handbook.cochrane.org/).

Data synthesis

For included studies, data analysis will be conducted in accordance with the guidance in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (http://handbook.cochrane.org/). All analyses will be conducted according to intention-to-treat. For dichotomous data, we will express relative treatment effects as odds or risk ratios, as appropriate, with 95% confidence intervals. For continuous data, we will use mean differences with 95% confidence intervals. A P value of less than 0.05 will be taken as statistically significant. Where there is no significant clinical or statistical heterogeneity, and if it appears sensible to combine the results, we will undertake a meta-analysis using a random-effects model.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses will include:

1. People with cognitive impairment vs. cognitively normal people.
2. People with atrial fibrillation vs. people without atrial fibrillation.
3. People with prior cardiovascular disease vs. people without prior cardiovascular disease (including history of stroke and TIA).
4. Presence vs. absence of cerebral microbleeds.
5. CT vs. MRI as the neuro-imaging tool.
6. Individual drug regimes used in comparison.

Sensitivity analysis

Sensitivity analysis will be undertaken if, for instance, there are questions about the methodological quality of the included studies, according to the guidance of Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (http://handbook.cochrane.org/).

Data presentation - 'Summary of findings' tables

We will use the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to assess the quality of the supporting evidence behind each estimate of treatment effect (Schunemann 2011a; Schunemann 2011b). We will present key findings of the review including a summary of the amount of data, the magnitude of the effect size and the overall quality of the evidence, in a 'Summary of findings' table, created using GRADEpro software (GRADEpro 2014). We have pre-selected the following outcomes:

1. Change in cognitive function between baseline and final follow-up using recognised cognitive assessment measures.
2. Incident dementia of any cause as defined by internationally-accepted diagnostic criteria.
3. Ischaemic stroke or TIA.
4. Functional/vital outcome e.g. dependency or disability.
5. Any adverse events including intracranial and extracranial haemorrhagic events.
6. Withdrawal from the allocated treatment.
7. Death.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. ("white matter" adj3 (ischemi* or ischaemi*)).ti,ab.
2. ("micro-bleed*" or microbleed*).ti,ab.
3. *Brain Ischemia/ or *Ischemia/ or White Matter/pathology
4. Leukoencephalopathies/ or Leukoaraiosis/
5. (Microhemorrhage* or Microhaemorrhage*).ti,ab.
6. or/1-5
7. antithrombo*.ti,ab.
8. Aspirin/
9. aspirin.ti,ab.
10. dipyridamole*.ti,ab.
11. Dipyridamole/
12. clopidogrel*.ti,ab.
13. triflusal.ti,ab.
14. prasugrel.ti,ab.
15. ticagrelor.ti,ab.
16. ticlopidine.ti,ab.
17. cilostazol.ti,ab.
18. vorapaxar.ti,ab.
19. abciximab.ti,ab.
20. eptifibatide.ti,ab.
21. tirofiban.ti,ab.
22. terutroban.ti,ab.
23. disgren.ti,ab.
24. plavix.ti,ab.
25. effient.ti,ab.
26. brilinta.ti,ab.
27. ticlid.ti,ab.
28. pletal.ti,ab.
29. zontivity.ti,ab.
30. ReoPro.ti,ab.
31. integrilin.ti,ab.
32. aggrastat.ti,ab.
33. persantine.ti,ab.
34. "acetylsalicylic acid".ti,ab.
35. "antiplatelet drug*".ti,ab.
36. Thromboxanes/
37. Glycoproteins/
38. Adenosine Diphosphate/
39. Anticoagulants/
40. Antithrombins/
41. "vitamin k".ti,ab.
42. phylloquinone.ti,ab.
43. phytomenadione.ti,ab.
44. phytonadione.ti,ab.
45. "thrombin* inhibitor*".ti,ab.
46. Factor Xa/
47. Fibrinolytic Agents/
48. dabigatran.ti,ab.

49. rivaroxaban.ti,ab.
50. apixaban.ti,ab.
51. coumarin*.ti,ab.
52. warfarin.ti,ab.
53. Warfarin/
54. Heparin/
55. heparin.ti,ab.
56. phenprocoumon.ti,ab.
57. Acenocoumarol.ti,ab.
58. atromentin.ti,ab.
59. brodifacoum.ti,ab.
60. phenindione.ti,ab.
61. "Xa inhibitor*".ti,ab.
62. or/7-61
63. 6 and 62
64. (randomized controlled trial or controlled clinical trial).pt. or randomized.tw. or placebo.tw. or clinical trials as topic.sh. or randomly.tw. or trial.ti.
65. animals/ not humans/
66. 64 not 65
67. 63 and 66

CONTRIBUTIONS OF AUTHORS

Drs Kwan, Myint, Wong and Mok designed and co-authored the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Medicine, the University of Hong Kong, Hong Kong.

External sources

- National Institute for Health Research (NIHR), UK.

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