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

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[Intervention Review]

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

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ABSTRACT

Background

Cerebral small vessel disease is a progressive disease of the brain's deep perforating blood vessels. It is usually diagnosed based on lesions seen on brain imaging. Cerebral small vessel disease is a common cause of stroke but can also cause a progressive cognitive decline. As antithrombotic therapy is an established treatment for stroke prevention, we sought to determine whether antithrombotic therapy might also be effective in preventing cognitive decline in people with small vessel disease.

Objectives

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

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Review Group's Specialised Register, and the Cochrane Stroke Group's Specialised Register; the most recent search was on 21 July 2021. We also searched MEDLINE, Embase, four other databases and two trials registries. We searched the reference lists of the articles retrieved from these searches. As trials with a stroke focus may include relevant subgroup data, we complemented these searches with a focussed search of all antithrombotic titles in the Cochrane Stroke Group database.

Selection criteria

We included randomised controlled trials (RCT) of people with neuroimaging evidence of at least mild cerebral small vessel disease (defined here as white matter hyperintensities, lacunes of presumed vascular origin and subcortical infarcts) but with no evidence of dementia. The trials had to compare antithrombotic therapy of minimum 24 weeks' duration to no antithrombotic therapy (either placebo or treatment as usual), or compare different antithrombotic treatment regimens. Antithrombotic therapy could include antiplatelet agents (as monotherapy or combination therapy), anticoagulants or a combination.

Data collection and analysis

Two review authors independently screened all the titles identified by the searches. We assessed full texts for eligibility for inclusion according to our prespecified selection criteria, extracted data to a proforma and assessed risk of bias using the Cochrane tool for RCTs.

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

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We evaluated the certainty of evidence using GRADE. Due to heterogeneity across included participants, interventions and outcomes of eligible trials, it was not possible to perform meta-analyses.

Main results

We included three RCTs (3384 participants). One study investigated the effect of antithrombotic therapy in participants not yet on antithrombotic therapy; two studies investigated the effect of additional antithrombotic therapy, one in a population already taking a single antithrombotic agent and one in a mixed population (participants on an antithrombotic drug and antithrombotic-naive participants). Intervention and follow-up durations varied from 24 weeks to four years.

Jia 2016 was a placebo-controlled trial assessing 24 weeks of treatment with DL-3-n-butylphthalide (a compound with multimodal actions, including a putative antiplatelet effect) in 280 Chinese participants with vascular cognitive impairment caused by subcortical ischaemic small vessel disease, but without dementia. There was very low-certainty evidence for a small difference in cognitive test scores favouring treatment with DL-3-n-butylphthalide, as measured by the 12-item Alzheimer's Disease Assessment Scale-Cognitive subscale (adjusted mean difference −1.07, 95% confidence interval (CI) −2.02 to −0.12), but this difference may not be clinically relevant. There was also very low-certainty evidence for greater proportional improvement measured with the Clinician Interview-Based Impression of Change-Plus Caregiver Input (57% with DL-3-n-butylphthalide versus 42% with placebo; P = 0.01), but there was no difference in other measures of cognition (Mini-Mental State Examination and Clinical Dementia Rating) or function. There was no evidence of a difference in adverse events between treatment groups.

The SILENCE RCT compared antithrombotic therapy (aspirin) and placebo during four years of treatment in 83 participants with 'silent brain infarcts' who were on no prior antithrombotic therapy. There was very low-certainty evidence for no difference between groups across various measures of cognition and function, rates of stroke or adverse events.

The Secondary Prevention of Subcortical Stroke Study (SPS3) compared dual antiplatelet therapy (clopidogrel plus aspirin) to aspirin alone in 3020 participants with recent lacunar stroke. There was low-certainty evidence of no effect on cognitive outcomes as measured by the Cognitive Abilities Screening Instruments (CASI) assessed annually over five years. There was also low-certainty evidence of no difference in the annual incidence of mild cognitive decline between the two treatment groups (9.7% with dual antiplatelet therapy versus 9.9% with aspirin), or the annual stroke recurrence rate (2.5% with dual antiplatelet therapy versus 2.7% with aspirin). Bleeding risk may be higher with dual antiplatelet therapy (hazard ratio (HR) 2.15, 95% CI 1.49 to 3.11; low certainty evidence), but there may be no significant increase in intracerebral bleeding risk (HR 1.52, 95% CI 0.79 to 2.93; low-certainty evidence).

None of the included trials assessed the incidence of new dementia.

Authors' conclusions

We found no convincing evidence to suggest any clinically relevant cognitive benefit of using antithrombotic therapy in addition to standard treatment in people with cerebral small vessel disease but without dementia, but there may be an increased bleeding risk with this approach. There was marked heterogeneity across the trials and the certainty of the evidence was generally poor.

PLAIN LANGUAGE SUMMARY

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

Background

Disruption of blood flow to the brain can cause problems with memory and thinking. In the condition called 'cerebral small vessel disease', there is damage to the smallest blood vessels that run deep in the brain. This damage can cause stroke but can also be seen on brain scans in people with no obvious stroke symptoms. Cerebral small vessel disease usually gets worse over time, and in some people can cause a decline in memory and thinking. If this decline gets severe enough to affect a person's ability to manage their daily activities independently, then it is described as a type of vascular dementia. We know that blood-thinning medications such as aspirin can prevent stroke. We wanted to know whether blood-thinning medications might also prevent the decline in memory and thinking that is seen in cerebral small vessel disease.

Review question

Are blood-thinning medications effective and safe in preventing the decline in memory and thinking in people with cerebral small vessel disease?

What we did

We searched the medical literature up to 21 July 2021 looking for studies that compared blood-thinning medications given over at least 24 weeks to a comparator, which could have been either usual care or a placebo (dummy) tablet. To make the comparison fair, the studies had to assign people randomly to blood-thinning medications or the comparator treatment. We were interested in the effects on participants' performance in memory and thinking tests, their ability to look after themselves, their risk of developing dementia and stroke, and side

effects (especially from bleeding). Because the studies were so different from each other in terms of the type of participants, medications and assessments, we were unable to combine the results in analyses. Rather, we described the results of individual studies and assessed how confident we were in their findings.

What we found

We included three studies with 3384 participants. These studies were very different in terms of the participants (some with and some without stroke), the medications studied (single and combinations of different blood-thinners), and how the effects on memory and thinking were measured (different tests used for assessment). No trial consistently demonstrated an improvement in performance in memory and thinking tests or in daily activities. No trial assessed for a new diagnosis of dementia. There was suggestion of blood-thinning medications possibly causing an increased risk of bleeding, including gastrointestinal bleeding, but the numbers were too small to be certain that this was not just a chance difference. Overall, we considered that the quality of the evidence was poor for answering our review question regarding memory and thinking. Much of the information we needed was not reported. Two of the three studies were small, meaning that there was uncertainty around their results. In the only study that reported any benefit from blood-thinning medication, different measures of memory and thinking did not all agree with each other. Lastly, where there was an improvement in memory and thinking, the size of this improvement may have been too small to make a noticeable difference to the individual in reality.

Conclusions

We found no convincing evidence that taking blood-thinning medications is beneficial for memory and thinking in people with cerebral small vessel disease. However, the studies were very different from each other, and each one had limitations with regard to our review question.

SUMMARY OF FINDINGS

Summary of findings 1. Antiplatelet drug compared to placebo in mixed populations (with or without pre-existing antiplatelet therapy) for the prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia

Antiplatelet drug compared to placebo, in populations with mixed prevalence of antiplatelet drug use at baseline, for the prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia

Patient or population: people with cerebral small vessel disease and no dementia either already on antiplatelet therapy or not
Setting: outpatient services
Intervention: adding antiplatelet therapy in populations where some participants may have been taking antiplatelet
Comparison: placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Change in cognitive function from baseline assessed with ADAS-Cog, CIBIC-plus, MMSE, CDR, CDR-SB,	1 trial reported a beneficial effect across 2 of 5 cognitive outcomes (ADAS-Cog and CIBIC-plus), but the size of benefit may be less than the minimal important clinical difference.	280 (1 RCT)	⊕⊖⊖⊖ **Very low**a,b,c
Incident dementia	No studies reported this outcome	—	—
Major bleeding (intracranial and extracranial)	1 trial reported no difference between treatment groups for this outcome.	280 (1 RCT)	⊕⊖⊖⊖ **Very low**a,b,c
Functional ability	1 trial reported no difference in functional anility between treatment groups	280 (1 RCT)	⊕⊖⊖⊖ **Very low**a,b,c
Stroke or transient ischaemic attack	1 trial reported no difference in stroke or transient ischaemic attacks between treatment groups	280 (1 RCT)	⊕⊖⊖⊖ **Very low**a,b,c
Any adverse events (excluding major bleeding)	1 study reported no difference in adverse events between treatment groups	280 (1 RCT)	⊕⊖⊖⊖ **Very low**a,b,c
Withdrawal from study medication	1 trial reported an increase in medication withdrawal in those taking additional antiplatelets in comparison to those taking a placebo (OR for withdrawal from treatment 1.88, 95% CI 0.90 to 3.42)	280 (1 RCT)	⊕⊖⊖⊖ **Very low**a,b,c

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale;**ADL:** activities of daily living;**CDR-SB:** Clinical Dementia Rating scale Sum of Boxes; **CI:** confidence interval; **MMSE:** Mini-Mental State Examination; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level because all participants had cognitive impairment at baseline, making it difficult to translate these findings to the general small-vessel disease population.
[b]Downgraded one level as it is arguable whether DL-3-n-butylphthalide should technically be classified as an antithrombotic therapy.
[c]Downgraded one level for imprecision as only one study contributed to this finding.

Summary of findings 2. Antiplatelet therapy compared to placebo for prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia

Antiplatelet therapy compared to placebo in antiplatelet naive populations for prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia

Patient or population: people with cerebral small vessel disease and no dementia not on antiplatelet therapy
Setting: outpatient services
Intervention: antiplatelet therapy
Comparison: placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Change in cognitive function from baseline assessed with: NPB, MMSE	1 trial reported no difference between treatment groups.	50 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]
Incident dementia	No studies reported this outcome	—	—
Major bleeding (intracranial and extracranial)	No studies reported this outcome	—	—
Functional ability	1 trial reported no difference in activities of daily living between treatment groups.	50 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]
Stroke or transient ischaemic attack	1 trial reported no difference between treatment groups.	50 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]
Any adverse events (excluding major bleeding)	1 trial reported no difference between treatment groups.	50 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]
Withdrawal from study medication	1 trial reported slightly more dropout in the intervention group (33.3%) than in the placebo group (19.2%)	50 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
MMSE: Mini-Mental State Examination; **NPB:** Neuropsychological test Battery; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*a*Downgraded one level as there was no (clear) statement whether participants with dementia were actively excluded.
*b*Downgraded one level due to serious risk of bias in included studies.
*c*Downgraded one level due to imprecision.

Summary of findings 3. Dual antiplatelet therapy compared to single antiplatelet therapy for prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia

Dual antiplatelet therapy compared to single antiplatelet therapy for prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia

Patient or population: people with cerebral small vessel disease and no dementia
Setting: outpatient services
Intervention: dual antiplatelet therapy
Comparison: single antiplatelet therapy

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Change in cognitive function from baseline assessed with CASI score	1 trial reported no beneficial effect of additional antiplatelet treatment over placebo on cognitive functioning assessed with the CASI score.	3020 (1 RCT)	⊕⊕⊝⊝ **Low**a,b
Incident dementia	No trials reported this outcome	—	—
Major bleeding (intracranial and extracranial)	1 trial reported a difference in major haemorrhagic events (105/1517 participants with intervention vs 56/1503 participants with control; HR 1.97, 95% CI 1.41 to 2.71)	3020 (1 RCT)	⊕⊕⊝⊝ **Low**a,b
Functional ability	No trials reported this outcome.	—	—
Stroke or transient ischaemic attack	1 trial reported there was probably no effect of additional antiplatelet treatment on stroke or TIA	3020 (1 RCT)	⊕⊕⊝⊝ **Low**a,b
Any adverse events (excluding major bleeding)	No trials reported this outcome.	—	—
Withdrawal from study medication	1 trial reported an increase in medication withdrawal in those taking additional antiplatelets in comparison to those taking a placebo (30% with intervention vs 27% with control; P = 0.02).	3020 (1 RCT)	⊕⊕⊝⊝ **Low**a,b

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CASI: Cognitive Abilities Screening Instrument;**CI:** confidence interval; **HR:** hazard ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*a*Downgraded one level for imprecision as only one study contributed to this finding.

[b]Downgraded one level for indirectness because most participants had mild cognitive impairment at baseline, making it difficult to translate these findings to the general small-vessel disease population.

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BACKGROUND

Description of the condition

Dementia is a progressive condition in which acquired cognitive impairment is severe enough to affect a person's ability to manage everyday activities. Usually it occurs in later life and is caused by neurodegenerative conditions, of which the most common are Alzheimer's disease and cerebrovascular disease. Dementia is an international public health concern, affecting 35 million people worldwide (Prince 2013), with a global annual cost of over USD 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). Currently, approved pharmacological treatments for dementia offer symptomatic benefit (Battle 2021; McShane 2019), but there is no proven drug intervention to prevent or reduce cognitive decline.

Cerebral small vessel disease (cSVD) is a dynamic, whole brain syndrome thought to result from pathology in the arterioles, capillaries and venules of the brain. cSVD may be an asymptomatic finding on neuroimaging or may present with a range of clinical manifestations, including clinical stroke, gait impairments, neuropsychiatric problems and frank dementia. The overall prevalence of asymptomatic small vessel ischaemia seen on brain imaging is high, up to 67% of older adults in one community-based study (Del Brutto 2015). As cSVD is associated with hypertension, diabetes and other vascular risk factors, treatment of cSVD has tended to focus on modifying vascular risk (Wardlaw 2019). Following a lacunar stroke (a form of cSVD), antithrombotic therapy is used to prevent further stroke. Whether this antithrombotic therapy has any effect on the progression or manifestation of the underlying cSVD is unclear.

The pathological changes of cSVD can be visualised using magnetic resonance imaging (MRI) or computed tomography (CT) brain scanning. MRI is the preferred tool for assessing cSVD owing to its greater sensitivity to the essential neuroimaging features of cSVD (Norrving 2015). Classical features of cSVD include subcortical infarcts, lacunes, white matter hyperintensities, prominent perivascular spaces, cerebral microbleeds and atrophy (Arba 2018; Boutet 2016; Mok 2015).

cSVD lesions may be associated with all-cause dementia, although the supporting evidence is not consistent (Mortamais 2013). The estimated proportion of dementia with contribution from cSVD ranges from 36% to 67% (Grau-Olivares 2009). Imaging evidence of cSVD is often seen in vascular dementia but the process may also be important in the pathogenesis of other types of dementia. Although the pathogenesis of Alzheimer's disease remains incompletely understood (Jack 2010), there is increasing support for a potential vascular basis (Grammas 2011). Autopsy studies have demonstrated important interactions between cSVD and Alzheimer's pathology (Iadecola 2010), and cSVD risk factors such as diabetes and hypertension appear to be independent predictors of Alzheimer's disease (Akinyemi 2013). Among people with stroke of mild-to-moderate severity, MRI evidence of cSVD and medial temporal lobe atrophy (one of the imaging indicators of Alzheimer's pathology) are highly prevalent and can predict post-stroke dementia at two years (Kwan 2016).

Many experts are already calling for improved vascular risk management for the primary prevention of dementia including Alzheimer's disease (Safouris 2015), yet the effectiveness of these strategies in altering the trajectory of dementia-related pathologies and cognitive decline remains unclear. The following clinical scenario is a common one: an older adult has no evidence of cognitive impairment or only a minor cognitive complaint but is keen to reduce their risk of developing dementia in the future. They have cSVD on an MRI scan performed for another reason, for example headache. For this patient: *should antithrombotic therapy be started to prevent future cognitive decline?* In this review, we looked into the effectiveness of antithrombotic therapy for both symptomatic and asymptomatic cSVD for the prevention of (further) cognitive decline and dementia.

Description of the intervention

Antithrombotic therapy reduces the formation of thrombus through acting on one or more aspect of the thrombotic cascade. Based on their mode of action, antithrombotic agents are categorised as antiplatelets, anticoagulants and fibrinolytic agents. In this review, we do not consider fibrinolytics as they tend to be used in the acute setting only and would not be used as a longer-term primary or secondary preventive intervention.

Antiplatelet agents include: cyclo-oxygenase inhibitors (e.g. aspirin); inhibitors of phosphodiesterases III and V and inhibitors of adenosine uptake by red cells (e.g. cilostazol, dipyridamole); blockade of the platelet ADP P2Y12 receptor (e.g. clopidogrel, prasugrel, ticagrelor); 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 direct oral anticoagulants (DOACs). DOACs include agents that inhibit activated factor Xa (e.g. apixaban, rivaroxaban and edoxaban) or thrombin (e.g. dabigatran) (Lip 2015).

How the intervention might work

Antiplatelet agents are the usual treatment for secondary stroke prevention after an ischaemic stroke (ATC 2002), including for lacunar (subcortical) stroke. Different regimens have been evaluated in this context, including both single agents and combinations of agents (Ishida 2014). Increasing potency of antiplatelet can often be accompanied by increasing risk of bleeding. Thus the use of antiplatelet agents in people with cSVD needs to balance the potential benefit against risks (Mok 2015).

Oral anticoagulants are the standard treatment for the primary and secondary prevention of stroke in high-risk patients with atrial fibrillation or certain other cardioembolic stroke aetiologies (Cameron 2014). In this review, we also included participants with cardioembolic stroke so long as they had concomitant cSVD, as we hypothesised that the pathophysiological mechanism for cognitive decline is comparable for this group.

Since antithrombotic agents have demonstrated efficacy in the prevention of symptomatic ischaemic stroke, it seems plausible that they might also prevent the asymptomatic (silent) infarcts that are thought to be part of cSVD. We hypothesised that this could in turn prevent the clinical manifestations of cSVD including cognitive decline.

Why it is important to do this review

There is currently no evidence-based or licensed drug treatment for the prevention of cognitive decline and dementia. If antithrombotic agents could prevent or delay cognitive impairment associated with cSVD, this could be an inexpensive intervention for the many people living with this condition.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

For this review, we considered only randomised controlled trials (RCTs).

Types of participants

To be eligible for inclusion, participants had to have evidence of cSVD on neuroimaging but no dementia, using the following definitions.

1. Presence of cSVD on neuroimaging (CT or MRI). Where possible, we used the definitions of the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) guidance as a reference (Wardlaw 2013), but a degree of flexibility of interpretation was employed and noted. Features of cSVD are often measured on ordinal scales; we included those studies where the degree of cSVD change was at least 'mild' (e.g. greater than 1 on the Fazekas scale in assessing white matter hyperintensity). In studies of mixed populations, at least 75% of the participants had to have imaging evidence of cSVD.
2. Absence of dementia of any cause. Where possible, we aimed to include studies using internationally accepted diagnostic criteria for dementia, however a degree of flexibility was needed because of heterogeneity of the operationalisation of this exclusion criterion in the included studies. Therefore, we also accepted cognitive testing that was plausible to detect incipient or existing dementia.

Participants with or without a history of symptomatic stroke were eligible for inclusion, as long as they met the above criteria for cSVD on neuroimaging and no dementia.

Types of interventions

Antithrombotic therapy included the following three treatment regimens.

1. Antiplatelet agents (as monotherapy or combination therapy).
2. Oral anticoagulants (vitamin K antagonists or DOACs).
3. Antiplatelet agent(s) combined with oral anticoagulant(s).

We considered all studies that compared antithrombotic therapy (administered for at least six months) to no antithrombotic therapy (either placebo or treatment as usual), or that compared different antithrombotic therapy regimens. We did not specify any restrictions based on dose, frequency or method of administration.

We opted for a minimal intervention duration of 24 weeks as cognitive decline due to cSVD is a slow process and little effect can be expected on cognitive decline for shorter intervention durations.

Types of outcome measures

We included the following primary and secondary outcomes.

Primary outcomes

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

Secondary outcomes

1. Functional outcome using validated functional assessment measures.
2. Incident ischaemic stroke or transient ischaemic attack.
3. Death.
4. Adverse events (excluding bleeding, as this is already reported as primary outcome).
5. Withdrawal from the allocated treatment within the scheduled follow-up period.
6. New cerebral microbleeds on repeat neuroimaging.
7. Incident mild cognitive impairment (MCI).

Search methods for identification of studies

We used the following search method to identify studies.

Electronic searches

We searched ALOIS (alois.medsci.ox.ac.uk) – 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 several major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and Lilacs;
2. monthly searches of the trial registers: the World Health Organization (WHO) International Clinical Trials Registry Platform (which covers ClinicalTrials.gov, ISRCTN, the Chinese Clinical Trials Register, the German Clinical Trials Register, the Iranian Registry of Clinical Trials, and the Netherlands National Trials Register, plus others) and ClinicalTrials.gov;
3. quarterly search of the Cochrane Library's Central Register of Controlled Trials (CENTRAL);
4. six-monthly searches of several grey literature sources from ISI Web of Science Core Collection.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'Methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group (dementia.cochrane.org/resources-review-authors). We performed additional searches in many of the

sources listed above to ensure that the search for the review was as up-to-date and comprehensive as possible.

We recognised that potentially relevant data may be available through subgroup analysis of stroke trials, for example a study of antiplatelet in stroke that had cognitive outcome data and where a subgroup of participant with lacunar stroke (a form of cSVD) could be derived. We worked with the Cochrane Stroke Group and handsearched all antithrombotic trials in their Centralised Register.

Our search strategies used are described in Appendix 1. The most recent search was carried out on 21 July 2021.

Searching other resources

We checked the reference lists of articles retrieved from the above searches. For included studies, we retrieved additionally published subpapers where appropriate, to ensure a comprehensive data extraction. Where clarification of information was needed, we attempted to contact the investigators of the relevant studies.

Data collection and analysis

We used the following method for data collection and data analysis.

Selection of studies

A minimum of two review authors independently screened all titles and abstracts of publications identified by the searches to assess their eligibility. Publications that clearly did not meet the inclusion criteria were excluded at this stage. We retrieved the full-text versions of potentially relevant studies. A minimum of two review authors independently assessed each full-text study according to the prespecified selection criteria. Disagreements were resolved by discussion.

Data extraction and management

A minimum of two authors independently extracted data from the published reports. Disagreements were resolved by discussion.

Assessment of risk of bias in included studies

A minimum of two review authors independently assessed risk of bias for each included study. We used the RoB 1 tool as described in the original *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This RoB assessment considered five domains: selection bias, performance bias, attrition bias, detection bias and reporting bias. Domains were assessed for eligible papers and we classified them as low or high risk of bias. Where there was insufficient detail in a study to assess the risk, we reported it as unclear.

Measures of treatment effect

For dichotomous data, we expressed relative treatment effects as odds ratio (OR) or risk ratios (RR) with 95% confidence intervals (CI). For continuous data, we used mean differences (MD) with 95% CIs.

Unit of analysis issues

The participant was the unit of analysis. Where studies reported outcomes at more than one time point, we used the outcome data from the end of the intervention period where possible.

Dealing with missing data

We reported the amount of missing outcome data in each trial. When reporting trialists' own analyses, we favoured intention-to-treat analyses and reported any imputation methods.

Assessment of heterogeneity

Assessment of heterogeneity was performed in accordance with the guidance in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed clinical heterogeneity and considered the characteristics of the participants, how cSVD was diagnosed, the type of antithrombotic agents tested, and how the outcomes were assessed and reported.

Assessment of reporting biases

If the trial data had allowed, we would have used visual inspection of funnel plot analyses to assess for potential reporting biases. However, for this review, there were insufficient studies to allow for this analysis.

Data synthesis

Due to the small number of eligible studies and the significant heterogeneity between them, we were unable to conduct any meta-analyses to derive summary treatment effects. We instead described the individual studies using a narrative approach and created a summary table detailing the potential class effects of antithrombotic therapy.

Subgroup analysis and investigation of heterogeneity

We did not conduct any subgroup analyses.

Sensitivity analysis

We did not conduct any sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the supporting evidence behind each estimate of treatment effect (Schünemann 2008). We presented key findings of the review including a summary of the amount of data, the magnitude of the effect size and the overall certainty of the evidence, in summary of findings tables, created using GRADEpro software (GRADEpro GDT). We had preselected the following outcomes for inclusion in the summary of findings tables.

1. Change in cognitive function from baseline.
2. Incident dementia.
3. Major bleeding events.
4. Functional outcome.
5. Ischaemic stroke or transient ischaemic attack.
6. Adverse events (excluding bleeding).
7. Withdrawal from the allocated treatment.

R E S U L T S

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification,

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and Characteristics of ongoing studies tables for details of the studies considered for this review.

Results of the search

The Information Specialists of the Cochrane Dementia and Cognitive Improvement Group performed electronic searches on 7 July 2016, 4 May 2017, 22 June 2018, 6 June 2019, 16 September 2020 and 21 July 2021. In total, we retrieved 9658 results through database searching and six results through other sources. After deduplication, there remained 8084 records, 8064 of which we excluded at the title and abstract stage. We downloaded the full-texts or sought further information for 23 articles to assess their eligibility. See Figure 1 and Appendix 1 for more details.

Figure 1.

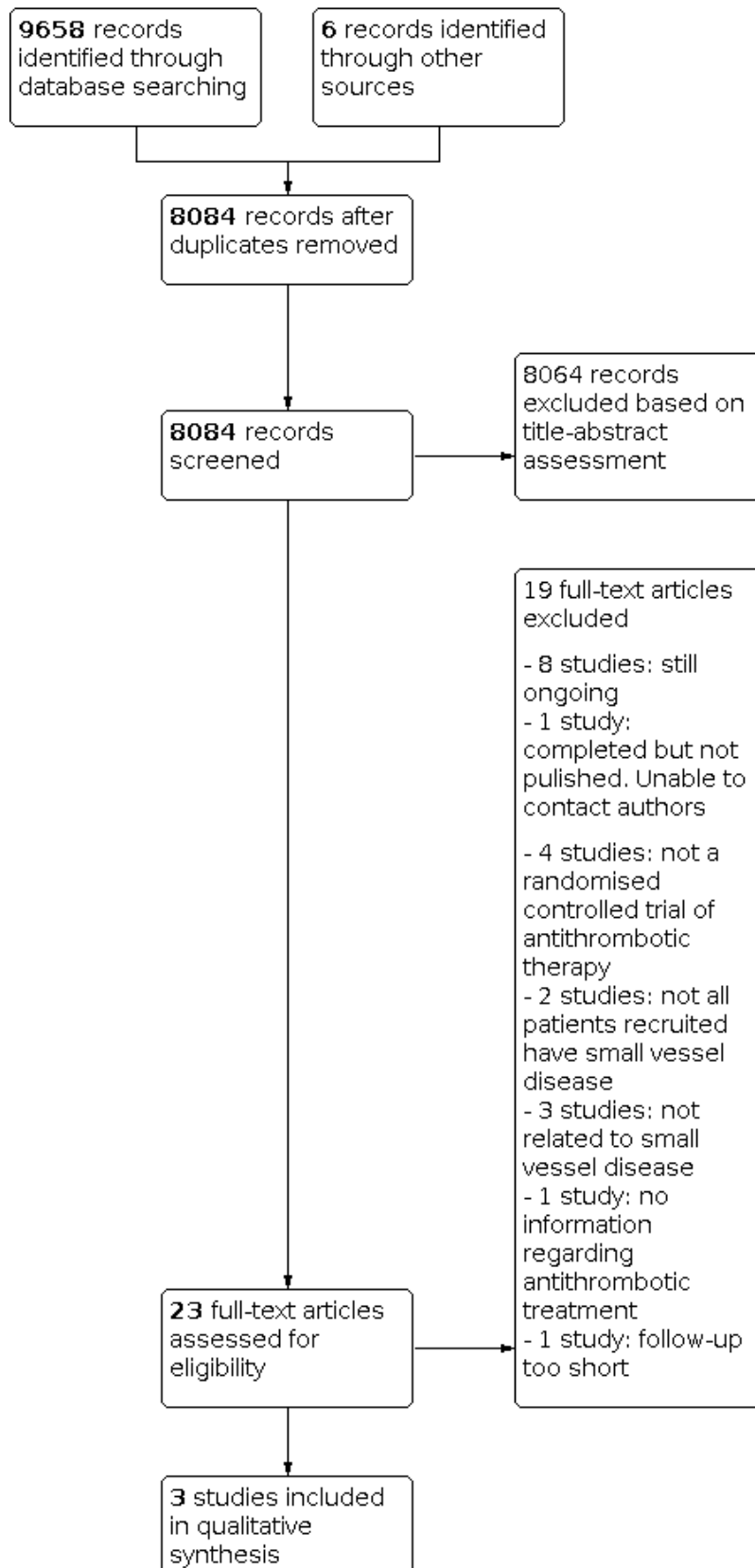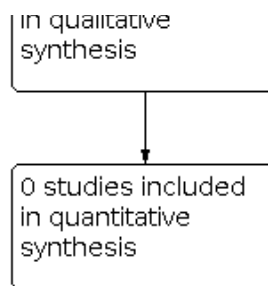**Antithrombotic therapy to prevent cognitive decline in people with small vessel disease on neuroimaging but without dementia (Review)**

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Figure 1. (Continued)

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in qualitative
synthesis

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0 studies included
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The review includes three studies (Jia 2016; Maestrini SILENCE 2018; Pearce SPS3 2014). We excluded 11 studies because they did not meet our inclusion criteria (AVERROES-MRI assessment study; COMPASS MRI; Douiri 2013; Han 2013; Jacobs 2015; Kwok 2015; Kwon 2016; LACI-1; Shinod-Tagawa 2002; Xu 2020; Zhang 2014). There are eight ongoing studies (ASPREE-NEURO; CAF; CHALLENGE; ChiCTR-TCS-14005054; LACI-2; NCT01932203; PICASSO-Cog; Reid ENVIS-ion 2012) and one study is awaiting classification as we were unable to contact the author for the necessary details (CAVAD). Details on these ongoing studies is reported in Ongoing studies. No studies that looked at white matter hyperintensity or lacunar infarctions only were identified.

See Figure 1 PRISMA Study flow diagram for the summary of our selection process.

Included studies

We included three RCTs (3384 participants) (Jia 2016; Maestrini SILENCE 2018; Pearce SPS3 2014).

Study design

Jia 2016 was a randomised, double-blind, placebo-controlled trial that assessed the effects of DL-3-n-butylphthalide in participants with vascular cognitive impairment without dementia, caused by subcortical ischaemic cSVD. DL-3-n-butylphthalide has multimodal effects and while not classically considered an antithrombotic agent, one of its actions is inhibition of platelet aggregation.The intervention period was 24 weeks and the follow-up duration six months.

The SILENCE trial was a randomised, placebo-controlled trial that assessed aspirin in a population with silent brain infarcts (Maestrini SILENCE 2018). A large proportion of 33 participants (40%) refused randomisation and were followed up as an observational cohort. The intervention and follow-up duration was four years.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial was a randomised, placebo-controlled, multicentre clinical trial that studied the effects of dual (aspirin plus clopidogrel) versus single (aspirin alone) antiplatelet therapy (Pearce SPS3 2014). The intervention duration was three years and the median follow-up for cognitive outcomes was 3.4 years.

Participants

Jia 2016 assessed 563 people at 15 Chinese academic medical centres and recruited 280 participants aged 50 to 70 years who had a diagnosis of subcortical vascular cognitive impairment with cSVD but without dementia. Of these participants, 76% had a history of stroke at baseline. Participants had subjective cognitive complaints or evidence of cognitive decline from an informant, but not sufficient to warrant a diagnosis of dementia. Dementia at baseline was ruled out according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV), with Clinical Dementia Rating (CDR) 0.5 or greater on at least one domain and global score of 0.5 or less; a Mini-Mental State Examination (MMSE) score of 20 or greater (with primary school education) or 24 or greater (with junior school education or above); and normal or slightly impaired activities of daily living (ADL) as defined by a total score of 1.5 or less on the three functional CDR domains (home and hobbies, community affairs and personal care). MRI inclusion criteria were evidence of cSVD, no cortical stroke and no medial temporal lobe atrophy. All participants were Han Chinese.

The SILENCE RCT recruited people from Italian neurology clinics on the basis of MRI evidence of silent brain infarcts, with most included participants having infarcts in keeping with our cSVD definition (Maestrini SILENCE 2018). The study assessed 350 participants of whom 50 were enrolled in the RCT (aspirin group 24; placebo group 26) and 33 in a non-randomised follow-up. In this review, we include only data from the 50 randomised participants.

The SPS3 study recruited 3020 participants aged 30 years or above from 81 clinical centres across seven different countries in the North and South Americas (Pearce SPS3 2014). People who had recent symptomatic small subcortical stroke (within six months) with MRI confirmation were eligible for this trial. This study differed from Jia 2016 and Maestrini SILENCE 2018 because it included participants with acute SVD. Of the 3020 recruited participants, 2916 had baseline assessment using the Cognitive Abilities Screening Instrument (CASI) and were included in the cognitive substudy. The study reported 26% of participants with incomplete testing (either left the study early or did not complete cognitive testing at their last follow-up). Compared to those with complete data, they were more educated and more likely to have MCI at study entry. Participants were excluded if they had an MMSE score less than 24 points at baseline.

Intervention

Participants in Jia 2016 were randomly assigned to receive either DL-3-n-butylphthalide capsule or placebo, taken orally three times daily for six months. The number of unused capsules were counted in the medicine bottles to assess drug compliance. Concomitant aspirin was used in 61.4% of the DL-3-n-butylphthalide group and 65.7% of the placebo group.

Participants in Maestrini SILENCE 2018 were randomly assigned to receive either enteric-coated aspirin 100 mg daily or placebo with identical appearance.

Participants in Pearce SPS3 2014 were randomly assigned to receive either enteric-coated aspirin 325 mg daily plus clopidogrel 75 mg daily or enteric-coated aspirin 325 mg daily plus matching placebo. Compliance was measured by tablet counts, and follow-up was five years.

Outcome measures

The primary outcomes in Jia 2016 included Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog; a 12-item global cognitive score ranging from 0 (best) to 70 (worst)); and Clinician Interview-Based Impression of Change-Plus Caregiver Input (CIBIC-plus; a global assessment of change based on a semi-structured, patient/caregiver interview, with scores ranging from 1 to 7, where 1 is "very much improved", 4 is "no change", and 7 is "very much worse"). Secondary outcomes were MMSE (range 30 with higher scores indicates better performance), Clinical Dementia Rating (CDR) global score (range 0 = no impairment to 3 = severe impairment), CDR-sum of boxes (CDR-SB, range 0 to 18, with higher scores representing greater severity of cognitive and functional impairment), Neuropsychiatric Inventory (NPI, a composite symptom domain score ranging from 0 = absence of behavioural symptoms to 144 = maximum severity of behavioural symptoms), Chinese Activities of Daily Living (ADL; range 20–80, with higher scores indicating worse functioning) and adverse events. Assessments were at baseline, week 12 and week 24.

The primary outcome in Maestrini SILENCE 2018 was a composite of clinical and radiological stroke events. Secondary outcomes included change in cognition using a multidomain neuropsychological test battery and the MMSE, an unspecified ADL measure and adverse events. Assessments were performed annually over four years of follow-up.

The primary outcomes in Pearce SPS3 2014 were recurrent stroke and bleeding. Cognitive function was a secondary outcome as measured by CASI; a global measure of cognition assessing attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, abstraction and judgement, with scores of 0 to 100, with higher scores indicating better performance. The CASI assessment was performed annually during five years of follow-up, and participants were only included in the cognitive substudy if they had at least one year of follow-up. Incident MCI was recorded. MCI (definition derived in posthoc analysis) was defined psychometrically at entry and annually on the basis of test scores as no cognitive impairment, MCI (single amnestic), MCI (multidomain) and MCI (non-amnestic). For a full description of MCI assessment see Characteristics of included studies table.

Excluded studies

We excluded 12 studies as they did not meet our predefined inclusion criteria. For the full details of the reasons for exclusion, see Characteristics of excluded studies table. The most common reasons for exclusion were using a non-randomised controlled trial design (Douiri 2013; Jacobs 2015; Kwok 2015; Zhang 2014), having a mixed population with no or too few participants with cSVD (ASPREE-NEURO; AVERROES-MRI assessment study; COMPASS MRI), or having no outcomes that were relevant to this review (Han 2013; Shinod-Tagawa 2002; Xu 2020).

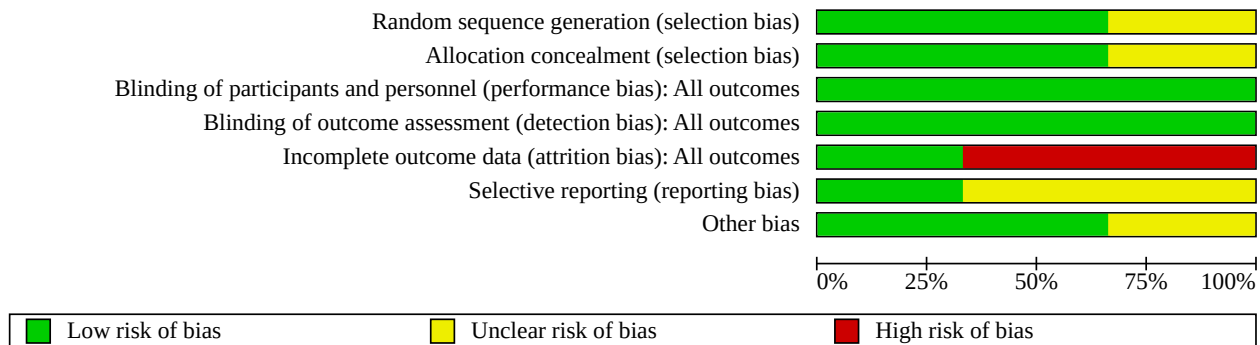## Risk of bias in included studies

The quality of included studies was variable. See the risk of bias in the Characteristics of included studies table, Figure 2, and Figure 3 for full details.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

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Figure 3.

Random sequence generation (selection bias)	
Allocation concealment (selection bias)	
Blinding of participants and personnel (performance bias): All outcomes	
Blinding of outcome assessment (detection bias): All outcomes	
Incomplete outcome data (attrition bias): All outcomes	
Selective reporting (reporting bias)	
Other bias	

0%   25%   50%   75%   100%

■ Low risk of bias   ■ Unclear risk of bias   ■ High risk of bias

Allocation

Both Pearce SPS3 2014 and Jia 2016 were at low risk of selection bias. We judged Maestrini SILENCE 2018 at unclear risk of bias, as we could not be sure how the possibility to combined randomised and non-randomised trial design had influenced the allocation of participants.

Blinding

We considered Jia 2016, Maestrini SILENCE 2018, and Pearce SPS3 2014 at low risk of performance and detection bias. Studies were described as double-blind with matching placebo. Participants, investigators and outcome assessors were masked to the treatment allocation and were unable to preview the randomised assignments.

Incomplete outcome data

There was substantial attrition in both Maestrini SILENCE 2018 and Pearce SPS3 2014. It is possible that missing follow-up data could have influenced the outcomes of interest, that is, those with cognitive or functional decline might be more likely to drop out of the full follow-up period. Jia 2016 was at low risk of attrition bias.

Selective reporting

We judged Jia 2016 at possible risk of reporting bias, as the protocol was retrospectively registered, the projected sample size did not match the recruitment as proposed by the authors, and several differing outcomes were labelled as "primary outcomes" in their protocol. We also judged Maestrini SILENCE 2018 at possible risk of reporting bias, as the trial was prematurely terminated and the protocol was no longer available on the protocol repository.

Other potential sources of bias

The study medication used in Jia 2016 was donated by Shijiazhuang Pharmaceutical Group Company, but the company was reported as having no other role in the study. The discussion section of Jia 2016 stated that they had underestimated their sample size due to an overestimation of the drug effect at the clinical trial planning stage. We considered that these two issues posed an unclear risk of other biases. Maestrini SILENCE 2018 and Pearce SPS3 2014 were at low risk of bias.

Effects of interventions

See: **Summary of findings 1** Antiplatelet drug compared to placebo in mixed populations (with or without pre-existing antiplatelet therapy) for the prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia; **Summary of findings 2** Antiplatelet therapy compared to placebo for prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia; **Summary of findings 3** Dual antiplatelet therapy compared to single antiplatelet therapy for prevention of cognitive decline and dementia in people with cerebral small vessel disease and no dementia

As the studies differed in their included participants, interventions and outcomes, we decided that a quantitative meta-analysis was inappropriate. Therefore, we described the three included studies in turn, assessing the strength of evidence at study level, and describing the relevant quantitative data in Table 1, Table 2, and Table 3, and present a narrative summary of the evidence in Summary of main results.

1. Change in cognitive function from baseline

Jia 2016: intention-to-treat (ITT) analysis involving 280 participants showed a difference in favour of DL-3-n-butylphthalide using the ADAS-Cog (adjusted MD −1.07, 95% CI −2.02 to −0.12), which equated to an effect size of 0.26 standard deviation. In the per-protocol analysis, the observed MD was slightly larger at 1.21 points in the same direction. The mean CIBIC-plus global score also showed a difference in favour of DL-3-n-butylphthalide (drug-placebo difference −0.29, 95% CI −0.48 to −0.10, P = 0.003), which equated to an effect size of 0.35 standard deviation. In the per-protocol analysis, the observed MD was larger at −0.33 points (P < 0.001) in the same direction. There is no consensus on what is a clinically important difference in ADAS-Cog or CIBIC-plus for a trial examining cognitive decline, but differences of these magnitudes is unlikely to be of clinical relevance. There were no significant differences for MMSE, CDR global score or CDR-SB between groups (Table 1). We considered this low-certainty evidence, downgrading twice for indirectness as it is arguable whether DL-3-n-butylphthalide should technically be classified as an antithrombotic therapy and because all participants had cognitive impairment at baseline, and for imprecision.

Maestrini SILENCE 2018 described various cognitive tests. There was no evidence of a difference between the aspirin and placebo

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groups in change in cognition, measured with a neuropsychological test battery, or in MMSE scores at the end of follow-up (Table 3). We considered this very low-certainty evidence, downgrading for risk of bias, indirectness and imprecision.

Pearce SPS3 2014: there was improvement in the CASI z-score from baseline to each of the years one to five in both the aspirin plus clopidogrel and placebo groups, but the study reported that only the improvement from study entry to year one was statistically significant (MD 0.11, SD 0.84, P < 0.0001). The CASI z-scores were not different between the two treatment groups over time (P = 0.858) (Pearce SPS3 2014). We considered this low-certainty evidence, downgrading for indirectness as most participants had MCI at baseline, making it difficult to translate these findings to the general small-vessel disease population, and for imprecision.

2. Incident dementia

No studies reported incident dementia.

3. Major bleeding events (intracranial and extracranial)

Jia 2016 reported two intracranial haemorrhagic events, one in each group (0.7% with DL-3-n-butylphthalide group versus 0.7% with placebo; P = 1.00). We considered this very low-certainty evidence, downgrading it twice for indirectness as it is arguable whether DL-3-n-butylphthalide should technically be classified as an antithrombotic therapy and because most participants had cognitive impairment at baseline, and once for imprecision because only one study contributed to this finding. The study did not report extracranial haemorrhage.

Maestrini SILENCE 2018 did not report major bleeding events. They reported fatal and non-fatal stroke rates, but these are not categorised as ischaemic or haemorrhagic. There were gastrointestinal adverse events, but it was unclear whether these related to bleeding.

Pearce SPS3 2014 reported both intracranial and extracranial haemorrhagic events. The overall risk of major haemorrhage was almost doubled with dual antiplatelet therapy (105 haemorrhages, 2.1% per year) compared with aspirin alone (56 haemorrhages, 1.1% per year) (HR 1.97, 95% CI 1.41 to 2.71; P < 0.001). Intracranial haemorrhagic events occurred in 15 participants assigned to aspirin and 22 participants assigned to aspirin plus clopidogrel (HR 1.52, 95% CI 0.79 to 2.93; P = 0.21). Extracranial haemorrhagic events occurred in 42 participants assigned to aspirin and 87 assigned to aspirin plus clopidogrel (HR 2.15, 95% CI 1.49 to 3.11; P < 0.001); 28 of these bleedings were gastrointestinal in the aspirin group and 58 in the aspirin plus clopidogrel group (HR 2.14, 95% CI 1.36 to 3.36; P < 0.001). There were four fatal haemorrhagic events in the aspirin group and nine in the aspirin plus clopidogrel group (HR 2.29, 95% CI 0.7 to 7.42; P = 0.17). All four fatal haemorrhages in the aspirin group were intracranial haemorrhage versus seven fatal intracranial haemorrhages in the aspirin plus clopidogrel group (HR 1.78, 95% CI 0.52 to 6.07; P = 0.36). The remaining two fatal haemorrhagic events in the aspirin plus clopidogrel group were extracranial. We considered this low-certainty evidence, downgrading once for indirectness because most participants had MCI at baseline and once for imprecision because only one study contributed to this finding.

4. Functional outcome (activities of daily living)

Jia 2016: there was no evidence of a difference in ADL between DL-3-n-butylphthalide and placebo groups (adjusted MD 0.18, 95% CI −0.70 to 1.07). It was unclear what the minimum clinically important difference would be for the ADL scale employed as it is not a commonly used measure. We considered this very low-certainty evidence, downgrading twice for indirectness and once for imprecision.

Maestrini SILENCE 2018: there was no evidence of a difference in ADL between aspirin and placebo (Table 3). The ADL scale employed was not described. We considered this to be very low certainty evidence, downgrading it for risk of bias, indirectness and imprecision.

Pearce SPS3 2014 did not report functional outcome.

5. Incident ischaemic stroke or transient ischaemic attack

Jia 2016: reported five participants who experienced new ischaemic stroke: two (1.4%) in the DL-3-n-butylphthalide group and three (2.1%) in the placebo group (P = 1.00). There was one TIA (0.7%) in the DL-3-n-butylphthalide group versus none in the placebo group. We considered this very low-certainty evidence, downgrading twice for indirectness and once for imprecision.

Maestrini SILENCE 2018 reported clinical stroke and TIA with no difference between groups. In the aspirin group, there was one stroke event (3%) and no TIA, while in the placebo group there were two strokes (4%) and two TIAs (2%). We considered this very low-certainty evidence, downgrading once each for risk of bias, indirectness and imprecision.

Pearce SPS3 2014 reported both ischaemic stroke and TIA. In total, 124 participants in the aspirin group versus 100 participants in the aspirin plus clopidogrel group had ischaemic stroke (HR 0.82, 95% CI 0.63 to 1.09; P = 0.13); while 39 participants in the aspirin group versus 28 in the aspirin plus clopidogrel group had TIA (HR 0.73, 95% CI 0.45 to 1.18; P = 0.19). We considered this low-certainty evidence, downgrading once for indirectness and once for imprecision.

6. Death

Jia 2016 reported four participants who died during the study: two (1.5%) in the DL-3-n-butylphthalide group and two (1.5%) in the place group (P = 1.00).

Maestrini SILENCE 2018 reported two (6%) cases of fatal myocardial infarction in the aspirin group and one (2%) event of fatal myocardial infarction in the placebo group. There were no other deaths reported.

Pearce SPS3 2014 reported 78 deaths in the aspirin group versus 113 deaths in the aspirin plus clopidogrel group (HR 1.5, 95% CI 1.1 to 2.0; P = 0.004). There were four fatal haemorrhagic events in the aspirin group and nine fatal haemorrhage events in the aspirin plus clopidogrel group (HR 2.29, 95% CI 0.7 to 7.42; P = 0.17).

7. Any adverse events (excluding bleeding)

Jia 2016: adverse events were mostly mild to moderate in severity. The overall adverse event rate was 21% in the DL-3-n-butylphthalide group versus 14% in the placebo group (P = 0.08). Adverse events were deemed possibly or probably related

to the study drug in nine participants: five (3.6%) in the DL-3-n-butylphthalide group and four (2.9%) in the placebo group (P = 1.00). We considered this very low-certainty evidence, downgrading twice for indirectness and once for imprecision.

Maestrini SILENCE 2018 reported any adverse event, including two events (8.3%) in the aspirin group and one event (3.8%) in the placebo group. We considered this very low-certainty evidence, downgrading once each for risk of bias, indirectness and imprecision.

Pearce SPS3 2014 did not report any adverse event (excluding bleeding).

8. Withdrawal from the allocated treatment (excluding death)

Jia 2016 reported 33/280 participants discontinued the allocated treatment: seven participants withdrew consent (four from the DL-3-n-butylphthalide group versus three from the placebo group); 18 participants were lost to follow-up (10 from the DL-3-n-butylphthalide group versus eight from the placebo group); three participants withdrew from the treatment due to possibly drug-related gastrointestinal reactions (all from the DL-3-n-butylphthalide group); and five participants withdrew due to worsened comorbidities (four from the DL-3-n-butylphthalide group versus one from the placebo group). The OR for withdrawal from treatment was 1.88 favouring placebo (95% CI 0.90 to 3.42). We considered this very low-certainty evidence, downgrading twice for indirectness and once for imprecision.

Maestrini SILENCE 2018 reported numbers completing follow-up as 16 (66.7%) in the aspirin group and 21 (80.8%) in the control group. We considered this very low-certainty evidence, downgrading once each for risk of bias, indirectness and imprecision.

Pearce SPS3 2014 reported mean rate of adherence to the assigned antiplatelet regimen was 94%. Permanent discontinuation of the assigned antiplatelet therapy occurred in 30% of participants receiving aspirin plus clopidogrel and 27% of those receiving aspirin (P = 0.02). We considered this low-certainty evidence, downgrading once for indirectness and once for imprecision.

9. New cerebral microbleeds on neuroimaging

No trial reported new cerebral microbleeds on neuroimaging.

10. Incident mild cognitive impairment

Jia 2016: not applicable as all participants had cognitive impairment at baseline.

Maestrini SILENCE 2018 did not report incident MCI.

Pearce SPS3 2014 reported the incidence of MCI. At study entry, 1303 (45%) participants already fulfilled a diagnosis of MCI. Of the remaining 1413 participants without MCI at study entry, 376 (27%) participants developed MCI and there was no difference between groups (annual incidence 9.7% (189 events in 721 participants over a mean of 2.7 years of follow-up) in the aspirin plus clopidogrel group versus 9.9% (187 events in 692 participants over a mean of 2.7 years of follow-up) in the aspirin plus placebo group (P = 0.704).

DISCUSSION

The three included trials were too heterogeneous to allow quantitative meta-analysis. We described each study as a narrative with corresponding tables describing the study results.

Summary of main results

We identified three studies that included 3384 participants in total and assessed the effects of antithrombotic therapy for the prevention of cognitive decline in people with cSVD on neuroimaging but without dementia (Jia 2016; Maestrini SILENCE 2018; Pearce SPS3 2014).

There was considerable heterogeneity across the studies in terms of population assessed, antithrombotic strategy studied and outcomes described. We considered it inappropriate to create quantitative summary estimates using these three very different studies. However, there were consistent findings across many of the outcomes of interest and this allowed us to offer a class effect summary of the evidence for a potent versus less potent antithrombotic approach in people living with cSVD.

Across the various measures of general cognition, incident cognitive syndromes (i.e. dementia and MCI) and ADL, there was no convincing evidence of a beneficial effect of antithrombotic therapy in addition to usual care. The single study that reported some potential improvement in cognitive function found inconsistent results with some cognitive outcomes suggesting benefit and others suggesting no effect. Even if we consider the positive cognitive outcomes from this trial in isolation, the size of effect was probably less than would be considered clinically meaningful. Based on the evidence from all three included studies, there is little support for a strategy of routinely using antithrombotic therapy to prevent cognitive decline associated with cSVD.

A signal of potential harm was suggested in the outcomes of bleeding (both intracranial and extracranial), adverse events and treatment discontinuation. This is a reminder that antithrombotic therapy is not a completely benign intervention and can be associated with risks of harm. However, there was also a signal, albeit not statistically significant, that a more potent antithrombotic strategy may reduce the risk of stroke, which is a common complication of cSVD. Recurrent stroke is a powerful risk factor for cognitive decline, so if antithrombotic therapy can reduce stroke incidence then, in theory at least, they could indirectly reduce the cognitive effects of further cerebrovascular events.

Overall completeness and applicability of evidence

The process of conducting this review highlighted general issues with research in the field of small vessel disease.

The first issue was with the definition of the population. Our interest was people who had neuroimaging markers of cSVD, but no evidence of dementia. We based our definition of neuroimaging cSVD on the STRIVE criteria where possible but majored on white matter disease and covert stroke lesions. Increasingly, other brain imaging lesions associated cSVD are recognised and these may serve as better biomarkers of cerebrovascular cognitive problems, for example enlarged perivascular spaces and certain patterns of atrophy (Arba 2018).

Our operationalisation of the neuroimaging of cSVD included any person with lacunar stroke. Baseline neuroimaging is mandated in stroke trials of antithrombotic therapy to exclude intracerebral haemorrhage. So, potentially any stroke trial of antithrombotic therapy that included cognitive outcomes could be eligible for our review. To ensure we did not miss relevant information, we complemented our primary search of the literature, which used a search strategy designed around cSVD and vascular cognitive impairment, with a second focussed search of all the antithrombotic therapy trials held within the Cochrane Stroke Group database. We found several studies that could have contributed data to our review if the results were presented for a subgroup restricted to lacunar stroke. Such subgroup analyses were not available in the primary studies and results were only presented in an aggregate format for all ischaemic stroke types. Requests to authors to share these data did not return data that we could have used.

Another issue with the population was around defining a minimum degree of cSVD change. Study populations with baseline neuroimaging were often mixed, with some participants showing evidence of a spectrum of cSVD and others showing none of the common features. We had to set a threshold for the proportion of baseline cSVD that we would accept and in doing so we had to exclude certain studies that could have been relevant to the broader question around antithrombotic therapy and progression of radiological and clinical features of cSVD. At the individual level, there are many markers of cSVD and these tend to increase with increasing age. There is then the issue of when are small vessel changes 'acceptable for age' and when do they become 'pathological'. There is no consensus on this issue, and many believe that all 'age-related changes' are pathological, although there have been attempts to offer age-related normative values (Smith 2017). Again, we had to set a threshold of a minimum of at least 'mild' cSVD, but we recognise that this is an arbitrary threshold with no agreed definition, and through this categorisation we may have excluded certain studies that could have been relevant to the broader issue of antithrombotic therapy and cognitive decline. Furthermore, we included both participants with recent lacunar infarctions (Pearce SPS3 2014) and with more chronic forms of SVD (Jia 2016; Maestrini SILENCE 2018). These populations are probably slightly different in risk profiles and secondary prevention, potentially mitigating the effect of the intervention. For our included studies, there was no effect of the intervention both for populations with acute and more chronic SVD.

As there are several antithrombotic agents used in vascular medicine, we were deliberately inclusive. All the included trials were of antiplatelet agents, with no eligible studies describing the effects of anticoagulants. Within the review remit, we included differing potency of drugs or combinations with one study assessing low-dose aspirin, one study comparing dual antiplatelet therapy versus single antiplatelet therapy, and one study of a compound (DL-3-n-butylphthalide) that some might argue does not primarily belong within the antithrombotic drug class.

Given the differing contexts of the studies, the comparator also differed between the studies and usual care could have included the routine use of an antithrombotic agent, for example in participants who were included on the basis of lacunar stroke. Thus, while our initial interest was the effect of antithrombotic compared to no antithrombotic, for many of the participants included in eligible studies the data described additional versus single antithrombotic.

The intervention and follow-up durations were different between included studies (varying from 24 weeks to four years of intervention and six months to four years of follow-up). Trials investigating preventive strategies for cognitive decline and dementia require long-term surveillance of participants due to the slow progression and low incidence of the condition under study (Richard 2012). Similarly, trials with a short intervention duration might pick up changes in cognition that are not sustainable over time (Beishuizen 2016). Therefore, some caution is warranted when interpreting findings from studies with a relatively short intervention or follow-up (or both) duration. Future trials should aim for long-term follow-up of cognitive decline or dementia and could potentially consider adding surrogate markers for cognitive decline and dementia (e.g. imaging markers or simple clinical (memory) test) as an interim outcome.

The decision to study a population free of dementia at baseline was taken because we anticipated that progression to frank dementia would be an important clinical outcome of relevant trials. In fact no trials reported useable data on incident dementia, although one study described incident MCI. Moreover, one study did not report how (or if) they formally excluded dementia, though this is highly likely as participants were able to give informed consent. Rather, the included studies reported a heterogeneous mix of cognitive assessment tools. This inconsistency in cognitive assessment methods is common to both dementia and stroke research.

The natural history and management of lacunar stroke, early-stage vascular cognitive impairment and incidentally detected neuroimaging features of cSVD are very different. In retrospect, and for future studies, it may have been more useful to distinguish 'silent' or 'covert' cSVD (with no clinical stroke and no frank cognitive syndrome) from 'clinically apparent' cSVD presenting with a stroke.

Quality of the evidence

We could not perform meta-analysis as the included trials were heterogeneous. Many of our prespecified key outcomes were not reported in the included trials, for example, no trial reported incident dementia. Moreover, the observed evidence was of very low to low certainty, meaning our confidence in the reported effect estimates is limited. The certainty of our evidence was compromised by several factors. Risk of bias was a major issue for one trial (Maestrini SILENCE 2018), while applicability to the study question was also an issue. Of the remaining trials, Pearce SPS3 2014 was a stroke secondary prevention trial and cognition was a secondary aim. Arguably Jia 2016 was the study closest to our original aim in terms of population and outcomes assessed, but the medication studied was not primarily tested as an antithrombotic therapy, although it does possess antithrombotic properties. Moreover, this study had relatively restricted age range (50 to 70 years), making it difficult to generalise these findings to the general population. Both Jia 2016 and Maestrini SILENCE 2018 had a small sample size and relatively short follow-up for a cognitive prevention study, and this is reflected in the uncertainty around their results. Even the largest trial may not have been adequately powered for some of our efficacy and safety outcomes, for example, incident MCI and intracerebral bleeding (Pearce SPS3 2014).

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Potential biases in the review process

To keep our review focussed, we operationalised our definitions of cSVD. This may have excluded some studies with potentially relevant data. The data did not allow for an assessment of publication bias. See Figure 2 and Figure 3 for full details.

Agreements and disagreements with other studies or reviews

Agreements with guidelines

The recently published European Stroke Organisation (ESO) guideline on covert cSVD gave a weak recommendation against using antithrombotic therapy such as aspirin for cognitive decline, but recognised that the quality of supporting evidence was weak (Wardlaw 2021). However, the ESO guideline did recommend people with covert cSVD and hypertension to have their blood pressure well controlled, and it emphasised that RCTs with specific clinical endpoints were a priority for covert cSVD. An accompanying expert consensus statement noted that antiplatelets should not be used unless there is another clinical indication as these drugs may be harmful, especially in older adults. While this guideline considered randomised and non-randomised evidence and had a broader definition of cSVD, the conclusions are aligned with the findings of our review.

The Geriatric Neurology Group of the Chinese Society of Geriatrics published a clinical practice guideline on cognitive impairment in cSVD (Peng 2019). This guideline referred to Pearce SPS3 2014, but did not make any recommendations on antithrombotic therapy; it recognised that the evidence around pharmacological treatment of vascular risk factors for cSVD was weak.

The American Heart Association/American Stroke Association published guidelines on prevention of stroke in people with silent cerebrovascular disease. Their neuroimaging definition of silent cerebrovascular disease is similar to our review definition of cSVD. No formal recommendations were made around antithrombotic therapy due to the lack of suitable trials (Smith 2017).

Agreements with other studies

While we strived to ensure that we included all studies relevant to our review question, there were other studies that offered insights into antithrombotic therapy and vascular cognitive decline. The ASPREE (Aspirin in Reducing Events in the Elderly) study described the use of aspirin to prevent cardiovascular events, and physical and cognitive decline in older adults (McNeil 2018). Although baseline neuroimaging was not mandated in this study, it is possible that a proportion of the participants might have had a degree of cSVD changes. The primary results of ASPREE are aligned with the summary findings in this review, and aspirin did not appear to have any apparent benefit on cognitive or physical function, but was associated with increased harm.

There are studies that describe the effect of antithrombotic therapy on the progression of neuroradiological markers of cSVD. We found two trials of an antiplatelet agent, cilostazol. In one RCT, 89 participants with type II diabetes mellitus and no brain lesions on baseline MRI scans were randomised to cilostazol or placebo, and followed up for three years (Shinoda-Tagawa 2002). The study found fewer silent infarcts in the cilostazol group. The LACI-1

(LACunar Intervention-1) RCT of 57 participants with recent lacunar stroke reported that 11 weeks of cilostazol reduced progression in white matter lesions compared to placebo (Blair 2019). While these data are interesting, the relationship between neuroimaging features of cSVD and clinical manifestations was unclear and so for our review, we did not include studies that only reported surrogate measures such as silent brain infarction.

Although we were unable to obtain individual participant data or subgroup data limited to cSVD, studies of antithrombotic therapy for stroke can still give some relevant information. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial showed no significant differences in cognitive outcomes between two antiplatelet regimens (aspirin plus extended-release dipyridamole versus clopidogrel) (Diener 2008). The agent DL-3-n-butylphthalide has also been studied in acute ischaemic stroke, where there was no difference in cognitive test scores. However, the sample size was small for a cognitive study (104 participants) and follow-up was only for one month (Yan 2017).

Agreement with other reviews

In a systematic review and meta-analysis looking at antithrombotic therapy following lacunar stroke (a form of cSVD), the authors described benefit of single antiplatelet versus placebo for prevention of recurrent stroke. However, there was no signal of superiority of one antithrombotic agent over another, and long-term dual antiplatelet was associated with harm. The review did not examine cognitive outcomes (Kwok 2015).

One Cochrane Review describing aspirin for prevention of cognitive decline found few studies, but noted no clear signal of benefit and the potential for harmful adverse effects (Jordan 2020).

We found no primary studies or reviews examining oral anticoagulants in our population of interest. In one systematic review that examined the relationship between atrial fibrillation thromboprophylaxis and cognitive decline (Moffitt 2016), the authors found no definitive evidence of cognitive benefit or harm from anticoagulation over antiplatelet therapy. Since the publication of this review, one large observational cohort study of 3284 older (over 65 years) Chinese people with AF followed up for 3.6 years found that anticoagulation with warfarin was associated with a significantly lower risk of new-onset dementia compared those with no therapy or aspirin, with an HR of 0.14 (95% CI 0.05 to 0.36; P < 0.001) (Wong 2020). Interestingly, in this study, people receiving warfarin with time in therapeutic range (TTR) of greater than 65% had a non-significant trend towards a lower risk of dementia compared with those with TTR less than 65% (Wong 2020).

In one narrative review of cSVD, Mok 2015 noted the substantial risk of bleeding when antithrombotics were used. Given the theoretical reduced bleeding risk with certain antithrombotic classes, a recommendation was made to consider using cilostazol or triflusal (over aspirin) in people living with cSVD.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the routine use of antithrombotic therapy to prevent cognitive decline in people with small vessel disease on neuroimaging but without dementia. We

identified only three studies reporting on our research question and their results were inconclusive. The overall evidence reported in this review was of very low to low certainty, meaning our confidence in the reported effect estimates is limited.

In this review, we considered cerebral small vessel disease (cSVD) as a single condition, but under this rubric is a spectrum of severity of neuroimaging and phenotypic features and people living with cSVD may have other potential indications for antithrombotics. At the individual patient level, a degree of risk stratification is required around antithrombotic prescription. Recommendations on antithrombotic therapy in practice cannot be made based on the findings of this review, as the studies were too heterogeneous in terms of populations (including both acute and chronic small vessel disease in both naïve and therapeutic populations) and interventions (including single and double antithrombotic therapy).

Implications for research

Our review highlights unanswered questions and aspects of research methods that could be improved for future studies.

The available evidence on adverse effects, particularly bleeding, is a reminder that longer-term administration of antithrombotics presents risks. Any potential long-term cognitive or stroke benefit would need to be greater than the bleeding risk. Arguments around using antithrombotic agents that have lesser bleeding risk and may have beneficial effects on other aspects of vascular biology (e.g. cilostazol) are compelling but so far lack convincing clinical trial evidence.

While one could argue that large-scale, long-term follow-up RCTs of antithrombotic therapy in cSVD are needed, given the associated bleeding risk and increasing evidence of no cognitive benefit of aspirin primary prevention, these trials may need more sophisticated risk stratification than presence/absence of cSVD change.

Novel antithrombotic agents with lower bleeding risk could have potential efficacy and we would support the calls for all future (cerebro) vascular trials to include cognitive outcomes.

The focus of our review is on cognition, but the clinical manifestations of cSVD are not restricted to cognitive decline. No cSVD trials assessed other aspects of the cSVD phenotype such as disordered gait, apathy, mood disturbance, continence, etc. It would be useful to find out the clinical features of greatest relevance to people living with cSVD and design trial outcomes around these.

Finally, the review process highlighted the difficulty of searching the published literature for studies of cSVD. Greater standardisation of terminology and indexing (as has been achieved for the neuroimaging aspects of cSVD) would aid future evidence synthesis. In the meantime, the development and validation of search syntax for cSVD would be a useful step.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

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

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Jia 2016 *(Continued)*

Study characteristics	
Methods	**Design:** randomised, double-blind, placebo-controlled trial
	Location/setting: 15 academic medical centres in China
	Date of study: 29 June 2009 to 2 May 2015 (participants screening: September 2008 to December 2009)
	Sample size: 563 people with a diagnosis of subcortical vascular cognitive impairment without dementia were enrolled and assessed for eligibility. 282 were excluded and 281 entered the study and underwent randomisation.
	Randomisation: among the 281 people who underwent randomisation, 141 were assigned to DL-3-n-butylphthalide (117/141 completed the 24 weeks' treatment) and 140 were assigned to placebo (126/140 completed the 24 weeks' treatment).
	Participants were randomly assigned in a 1:1 ratio to receive kits containing DL-3-n-butylphthalide 200 mg or placebo, which were labelled with sequential numbers according to a randomisation list (stratified by investigation site, in blocks of 4) generated by an independent statistician.
Participants	**Number in study:** 281
	Participant diagnosis: subcortical vascular cognitive impairment without dementia
	Inclusion criteria
	1. Han Chinese
	2. Aged: 50–70 years
	3. With a consistent carer who accompanied the participants ≥ 4 days a week
	4. Complaint or informant (or both) report of cognitive impairment involving memory or other cognitive domains (or both) lasting ≥ 3 months
	5. Neither normal nor demented according to the criteria of the DSM-IV, with CDR ≥ 0.5 on ≥ 1 domain and global score ≤ 0.5
	6. MMSE score ≥ 20 (primary school education) or ≥ 24 (junior school or above education)
	7. Normal or slightly impaired ADL defined by total score ≤ 1.5 on the 3 functional CDR domains (home and hobbies, community affairs and personal care)
	8. MRI brain criteria as follows:
	a. multiple (i.e. ≥ 3) supratentorial subcortical small infarcts (3–20 mm in diameter), with or without WML of any degree; or moderate to severe WML (score 2 according to the Fazekas Rating Scale) with or without small infarct; or ≥ 1 strategically located subcortical small infarcts in the caudate nucleus, globus pallidus, or thalamus
	b. absence of cortical and watershed infarcts, haemorrhages, hydrocephalus, and WMLs with specific causes (e.g. multiple sclerosis)
	c. no hippocampal or entorhinal cortex atrophy (scored 0 according to medial temporal lobe atrophy scale of Scheltens)
	d. all scans read by a central neuroimaging reader to determine eligibility, ensuring consistent application of the criteria
	Exclusion criteria
	1. Severe aphasia
	2. Physical disabilities or any other factor that may precluded completion of neuropsychological testing
	3. Disorders other than subcortical vascular cognitive impairment without dementia that may affect cognition
	4. HAMD score > 17, or schizophrenia
	5. New stroke within 3 months before baseline
	6. Inherited or inflammatory small vessel disease
	7. Clinically significant gastrointestinal, renal, hepatic, respiratory, infectious, endocrine or cardiovascular system disease

8. Cancer
9. Alcoholism
10. Drug addiction
11. Use of medications that may affect cognitive functioning (including tranquilisers, anxiolytics, hypnotics, nootropics and cholinomimetic agents)
12. Known hypersensitivity to celery
13. Inability to undergo brain MRI

Mean age: DL-3-n-butylphthalide: 68.0 (SD 8.8) years; placebo: 66.7 (SD 7.7) years

Females: DL-3-n-butylphthalide: 48 participants (34.3%); placebo: 48 participants (34.3%)

Education: DL-3-n-butylphthalide: < 5 years: 50 participants (35.7%); > 5 years: 90 participants (64.3%); placebo: < 5 years: 52 participants (37.1%); > 5 years: 88 participants (62.9%)

Baseline comorbidities

1. Hypertension: DL-3-n-butylphthalide: 70%; placebo: 65.7%
2. Diabetes mellitus: DL-3-n-butylphthalide: 18.6%; placebo: 17.1%
3. Atrial fibrillation: DL-3-n-butylphthalide: 3.6%; placebo: 2.1%
4. Previous stroke: DL-3-n-butylphthalide: 74.3%; placebo: 77.9%
5. TIA: DL-3-n-butylphthalide: 11.4%; placebo 9.3%

Baseline concomitant aspirin: DL-3-n-butylphthalide: 61.4%; placebo: 65.7%

Consent: written informed consent

Interventions	**Pharmacological intervention:** DL-3-n-butylphthalide 200 mg for 24 weeks **Control:** placebo for 24 weeks
Outcomes	**Primary outcomes** (all measured at baseline and after 6 months of treatment) 1. Changes in 12-item ADAS-Cog 2. CIBIC-plus **Secondary outcomes** (all measured at baseline and after 6 months of treatment) 1. MMSE 2. CDR 3. CDR-SB 4. ADL 5. NPI **Withdrawal from trial drug** Of the 280 participants initially included: DL-3-n-butylphthalide: 3 had drug-related adverse events, 10 lost to follow-up, 4 comorbidities worsened, 4 withdrew from treatment in the group; placebo: 8 lost to follow-up, 1 comorbidity worsened and 3 withdrew from treatment. 37 participants discontinued treatment across both arms, therefore only 243 participants completed the 24 weeks of either DL-3-n-butylphthalide or placebo treatment.
Notes	**PubMed link:** www.ncbi.nlm.nih.gov/pubmed/26086183 **Chinese Clinical Trial Registry number:** ChiCTR-TRC-09000440 **Funding source**: "Eleven Five-Year" Scientific Support Plan Project of State Science and Technology Commission: Diagnosis and Intervention of Mild Cognitive Impairment. The State Science and Technology Commission had no other role in the study. **Research protocol approval:** institutional review board at each participating institution

Jia 2016 *(Continued)*

Study medication: donated by Shijiazhuang Pharmaceutical Group Company. It was stated that, "The company had no other role in the study."

Conduct, safety and adherence to protocol monitoring: by an independent data and safety monitoring board.

Declaration of interest: (quote) "Authors declared that they have no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned in a 1:1 ratio to received three times daily oral DL-3-n-butylphthalide 200 mg or placebo of identical appearance for 24 weeks. The randomisation list (stratified by investigation site, in blocks of four) was generated by an independent statistician."
Allocation concealment (selection bias)	Low risk	Quote: "Every site was supplied with kits of study drug that were labelled with sequential numbers corresponding to the randomisation list."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, caregivers and site investigators were blinded to the treatment allocation." Comment: the trial drug and placebo were of identical appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The clinician completing the CIBIC-plus was blind to the other psychometric assessments and adverse events."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate: DL-3-n-butylphthalide: 23/140 (16.4%) participants; placebo: 14/140 (10%) participants.
Selective reporting (reporting bias)	Unclear risk	Comment: outcome measures were reported as adjusted mean, but the adjustments made were not clearly stated. Multiple outcomes listed as primary on trial register. Sample size in protocol and sample size reported in study did not correspond.
Other bias	Unclear risk	Industry support Quote: "The Shijiazhuang Pharmaceutical Group Company donated the study medication but had no other role in the study." Sample size Quote: "Thus, the sample size was under-estimated, and the desired power was not achieved." Potential "significant-result bias."

Maestrini SILENCE 2018

Study characteristics

Methods	**Design:** longitudinal, randomised, double-blind controlled vs placebo study
	Location/setting: 8 Italian centres

Maestrini SILENCE 2018 *(Continued)*

Sample size: 350 people underwent baseline screening, 124 people recruited, 41 excluded after neuro-radiological diagnosis review, 50 participants enrolled in double-blind study (aspirin: 24; placebo: 26)

Participants	**Number in study:** 50

Inclusion criteria

1. Aged ≥ 45 years
2. Presented with ≥ 1 SBI on MRI

Exclusion criteria

1. Presence of stroke or TIA
2. Contraindication to aspirin use
3. Presence of microbleeds
4. Indication for anticoagulant therapy
5. Malignant arterial hypertension
6. Cardiac failure (IV class NYHA)
7. Haemoglobin ≤ 8 g/dL
8. Platelet count < 100,000/μL
9. Haemorrhagic disorders
10. Ongoing antiplatelet or anticoagulant therapy
11. Serious intercurrent illness

Median age: 66 (IQR: 54–72) years; placebo: 68 years (IQR: 60–73) years

Education: ≥ 9 years: aspirin: 11 (32.4%); placebo: 18 (42.9%)

Baseline comorbidities

1. Atrial fibrillation: aspirin: 1 (2.8%); placebo: 0
2. Ischaemic heart disease: aspirin: 1 (2.8%); placebo: 0
3. Heart failure: 0
4. ADL: aspirin: 6 (IQR 6–6); placebo: 6 (IQR 6–6)
5. Instrumental ADL: aspirin: 8 (IQR 8–8); placebo: 8 (IQR 8–8)
6. MMSE: aspirin: 29 (IQR 27–30); placebo: 29 (IQR 27–30)
7. Beck Depression Index: aspirin: 3.5 (IQR 1.8–); placebo: 5 (IQR 1–7)
8. Hamilton Depression Rating Scale: aspirin: 11 (IQR 14–15.5); placebo: 13 (IQR 9–14.5)
9. Montgomery Åsberg Depression Rating Scale: aspirin: 6 (IQR 2.5–10.5); placebo: 8 (IQR 3–12.5)
10. Informant questionnaire for cognitive decline in the elderly: aspirin: 81 (IQR 78.5–85.5); placebo: 81.5 (IQR 79–87)

Interventions	**Active intervention:** aspirin 100 mg administered as an enteric-coated white tablet for 4 years

Control intervention: enteric-coated white tablet with identical appearance for 4 years

Management of vascular risk factors was administered to all eligible participants at screening visits and throughout study.

Outcomes	Follow-up: 4 years

Primary outcome

1. Composite endpoint of new SBI, stroke and TIA

Secondary outcomes

1. Composite of mortality, non-fatal MI, non-fatal stroke, TIA,
2. SBIs

Maestrini SILENCE 2018 *(Continued)*

3. Adverse events
4. Cognitive decline (neuropsychological evaluation, 3 domains explored: speed of cognitive processing, memory function and global cognitive function

Notes	EudraCT Number: 200-000996-16; Sponsor Protocol Number: 694/30.06.04

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A group of patients were not enrolled in the study because they refused to participate in the pharmacological trial. These subjects were studied prospectively and underwent the same baseline screening and flow chart of exams of those who were randomized." For this study, only randomised participants were included. However, we regarded this domain at unclear risk of bias, as we could not be certain how the combined randomised and non-randomised trial design influenced allocation of participants.
Allocation concealment (selection bias)	Unclear risk	No details givens.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment allocation remained blinded to investigators and subjects until the conclusion of the study, except for patients who withdraw for any collateral or adverse effect and/or any new cardiovascular events."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A neuroradiologist, blinded to the patient's medical history, classified SBIs according to size and location." An experienced neurologist, blinded to MRI results, reviewed the medical history to exclude any previous cerebrovascular overt episode.
Incomplete outcome data (attrition bias) All outcomes	High risk	Lost to follow-up: aspirin: 9 (25%); placebo: 9 (19%) Withdraws consent: aspirin: 4 (11%); placebo: 0 Completed follow-up: aspirin: 15 (42%); placebo: 23 (49%)
Selective reporting (reporting bias)	Unclear risk	EudraCT stated, "Trial prematurely ended" (not described in paper). Full protocol no longer available through EudraCT.
Other bias	Low risk	No other bias detected.

Pearce SPS3 2014

Study characteristics

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Location/setting:** 81 clinical centres in North America, Latin America and Spain (7 countries) **Date of study:** March 2003 to May 2012 (enrolment period 2003–2011) **Sample size:** 3020 people, but only 2916 participants had cognitive assessment (CASI) assessment at study entry.

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Pearce SPS3 2014 *(Continued)*

Randomisation: among the 2916 participants with CASI assessment at study entry, 1468 were assigned to aspirin + clopidogrel and 1448 to aspirin + placebo; 74% of the 2916 participants had the CASI assessment completed at their last annual visit.

Quote: "Participants were simultaneously randomised in a 2-by-2 factorial design to both an antiplatelet intervention (1:1. double-blind, aspirin + placebo vs. aspirin + clopidogrel). Randomization assignments (permuted block design of variable size, stratified by clinical centre and hypertension status) were unavailable for preview and stored electronically at each clinical centre and at the SPS3 Statistical Centre."

Participants	**Number in study:** 2916

Mean age: aspirin + clopidogrel: 63.5 (SD 10.8) years; aspirin + placebo: 63.1 (SD 10.7) years

Female: aspirin + clopidogrel: 557 (38%); aspirin + placebo: 531 (37%)

Education: aspirin + clopidogrel: 0–8 years: 391 (27%); 9–12 years: 527 (36%); > 12 years: 550 (37%); aspirin + placebo: 0–8 years: 374 (26%); 9–12 years: 578 (40%); > 12 years: 496 (34%)

Ethnicity: aspirin + clopidogrel: White, not Hispanic: 751 (51%); Hispanic: 454 (31%); Black: 237 (16%); other or multiracial: 26 (2%); aspirin + placebo: White, not Hispanic: 745 (51%); Hispanic: 452 (31%); Black: 236 (16%); other or multiracial: 15 (1%)

Medical history: aspirin + clopidogrel: diabetes: 524 (36%); hypertension: 1107 (75%); ischaemic heart disease: 157 (11%); lacunar stroke: 154 (11%); subcortical TIA: 80 (5%); aspirin + placebo: diabetes: 546 (38%); hypertension: 1172 (74%); ischaemic heart disease: 150 (10%); lacunar stroke: 146 (10%); subcortical TIA: 78 (5%)

Days from index event to neuropsychological testing, mean: aspirin + clopidogrel: 78 (SD 50) days; aspirin + placebo: 74 (SD 51) days

Modified Rankin stroke disability score: aspirin + clopidogrel: 0: 230 (16%); 1: 763 (52%); 2: 348 (24%); 3: 127 (9%); aspirin + placebo: 0: 209 (14%); 1: 741 (51%); 2: 368 (25%); 3: 130 (9%)

Barthel index score ≥ 95: aspirin + clopidogrel: 1173 (80%); aspirin + placebo: 1148 (79%)

Mild cognitive impairment: aspirin + clopidogrel: 649 (45%); aspirin + placebo: 654 (46%)

Additional small subcortical infracts on MRI: aspirin + clopidogrel: 573 (40%); aspirin + placebo: 553 (39%)

White matter lesion (ARWMC score): aspirin + clopidogrel: none/mild (score 0–4): 709 (49%); moderate (score 5–8): 407 (28%); severe (score ≥ 9): 327 (23%); aspirin + placebo: none/mild (score 0–4): 728 (51%); moderate (score 5–8): 397 (28%); severe (≥ 9): 298 (21%)

Inclusion criteria

People with symptomatic small subcortical stroke (S3) confirmed by MRI, randomised within 6 months of S3 qualification and satisfying all the following criteria

1. Clinical lacunar stroke syndrome (modified from the Fisher 1991 criteria)
2. Absence of signs and symptoms of cortical dysfunction
3. No ipsilateral cervical carotid stenosis (≥ 50%), if the qualifying event was hemispheric
4. No major-risk cardioembolic source requiring anticoagulation or other specific therapy (minor-risk cardioembolic sources were allowed if anticoagulation was not prescribed)
5. MRI presence of an S3 (≤ 2 cm in diameter) corresponding to the qualifying event (required for all brainstem events) or multiple S3s and absence of cortical stroke and large subcortical stroke (recent or remote)

Exclusion criteria

1. Disabling stroke (modified Rankin scale ≥ 4)
2. Previous intracranial haemorrhage (excluding traumatic) or haemorrhagic stroke

3. Aged < 30 years

4. High risk of bleeding (e.g. recurrent gastrointestinal or genitourinary bleeding, active peptic ulcer disease)

5. Anticipated requirement for long-term use of anticoagulants (e.g. recurrent deep vein thrombosis) or other antiplatelets

6. Prior cortical or retinal stroke/TIA (diagnosed either clinically or by neuroimaging)

7. Prior ipsilateral carotid endarterectomy/stent

8. Impaired renal function: glomerular filtration rate < 40 mL/minute/1.73 m^2

9. Intolerance or contraindications to aspirin or clopidogrel (including thrombocytopenia, prolonged INR)

10. MMSE < 24 (adjusted for age and education) (Crum 1993)

11. Medical contraindication to MRI

12. Pregnancy or women of child-bearing potential who were not following an effective method of contraception

13. Unable or unwilling to provide informed consent

14. Unlikely to be compliant with therapy/unwilling to return for frequent clinic visits

15. People concurrently participating in another study with an investigational drug or device

16. Other likely specific cause of stroke (e.g. dissection, vasculitis, prothrombotic diathesis, drug abuse

Consent: (quote): "Participation required written informed consent and study protocol approval by the human research subjects committee at each study centre."

Protection of human participants: (quote): "All clinical sites are required to comply with their local Institutional Review Boards and Human Subject Protection policies. All participants provide written informed consent in their preferred language (English, French, or Spanish) before undergoing any study procedures. The safety of all participants is closely monitored."

Interventions	Both groups received antiplatelet intervention.
	Pharmacological intervention (dual antiplatelet therapy): aspirin + clopidogrel
	Control (single antiplatelet therapy): aspirin + placebo
	Treatment duration: 3 years
Outcomes	Mean follow-up: 3.4 years

Primary cognitive outcome

1. Change in CASI during follow-up

SPS3 primary outcome

1. Time to recurrent stoke (first of fatal or non-fatal ischaemic stroke or central nervous system haemorrhage)

SPS3 secondary outcomes

1. Rate of cognitive decline measured by CASI
2. Incident mild cognitive impairment, defined as: no cognitive impairment if no definite impairment was present in any cognitive domain; mild cognitive impairment (single amnestic type) if there was definite impairment on ≥ 2 of the memory (California Verbal Learning Test) scores, with non-memory scores normal; mild cognitive impairment (multidomain) if there was definite impairment on ≥ 2 memory test scores, and definite impairment on ≥ 2 non-memory test scores (block design, symbol search, Controlled Oral Word Association, and digit span, or definite impairment on the Clox test if the participant had > 8 years of education); and mild cognitive impairment (non-amnestic) if there was definite impairment on ≥ 2 non-memory test scores only. Definite impairment was defined as a Z score ≤ −1.5, ≥ 1.5 SDs below the mean.
3. TIA, defined as an acute focal neurological deficit due to cerebral ischaemia that resolved completely within 24 hours, regardless of neuroimaging findings

Pearce SPS3 2014 *(Continued)*

4. Acute myocardial infarct, defined by standard criteria consisting of ECG and cardiac enzyme changes requiring acute hospitalisation
5. Non-central nervous system thromboembolism, and
6. Death, classified as vascular or non-vascular

Notes	**PubMed link:** www.ncbi.nlm.nih.gov/pubmed/25453457
	ClinicalTrials.gov Registry number: NCT00059306
	Funding source: National Institute of Neurological Disorders and Stroke (US) (U01 NS38529-04A1)
	Role of funding source: (quote) "The sponsor of the study participated in study design, data collection, data analysis and data interpretation."
	Declaration of interest: (quote) "The authors declare that they have no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were simultaneously randomised in a 2-by-2 factorial design to both an antiplatelet intervention (1:1, double-blind, aspirin + placebo vs. aspirin + clopidogrel)."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization assignments (permuted block design of variable size, stratified by clinical centre and hypertension status) were unavailable for preview and stored electronically at each clinical centre and at the SPS3 Statistical Centre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All SPS3 participants take enteric-coated aspirin 325mg daily and are randomly assigned (double-blind) to take clopidogrel 75mg daily or the matching placebo. Antiplatelet medications are provided to patients at randomisation and each quarterly follow-up visit, with adherence measured by pill counts."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All possible outcome and safety events are reviewed by the blinded Events Adjudication Committee made up of neurologists, cardiologists, and internists who are not otherwise involved in SPS3. Event materials, including diagnostic information, blinded to patient identity are submitted by the clinical sites to the Events Coordinator, who blinds them to any information potentially revealing SPS3 treatment assignments and distributes to at least two committee members for review."
Incomplete outcome data (attrition bias) All outcomes	High risk	74% of the 2916 participants had the CASI assessment completed at their last annual visit. Missing cognitive assessments likely to be related to cognitive outcome.
Selective reporting (reporting bias)	Low risk	Comment: both primary and secondary outcomes were reported as described in the study protocol.
Other bias	Low risk	No evidence of other bias noted.

ADL: activities of daily living; ARWMC: age-related white matter change; CASI: Cognitive Abilities Screening Instrument; CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating scale Sum of Boxes; CIBIC-plus: Clinician Interview-Based Impression of Change-Plus Caregiver Input; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; ECG: electrocardiogram; HAMD: Hamilton Depression Scale; INR: international normalised ratio; IQR: interquartile range; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; NPI: Neuropsychiatric Inventory; NYHA: New York Heart Association; SBI: silent brain infarction; SD: standard deviation; SPS3: Secondary Prevention of Small Subcortical Strokes; TIA: transient ischaemic attack; WML: white matter lesions.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ASPREE-NEURO	Wrong population.
AVERROES-MRI assessment study	Too few participants with small vessel disease and no subgroup data available.
COMPASS MRI	Too few participants with small vessel disease and no subgroup data available.
Douiri 2013	Not an RCT.
Han 2013	Irrelevant outcomes.
Jacobs 2015	Not an RCT.
Kwok 2015	Not an RCT.
Kwon 2016	Not an antithrombotic trial.
LACI-1	Follow-up too short.
Shinod-Tagawa 2002	Irrelevant outcomes#.
Xu 2020	Irrelevant outcomes.
Zhang 2014	Not an RCT.

RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

CAVAD

Methods	Randomised, blinded trial
Participants	Inclusion criteria

Inclusion criteria

1. Age range 40–80 years
2. After newly ischemic stroke from 3 months to 2 years
3. Brain CT or MRI shows stroke lesions and white matter lesions, ARWMC ≥ 4
4. Moderate or mild cognitive deficits: MMSE 12–26
5. Vascular or mixed dementia: Hachinski ischaemic score > 4
6. Moderate or mild disability: mRS ≤ 4, NIHSS < 20
7. Informed consent

Exclusion criteria

1. Definitive diagnosis of dementia prior to the stroke
2. Cerebral haemorrhage in the past
3. Cerebral embolism resulting from cardiogenic embolus
4. Critically ill: mRS > 4, NIHSS ≥ 20
5. Immobile person with undiagnosed new stroke
6. Severe cardiac, hepatic or nephric complication
7. Dementia not caused by vascular lesions

CAVAD (Continued)

8. Other diseases disturbing cognitive evaluation
9. Susceptibility to varieties of allergen
10. Contraindication to cilostazol or aspirin
11. Antiplatelet treatment, anticoagulation or fibrinolysis needed for other diseases
12. Rejected from participation by the patient or the family

Interventions	Cilostazol 100 mg twice daily for 12 months
	Aspirin 100 mg once daily for 12 months
Outcomes	Primary outcomes: changes in cognitive scores (MMSE, Montreal Cognitive Assessment, Clinical Dementia Rating and Blessed-Roth (time frame 1 year)
Notes	Requested further information but no response from trial team.

CT: computed tomography; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; mRS: Modified Rankin Score; NIHSS: National Institutes of Health Stroke Scale.

Characteristics of ongoing studies *[ordered by study ID]*

CAF

Study name	Impact of anticoagulation therapy on the cognitive decline and dementia in patients with nonvalvular –atrial fibrillation (CAF)
Methods	Phase 4 randomised parallel assignment open-label trial
Participants	Inclusion criteria

Inclusion criteria

1. People aged > 65 years
2. Non-valvular atrial fibrillation documented by electrocardiogram, ambulatory event monitor, or telemetry within 12 months of enrolment
3. Moderate risk of thromboembolism based upon a CHADS score or CHADS2 Vasc score ≥ 2
4. Ability to complete an MMSE
5. Ability to independently comprehend and complete quality of life and dementia questionnaires
6. Ability to provide informed consent for study participation
7. Willing and able to comply with the prescribed follow-up tests and schedule of evaluations

Exclusion criteria

1. Inability to take an anticoagulant due to known or perceived bleeding risk.
2. Known coagulopathy that may impact the choice, duration, efficacy and safety of anticoagulation therapy
3. Atrial fibrillation in the setting of valvular heart disease. Valvular heart disease defined as any surgical valve, mitral stenosis or moderate-severe valvular heart disease
4. Severe renal dysfunction, defined as a CrCl rate < 15 mL/minute (documented within the last 3 months)
5. History of any form of dementia
6. Life expectancy < 24 months
7. Inability to comply with the follow-up schedule
8. Current participation in a clinical investigation that includes an active pharmacological treatment arm
9. An upper age limit not to be used if participation inclusion criteria are met
10. Participation in any other clinical trials involving investigational or marketed products within 30 days prior to entry in the study

CAF *(Continued)*

	11. Other conditions that in the opinion of the Principal Investigator(s) may increase risk to the person or compromise the quality of the clinical trial, or both
	12. Concurrent pharmacological treatment that is required to treat a condition long-term in which concurrent use of dabigatran etexilate is contraindicated
	13. Treatment with any anticoagulant drug for stroke prevention for > 30 days a. Aspirin and P2Y12 inhibitors (e.g. clopidogrel or prasugrel) are not considered anticoagulant drugs b. If the person has received any anticoagulant drug for stroke prevention for < 30 days, the Principal Investigator(s) or a Co-Investigator will decide whether or not the person is eligible for the study
	14. The Principal Investigator(s) determine(s) that the person is not eligible for participation in this research study
Interventions	Experimental: dabigatran etexilate 150 mg twice daily (if CrCl > 30 mL/minute) or 75 mg twice daily (CrCl 15–30 mL/minute) Active comparator: warfarin Dose-adjusted warfarin (INR 2.0–3.0)
Outcomes	Primary outcomes 1. Incident dementia determined by a formal diagnosis of dementia by a neurologist. Determined by measuring the change from baseline to study conclusion on the ADAS-Cog-11, with scores ranging from 0 to 70, and higher scores indicating greater impairment) and the DAD (with scores ranging from 0 to 100, and higher scores indicating less impairment). An increase in ADAS-Cog-11 > 30% is considered significant for moderate cognitive decline. In people who have a DAD score < 50%, there is a direct correlation with global deterioration scales and scores. People with a 30% decrease in DAD score or those with a score < 50% will be considered to have moderate cognitive decline. These scores will be aggregated and if a participant meets either of the cognitive decline definitions, they will be deemed positive for cognitive impairment. 2. Incident dementia determined by a formal diagnosis of dementia by a neurologist (time frame 24 months) 3. Moderate decline in cognitive function based on results of the ADAS and the DAD (time frame 24 months) Secondary outcomes 1. Stroke or TIA, intracranial bleed (time frame 24 months) 2. Changes from baseline scores on the MMSE and the Hachinski Ischemic Scale (time frame 24 months)
Starting date	2017
Contact information	Contact: T Jared Bunch, MD; 801-507-4701; jared.bunch@imail.org Contact: Patti Spencer; 801-507-4778; patti.spencer@imail.org
Notes	

CHALLENGE

Study name	Efficacy study of cilostazol and aspirin on cerebral small vessel disease (Challenge)
Methods	Multicentre, randomised, double-blind study
Participants	Inclusion criteria

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CHALLENGE *(Continued)*

1. Aged 50–85 years
2. Can walk to the hospital (walking frame or stick is permissible).
3. Cerebral small vessel disease is observed on brain MRI: presence of ≥ 1 lacunar infarction and moderate or severe confluent leukoaraiosis (defined as grade 2 or 3 on a modified Fazekas scale): periventricular WMCs with cap or rims > 5 mm and deep subcortical WMCs > 10 mm in maximum diameter
4. Written informed consent

Exclusion criteria

1. Any contraindication of antiplatelets
2. Any person with cardioembolic source
3. Carotid bruit or large cerebral artery stenosis > 50%
4. Cortical infarction or subcortical infarction > 1.5 cm
5. Bleeding tendency
6. Chronic liver disease (AST or ALT > 100 IU/L)
7. Chronic renal disease (creatinine > 3.0 mg/dL)
8. Active gastrointestinal ulcer
9. People with any severe or unstable medical disease that may prevent them from completing study requirements (i.e. unstable or severe asthma)
10. Anaemia (haemoglobin < 10 g/dL) or thrombocytopenia
11. Cardiac pacemaker or contraindication to MRI
12. Pregnancy or breastfeeding
13. Drug or alcohol addiction
14. Any other white matter disease (i.e. multiple sclerosis, sarcoidosis or brain irradiation, etc.) or brain tumour
15. Parkinson's disease, Alzheimer's disease or any other neurodegenerative disease
16. Any hearing or visual impairment that can disturb the efficient evaluation of the patient
17. Recent cerebral infarction with 3 months

Interventions	Aspirin 100 mg once daily for 104 weeks
	Cilostazol 200 mg once daily for 104 weeks
Outcomes	Primary outcome

Primary outcome

1. Volume of WMCs on brain MRI on week 104 vs baseline

Secondary outcomes

1. Mean diffusivity and fraction anisotropy on diffusion tensor imaging
2. Number of lacunes
3. Number of micro-bleeds
4. Brain volume and cortical thickness
5. MMSE
6. Neuro-cognitive test (Seoul Verbal Learning Test, Boston Naming test-short form, complex figure copy, animal fluency, phonemic fluency, Stroop test, Digit-symbol test, Trail Making Test)
7. Clinical Dementia Rating scale Sum of Boxes
8. King's Health Questionnaire
9. Geriatric Depression Scale – Short Form
10. Caregiver-Administered Neuropsychiatric Inventory
11. Bayer Activities of Daily Living
12. Barthel Index
13. Pyramidal and Extrapyramidal Scale
14. Timed Up and Go test
15. Adverse events

CHALLENGE *(Continued)*

'Other' outcomes

1. All ischaemic stroke events (cerebral infarction and TIA) – all vascular events (including ischaemic stroke, TIA, myocardial infarction, angina pectoris, cerebral venous thrombosis, pulmonary embolism, symptomatic deep vein thrombosis, symptomatic peripheral artery occlusion, other vascular occlusion and any revascularisation procedure

Starting date	2013
Contact information	Principal Investigator: Seong Hye Choi, Inha University Hospital
Notes	

ChiCTR-TCS-14005054

Study name	Cilostazol in decreasing progression of cerebral white matter hyperintensities (DREAM)
Methods	Parallel double-blind randomised trial
Participants	140 men and women aged 65–85 years
Interventions	Cilostazol Placebo
Outcomes	Primary outcome 1. Change of WMH volume on MRI between baseline and end of study Secondary outcomes 1. Change in other brain measures in MRI (lacunes, microbleeds, brain volumes (cortical grey matter, white matter, ventricular and sulcal CSF) and 2. Diffusing tensor imaging measures (mean fractional anisotropy of WMH, normal appearing white matter, grey matter) or 3. Clinical measures (Montreal Cognitive Assessment, 30-minute battery of the NINDS-CSN VCI Neuropsychology Protocols, NPI, Instrumental Activities of Daily Living, gait and balance, incident clinical events (e.g. stroke, dementia)
Starting date	27 October 2014
Contact information	Name: Prof Vincent Chung Tong Mok Address: Rm 124010, 10/F, Clinical Sciences Building, Prince of Wales Hospital, Shatin, N.T. Hong Kong Contact number: +852 2632 2195 Contact email: vctmok@cuhk.edu.hk
Notes	CUHK_CCT00430; ChiCTR-TCS-14005054 www2.ccrb.cuhk.edu.hk/registry/public/269

ECISBI

Study name	Efficacy of Clopidogrel on Incidence of Silent Brain Infarction (ECISBI)
Methods	Randomised controlled trial
Participants	152 participants admitted for stroke/TIA, with indication for antiplatelet therapy as secondary prevention (decision independent of the study and based on individual clinical decision for each patient by the treating physician)
Interventions	Clopidogrel Aspirin
Outcomes	Primary outcome 1. New silent brain infarction Secondary outcome 1. Cognitive impairment
Starting date	30 September 2021
Contact information	Calin I Prodan, MD; 405-456-1479; calin.prodan@va.gov
Notes	

LACI-2

Study name	LACunar Intervention (LACI-2) Trial-2: assessment of safety and efficacy of cilostazol and isosorbide mononitrate to prevent recurrent lacunar stroke and progression of cerebral small vessel disease
Methods	Phase 2b preparatory to phase 3 randomised, partial factorial, open-label, blinded endpoint trial
Participants	400
Interventions	Isosorbide mononitrate oral titrated dosing Cilostazol oral titrated dosing Isosorbide mononitrate + cilostazol
Outcomes	1. Dose-specific trial medication tolerability (over 36 months) 2. Incidence of treatment emergent adverse effects (safety) over 36 months 3. Treatment efficacy: rate of individual participant events (stroke, TIA, myocardial ischaemia, cognitive impairment and dementia) over 36 months
Starting date	2018
Contact information	Chief Investigator: Joanna M Wardlaw, University of Edinburgh, UK
Notes	

NCT01932203

Study name	A multicenter, randomized, double blind study to compare the efficacy between cilostazol and aspirin on white matter changes by cerebral small vessel disease
Methods	Parallel double-blind randomised trial
Participants	255 adults aged 50–85 years
Interventions	Enteric-coated aspirin 100 mg
	Cilostazol 200 mg once a day
Outcomes	**Primary outcome**

Primary outcome

1. Volume of WMCs at baseline and week 104

Secondary outcomes

1. Mean diffusivity and fraction anisotropy on diffusion tensor imaging at baseline and week 104
2. Number of lacunes at baseline and week 104
3. Number of microbleeds at baseline and week 104
4. Brain volume and cortical thickness at baseline and week 104
5. MMSE at baseline, and weeks 52 and 104
6. Neurocognitive test at baseline, and weeks 52 and 104: Seoul Verbal Learning Test, Boston Naming test-short form, Rey–Osterrieth Complex Figure test, animal fluency, phonemic fluency, Stroop test, Digit-symbol test, Trail Making Test
7. Clinical Dementia Rating scale at baseline, and weeks 52 and 104
8. King's Health Questionnaire at baseline, and weeks 42 and 104
9. Geriatric Depression Scale – Short Form at baseline, and week 52 and 104
10. Caregiver-Administered Neuropsychiatric Inventory at baseline, and weeks 52 and 104
11. Bayer Activities of Daily Living at baseline, and weeks 52 and 104
12. Barthel Index at baseline, and weeks 52 and 104
13. Pyramidal and Extrapyramidal Scale at baseline, and weeks 52 and 104
14. Timed Up and Go test at baseline, week 52 and week 104
15. Adverse events at baseline, and weeks 4, 16, 28, 40, 52, 64, 76, 88 and 104

Other outcomes

1. von Willebrand factor, TF, intercellular adhesion molecule 1, vascular cell adhesion molecule 1, interleukin-6, interleukin-18, high-sensitivity C-reactive protein, apolipoprotein E genotyping, RAS gene polymorphism (at baseline)
2. Blood urea nitrogen, creatinine, haemoglobin, platelet, AST, ALT, albumin, glycated haemoglobin, glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, total cholesterol, uric acid, albumin (micro, random urine)/creatinine ratio (at baseline)

Starting date	July 2013
Contact information	Principal Investigator: Seong Hye Choi, MD, PhD: Inha University Hospital; 82 32 890 3659; seonghye@inha.ac.kr
Notes	ClinicalTrial.gov: NCT01932203

PICASSO-Cog

Study name	PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage for reducing COGnitive decline

PICASSO-Cog *(Continued)*

Methods	Substudy of the PICASSO trial – an ongoing randomised, double-blind, placebo-controlled multinational trial
Participants	**Key inclusion criteria** 1. Non-cardioembolic ischemic stroke or TIA within 180 days 2. Age > 20 years 3. Previous intracerebral haemorrhage based on clinical or radiological findings or multiple cerebral microbleeds on gradient echo imaging; no history of recent clinical haemorrhagic stroke within 180 days; no contraindication for long-term antiplatelet therapy. For the PICASSOCOG substudy, participants unable to perform the cognitive test because of severe dysphasia or severe neurological deficits will be further excluded.
Interventions	Cilostazol 100 mg twice daily Aspirin 100 mg once daily Probucol 250 mg twice daily No probucol The trial is a double-blind and double-dummy study using matched placebo to compare cilostazol versus aspirin groups, and an open-labelled, blinded endpoint evaluation to compare probucol versus non-probucol groups.
Outcomes	1. Cognitive function (Korean version of the MMSE; the Korean-Montreal Cognitive Assessment
Starting date	
Contact information	Sun U Kwon, MD, PhD, Stroke Center and Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, Republic of Korea. E-mail: sukwon@amc.seoul.kr
Notes	

Reid ENVIS-ion 2012

Study name	Aspirin for the prevention of cognitive decline in the elderly: rationale and design of a neurovascular imaging study (ENVIS-ion) Substudy of: Aspirin in Reducing Events in the Elderly (ASPREE)
Methods	Double-blind, placebo-controlled trial of 3 years' duration set in 2 Australian academic medical centre outpatient clinics
Participants	600 adults aged ≥ 70 years with normal cognitive function and without overt cardiovascular disease
Interventions	Aspirin 100 mg daily Placebo
Outcomes	**Primary outcome** 1. Death from any cause or incident, dementia or persistent physical disability (every 6 months) Secondary outcomes 1. All-cause mortality (every 6 months)

2. Fatal and non-fatal cardiovascular events including: death due to coronary heart disease, non-fatal myocardial infarction, fatal and non-fatal stroke and any hospitalisation for heart failure (every 6 months)

3. Fatal and non-fatal cancer, excluding non-melanoma skin cancer (every 6 months)

4. Dementia (every 6 months)

5. Mild cognitive impairment (assessed using Modified MMSE and other cognitive function measures) (every 6 months)

6. Physical disability (every 6 months)

7. Major haemorrhagic events (every 6 months)

8. Depression (annually)

Starting date	January 2010
Contact information	Principal Investigators: Richard Grimm, MD, PHD: Berman Center for Outcomes and Clinical Research, Minneapolis, MN, US; John McNeil, MBBS, PHD: Monash University; Berman Center for Outcomes & Clinical Research; ASPREE Project Manager, Brenda Kirpach Contact number: 612-873-6905 Contact email: bkirpach@bermancenter.org
Notes	Clinicaltrial.gov: NCT01038583 Study protocol: www.ncbi.nlm.nih.gov/pmc/articles/PMC3297524/

ADAS-Cog-11: 11-item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ALT: alanine aminotransferase; AST: aspartate transaminase; CHADS: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack; CrCl: creatinine clearance; CSF: cerebrospinal fluid; DAD: Disability Assessment for Dementia; INR: international normalised ratio; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; NINDS-CSN: National Institute of Neurological Disorders and Stroke – Canadian Stroke Network; TIA: transient ischaemic attack; VCI: vascular cognitive impairment; WMC: white matter change; WMH: white matter hyperintensity.

ADDITIONAL TABLES

Table 1. Results of Jia 2016 (efficacy outcomes in intention-to-treat population at week 24)

Psychometric scores	Adjusted mean change from baseline		Difference in adjusted mean (95% CI)
	DL-3-n-butylphthalide (n = 140)	Placebo (n = 140)	
ADAS-Cog	−2.46 (SE 0.35)	−1.39 (SE 0.35)	−1.07 (−2.02 to −0.12)
CIBIC-plus	3.24 (SE 0.07)	3.53 (SE 0.07)	−0.29 (−0.48 to −0.10)
MMSE	1.51 (SE 0.19)	1.26 (SE 0.18)	0.26 (−0.25 to 0.76)
CDR	−0.05 (SE 0.01)	−0.02 (SE 0.01)	−0.02 (−0.06 to 0.02)
CDR-SB	−0.03 (SE 0.08)	−0.07 (SE 0.07)	0.04 (−0.16 to 0.24)
ADL	−0.62 (SE 0.33)	−0.80 (SE 0.33)	0.18 (−0.70 to 1.07)
NPI	−0.13 (SE 0.17)	−0.43 (SE 0.17)	0.29 (−0.15 to 0.74)

Results table extracted from Table 2, Jia 2016. The adjustments made to the mean were not clearly stated in the publication.
ADAS-Cog: 12-item Alzheimer's Disease Assessment Scale-Cognitive subscale; ADL: activities of daily living; CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating scale Sum of Boxes; CI: confidence interval; CIBIC-plus: Clinician's Interview-Based Impression of Change-Plus Caregiver Input; MMSE: Mini-Mental State Examination; n: number of participants; NPI: Neuropsychiatric Inventory; SE: standard error.

Table 2. Results of SPS3 2014 (mean Cognitive Abilities Screening Instrument (CASI) z-score over time by assigned antiplatelet treatment)

Time since base-line assessment (years)	Aspirin + clopidogrel			Aspirin + placebo		
	n	Mean	SD	n	Mean	SD
0	1468	−0.58	1.38	1448	−0.61	1.48
1	1242	−0.38	1.28	1230	−0.42	1.43
2	974	−0.31	1.28	994	−0.39	1.37
3	752	−0.28	1.32	769	−0.39	1.42
4	559	−0.27	1.35	576	−0.33	1.45
5	392	−0.29	1.37	411	−0.43	1.60

Results table extracted from Pearce SPS3 2014. Higher score indicates better performance.
n: number of participants; SD: standard deviation.

Table 3. Results of SILENCE 2018 (efficacy outcomes of the randomised participants)

Outcome	Aspirin (n = 24)	Placebo (n = 26)
MMSE (median)	29 (IQR 27–30)	29 (IQR 27–30)
IADL (median)	8 (IQR 8–8)	8 (IQR 8–8)
ADL (median)	6 (IQR 6–6)	6 (IQR 6–6)
Loss to follow-up (n)	8 (33.3%)	5 (19.2%)
Adverse events (n)	2 (8.3%)	1 (3.8%)
Change in global cognitive score (mean)	−0.10 (SD 0.40)	−0.06 (SD 0.55)

Unpublished data provided by the authors of Maestrini SILENCE 2018.
ADL: activities of daily living; IADL: Instrumental Activities of Daily Living; IQR: interquartile range; MMSE: Mini-Mental State Examination; n: number of participants; SD: standard deviation.

A P P E N D I C E S

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
CENTRAL (the Cochrane Library) cr-so.cochrane.org/SearchSimple.php [Date of most recent search: 21 July 2021]	#0 ("micro-bleed*" or microbleed*):TI,AB,KY	Jul 2016: 722
	#1 ("white matter" adj3 (ischemi* or ischaemi*)):TI,AB,KY	May 2017: 27
	#2 (Brain Ischemia):MH	Jun 2018: 335
	#3 Ischemia:MH	Jun 2019: 51
	#4 (White Matter/pathology):MH	Sep 2020: 290
	#5 (White Matter):MH	July 2021:
	#6 Leukoencephalopathies:MH	240
	#7 Leukoaraiosis:MH	
	#8 Microhemorrhage*:TI,AB,KY	
	#9 Microhaemorrhage*:TI,AB,KY	
	#10 #0 OR #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	
	#11 antithrombo*:TI,AB,KY	
	#12 Aspirin:MH	
	#13 Aspirin:TI,AB,KY	
	#14 dipyridamole*:TI,AB,KY	
	#15 Dipyridamole:MH	
	#16 clopidogrel*:TI,AB,KY	
	#17 triflusal:TI,AB,KY	
	#18 prasugrel:TI,AB,KY	
	#19 ticagrelor:TI,AB,KY	
	#20 ticlopidine:TI,AB,KY	
	#21 cilostazol:TI,AB,KY	
	#22 vorapaxar:TI,AB,KY	
	#23 abciximab:TI,AB,KY	
	#24 eptifibatide:TI,AB,KY	
	#25 tirofiban:TI,AB,KY	
	#26 terutroban:TI,AB,KY	
	#27 disgren:TI,AB,KY	
	#28 plavix:TI,AB,KY	
	#29 effient:TI,AB,KY	
	#30 brilinta:TI,AB,KY	
	#31 ticlid:TI,AB,KY	

(Continued)

#32 pletal:TI,AB,KY

#33 zontivity:TI,AB,KY

#34 ReoPro:TI,AB,KY

#35 integrilin:TI,AB,KY

#36 aggrastat:TI,AB,KY

#37 persantine:TI,AB,KY

#38 ("acetylsalicylic acid"):TI,AB,KY

#39 ("antiplatelet drug*"):TI,AB,KY

#40 Thromboxanes:MH

#41 Glycoproteins:MH

#42 (Adenosine Diphosphate):MH

#43 Anticoagulants:MH

#44 Antithrombins:MH

#45 ("vitamin k"):MH

#46 phylloquinone:TI,AB,KY

#47 phytomenadione:TI,AB,KY

#48 phytonadione:TI,AB,KY

#49 ("thrombin* inhibitor*"):TI,AB,KY

#50 (Factor Xa):TI,AB,KY

#51 (Fibrinolytic Agents):MH

#52 dabigatran:MH

#53 rivaroxaban:MH

#54 apixaban:MH

#55 coumarin*:MH

#56 dabigatran:TI,AB,KY

#57 rivaroxaban:TI,AB,KY

#58 apixaban:TI,AB,KY

#59 coumarin*:TI,AB,KY

#60 warfarin:TI,AB,KY

#61 Warfarin:MH

#62 Heparin:MH

#63 heparin:TI,AB,KY

#64 phenprocoumon:TI,AB,KY

#65 Acenocoumarol:TI,AB,KY

(Continued)

	#66 atromentin:TI,AB,KY	
	#67 brodifacoum:TI,AB,KY	
	#68 phenindione:TI,AB,KY	
	#69 ("Xa inhibitor*"):TI,AB,KY	
	#70 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69	
	#71 #10 AND #70	
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (OvidSP)	1 ("white matter" adj3 (ischemi* or ischaemi*)).ti,ab.	Jul 2016: 794
	2 ("micro-bleed*" or microbleed*).ti,ab.	May 2017: 83
	3 *Brain Ischemia/ or *Ischemia/ or White Matter/pathology	Jun 2018: 121
	4 Leukoencephalopathies/ or Leukoaraiosis/	Jun 2019: 84
[Date of most recent search: 21 July 2021]	5 (Microhemorrhage* or Microhaemorrhage*).ti,ab.	Sep 2020: 146
	6 or/1-5	July 2021: 128
	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.	

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

46

(Continued)

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.

(Continued)

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 random-ized.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

Embase (OvidSP)	1 ("white matter" adj3 (ischemi* or ischaemi*)).ti,ab.	Jul 2016: 1286
1974 to 5 June 2019	2 ("micro-bleed*" or microbleed*).ti,ab.	May 2017: 214
	3 *Brain Ischemia/ or *Ischemia/ or *white matter/	Jun 2018: 570
[Date of most recent search: 21 July 2021]	4 Leukoencephalopathies/ or Leukoaraiosis/	Jun 2019: 388
	5 (Microhemorrhage* or Microhaemorrhage*).ti,ab.	Sep 2020: 446
	6 or/1-5	July 2021: 388
	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.	

(Continued)

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.

(Continued)

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/

65 controlled clinical trial/

66 random$.ti,ab.

67 randomization/

68 intermethod comparison/

69 placebo.ti,ab.

70 (compare or compared or comparison).ti.

71 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

72 (open adj label).ti,ab.

73 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

74 double blind procedure/

75 parallel group$1.ti,ab.

76 (crossover or cross over).ti,ab.

77 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

78 (assigned or allocated).ti,ab.

79 (controlled adj7 (study or design or trial)).ti,ab.

80 (volunteer or volunteers).ti,ab.

81 trial.ti.

82 or/64-81

83 63 and 82

PsycINFO (OvidSP)	1 ("white matter" adj3 (ischemi* or ischaemi*)).ti,ab.	Jul 2016: 38
[Date of most recent search: 21 July 2021]	2 ("micro-bleed*" or microbleed*).ti,ab.	May 2017: 20
	3 Cerebral Ischemia/ or White Matter/	Jun 2018: 3
	4 Leukoencephalopathies/ or Leukoaraiosis/	Jun 2019: 1
	5 (Microhemorrhage* or Microhaemorrhage*).ti,ab.	Sep 2020: 5
	6 or/1-5	July 2021: 4
	7 antithrombo*.ti,ab.	
	8 Aspirin/	

(Continued)

9 aspirin.ti,ab.

10 dipyridamole*.ti,ab.

11 clopidogrel*.ti,ab.

12 triflusal.ti,ab.

13 prasugrel.ti,ab.

14 ticagrelor.ti,ab.

15 ticlopidine.ti,ab.

16 cilostazol.ti,ab.

17 vorapaxar.ti,ab.

18 abciximab.ti,ab.

19 eptifibatide.ti,ab.

20 tirofiban.ti,ab.

21 terutroban.ti,ab.

22 disgren.ti,ab.

23 plavix.ti,ab.

24 effient.ti,ab.

25 brilinta.ti,ab.

26 ticlid.ti,ab.

27 pletal.ti,ab.

28 zontivity.ti,ab.

29 ReoPro.ti,ab.

30 integrilin.ti,ab.

31 aggrastat.ti,ab.

32 persantine.ti,ab.

33 "acetylsalicylic acid".ti,ab.

34 "antiplatelet drug*".ti,ab.

35 Globulins/

36 Adenosine/

37 "vitamin k".ti,ab.

38 phylloquinone.ti,ab.

39 phytomenadione.ti,ab.

40 phytonadione.ti,ab.

41 "thrombin* inhibitor*".ti,ab.

42 dabigatran.ti,ab.

(Continued)

43 rivaroxaban.ti,ab.

44 apixaban.ti,ab.

45 coumarin*.ti,ab.

46 warfarin.ti,ab.

47 heparin.ti,ab.

48 phenprocoumon.ti,ab.

49 Acenocoumarol.ti,ab.

50 atromentin.ti,ab.

51 brodifacoum.ti,ab.

52 phenindione.ti,ab.

53 "Xa inhibitor*".ti,ab.

54 or/7-53

55 exp Clinical Trials/

56 randomly.ab.

57 randomi?ed.ti,ab.

58 placebo.ti,ab.

59 groups.ab.

60 "double-blind*".ti,ab.

61 "single-blind*".ti,ab.

62 RCT.ti,ab.

63 or/55-62

64 6 and 54 and 63

CINAHL (EBSCOhost)	S1 TX ("white matter" N3 (ischemi* or ischaemi*))	Jul 2016: 99
[Date of most recent search: 21 July 2021]	S2 TX "micro-bleed*" or microbleed*	May 2017: 16
	S3 MH Ischemia	Jun 2018: 99
	S4 TX Microhemorrhage* or Microhaemorrhage*	Jun 2019: 24
	S5 (S1 OR S2 OR S3 OR S4)	Sep 2020: 19
	S6 TX antithrombo*	July 2021: 20
	S7 MH Aspirin	
	S8 TX Aspirin	
	S9 MH dipyridamole	
	S10 TX dipyridamole*	
	S11 TX clopidogrel*	

(Continued)

S12 TX triflusal

S13 TX prasugrel

S14 TX ticagrelor

S15 TX ticlopidine

S16 TX cilostazol

S17 TX vorapaxar

S18 TX abciximab

S19 TX tirofiban

S20 TX disgren

S21 TX plavix

S22 TX effient

S23 TX brilinta

S24 TX ticlid

S25 TX pletal

S26 TX zontivity

S27 TX ReoPro

S28 TX integrilin

S29 TX aggrastat

S30 TX "acetylsalicylic acid"

S31 TX "antiplatelet drug*"

S32 MH Thromboxanes

S33 MH Glycoproteins

S34 MH Adenosine Diphosphate

S35 MH Anticoagulants

S36 TX "vitamin k"

S37 TX phylloquinone

S38 TX phytomenadione

S39 TX phytonadione

S40 TX "thrombin* inhibitor*"

S41 MH Fibrinolytic Agents

S42 TX dabigatran

S43 TX rivaroxaban

S44 TX apixaban

S45 TX coumarin*

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

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(Continued)

S46 TX warfarin

S47 MH warfarin

S48 MH Heparin

S49 TX Heparin

S50 TX phenprocoumon

S51 TX Acenocoumarol

S52 TX atromentin

S53 TX brodifacoum

S54 TX "Xa inhibitor*"

S55 (S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54)

S56 MH "Clinical Trials" OR TX trial OR TX "single-blind*" OR TX "double-blind*" OR TX "treatment as usual" OR TX randomly

S57 (S5 AND S55 AND S56)

Web of Science (Clarivate) – all databases [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports] [Date of most recent search: 21 July 2021]	# 1 TS=("white matter ischemi*" Or "white matter ischaemi*" OR "micro-bleed*" OR microbleed* OR "Brain Ischemia" OR "White Matter pathology" OR Leukoencephalopathies OR Leukoaraiosis OR Microhemorrhage* OR Microhaemorrhage*) # 2 TS=(antithrombo* OR asprin OR dipyridamole* OR clopidogrel* OR Thromboxanes OR Glycoproteins OR "Adenosine Diphosphate" OR Anticoagulants OR Antithrombins OR "Factor Xa" OR "Fibrinolytic Agents" OR Warfarin OR Heparin) # 3 TS=(randomly OR randomised OR randomized OR "random allocat*" OR RCT OR CCT OR "double blind*" OR "single blind*" OR "double blind*" OR "single blind*") # 4 #3 AND #2 AND #1 Timespan=All years Search language=Auto	Jul 2016: 941 May 2017: 95 Jun 2018: 167 Jun 2019: 9 Sep 2020: 15 July 2021: 112
LILACS (BIREME) [Date of most recent search: 21 July 2021]	ischemi$ OR micro-bleed$ OR microbleed$ OR Brain Ischemia OR Leukoencephalopathies OR Leukoaraiosis OR Microhemorrhage$ OR Microhaemorrhage$ [Words] and antithrombo$ OR dipyridamole OR clopidogrel OR Thromboxanes OR Glycoproteins OR Adenosine Diphosphate OR Anticoagulants OR Antithrombins OR Factor Xa OR Fibrinolytic Agents OR Warfarin OR Heparin [Words] and randomly OR randomised OR randomized OR RCT OR "controlled trial" OR "double blind$" OR placebo [Words]	Jul 2016: 17 May 2017: 3 Jun 2018: 4 Jun 2019: 0 Sep 2020: 0 July 2021: 0
ClinicalTrials.gov (www.clinicaltrials.gov) [Date of most recent search: 21 July 2021]	ischemiA OR micro-bleed$ OR microbleed OR Brain Ischemia OR Leukoencephalopathies OR Leukoaraiosis OR Microhemorrhage OR Microhaemorrhage | antithromboTIC OR dipyridamole OR clopidogrel OR Thromboxanes OR Glycoproteins OR Adenosine Diphosphate OR Anticoagulants OR Antithrombins OR Factor Xa OR Fibrinolytic Agents OR Warfarin OR Heparin	Jul 2016: 955 May 2017: 0 Jun 2018: 134

(Continued)

		Jun 2019: 125
		Sep 2020: 139
		July 2021: 108
ALOIS (via CRS web) [Date of most recent search: 21 July 2021]	(ischemia OR micro-bleed OR microbleed OR Brain Ischemia OR Leukoencephalopathies OR Leukoaraiosis OR Microhemorrhage OR Microhaemorrhage) AND (antithrombotic OR dipyridamole OR clopidogrel OR Thromboxanes OR Glycoproteins OR Adenosine Diphosphate OR Anticoagulants OR Antithrombins OR Factor Xa OR Fibrinolytic Agents OR Warfarin OR Heparin)	Jul 2016: 9 May 2017: 4 Jun 2018: 3 Jun 2019: 0 Sep 2020: 18 July 2021: 0
ICTRP [Date of most recent search: 6 June 2019. Database not available 16 September 2020, or July 2021]	(ischemia OR micro-bleed OR microbleed OR Brain Ischemia OR Leukoencephalopathies OR Leukoaraiosis OR Microhemorrhage OR Microhaemorrhage) AND (antithrombotic OR dipyridamole OR clopidogrel OR Thromboxanes OR Glycoproteins OR Adenosine Diphosphate OR Anticoagulants OR Antithrombins OR Factor Xa OR Fibrinolytic Agents OR Warfarin OR Heparin)	Jul 2016: 59 May 2017: 111 Jun 2018: 24 Jun 2019: 22
TOTAL before deduplication		Jul 2016: 4920 May 2017: 573 Jun 2018: 1380 Jun 2019: 706 Sep 2020: 1078 July 2021: 1001 **TOTAL: 9658**
TOTAL after deduplication		Jul 2016: 4015 May 2017: 368 Jun 2018: 1211 Jun 2019: 663 Sep 2020: 934 July 2021: 893 **TOTAL: 8084**

WHAT'S NEW

Date	Event	Description
14 July 2022	Amended	Minor typos corrected, author order changed.

HISTORY

Protocol first published: Issue 7, 2016
Review first published: Issue 7, 2022

CONTRIBUTIONS OF AUTHORS

1. Lead review author (designed, conducted and led the writing of the review): JK.
2. Main co-review authors (conducted and co-wrote the review): LLWC, MH, LSW, TQ.
3. Specialist advisory co-reviewer (consulted, advised, and edited the review): PM.

DECLARATIONS OF INTEREST

JK: none.

MH: none.

LC: none.

PM: none.

TQ: none.

LW: none.

SOURCES OF SUPPORT

Internal sources

- Department of Medicine, the University of Hong Kong, Hong Kong
- School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, UK

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from the published protocol (Kwan 2016b).

1. "Absence of dementia of any cause as defined by internationally-accepted diagnostic criteria" was one of the inclusion criteria for participants. However, all three included studies reported differing inclusion/exclusion criteria at baseline. We updated the wording to "Absence of dementia of any cause as defined by internationally accepted diagnostic criteria, however a degree of flexibility was needed because of heterogeneity of the operationalisation of this exclusion criterion in the included studies. Therefore, we also accepted cognitive testing that was plausible to detect incipient or existing dementia."
2. We added the secondary outcome mild cognitive impairment, as there was important evidence on this outcome, but we wanted to keep a distinction with incident dementia.
3. We further operationalised our definition of cSVD, by setting criteria around a minimum proportion of people with cSVD in studies of mixed populations and a minimum degree of cSVD features for individual participants.
4. We had a minimum intervention duration of six months; however, we also accepted studies with an intervention duration of minimum 24 weeks (5.5 months).

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INDEX TERMS

Medical Subject Headings (MeSH)

Aspirin [therapeutic use]; *Cerebral Small Vessel Diseases [complications] [diagnostic imaging] [drug therapy]; *Cognitive Dysfunction [drug therapy] [prevention & control]; *Dementia [prevention & control]; Neuroimaging; Platelet Aggregation Inhibitors [therapeutic use]; *Stroke [diagnostic imaging] [drug therapy] [prevention & control]

MeSH check words

Humans