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[Intervention Protocol]

Pharmacological interventions for asymptomatic carotid stenosis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of pharmacological interventions for the treatment of asymptomatic carotid stenosis, to prevent neurological impairment, stroke, disability, death, and other complications.

BACKGROUND

See [Table 1](#) for a glossary of terms.

Description of the condition

Strokes, characterised by brain tissue injury due to stenosis or arterial occlusion, can cause death or permanent neurological disability and approximately 90% are ischaemic. This largely occurs as a result of carotid stenosis, hypertension, or cardiac arrhythmia ([Brott 2013](#); [Flumignan 2017](#); [Mozaffarian 2016](#)). Carotid artery stenosis (narrowing of the carotid arteries) is an important cause of cerebrovascular disease and transient ischaemic attack (TIA), underlying almost 15% of strokes ([Easton 2009](#)). The cumulative risk of stroke related to severe carotid stenosis is nearly 12% in the first year (approximately 15% to 18% in one year and 26% over two years ([NASCET 1991](#)), and approximately 30% over five years ([Moore 1995](#); [NASCET 1991](#)). Significant stenosis (of more than 50% of vessel diameter) is usually responsible for 8% of all strokes and increases the risk of recurrence after the first episode to 16% over five years ([Hillen 2003](#)), mostly due to cerebral embolisms caused by biological changes to the atherosclerotic plaque ([Flaherty 2013](#)).

Ischaemic stroke is a major global public health problem. Nearly 800,000 events are reported annually in the USA, approximately 610,000 of which represent the first attack in the patient. Stroke is the second most common cause of death, accounting for nearly 5.5 million deaths worldwide in 2016 ([De Waard 2017](#); [Feigin 2014](#); [Naylor 2018](#); [NICE 2019](#); [Venkatchalam 2014](#)).

Furthermore, stroke is a significant cause of permanent neurological disability in Europe; out of approximately 1.2 million stroke survivors in the UK, 60% are discharged with some impairment ([CDC 2001](#); [NICE 2019](#); [Strong 2007](#)).

The direct costs of stroke alone amounted to approximately USD 28 billion between the years 2014 and 2015 in the USA, and this cost is estimated to more than double in the next 20 years ([Benjamin 2019](#); [Feigin 2016](#); [Gorelick 1999](#)). It is expected that by 2030 there will be 80 million strokes worldwide, with 12 million deaths (an increase of 50% compared with 2012), and 200 million disability-adjusted life years lost worldwide ([Benjamin 2019](#); [Feigin 2014](#)).

Extracranial carotid stenosis may be asymptomatic or symptomatic. The embolisation of atherosclerotic debris or thrombotic material from plaques of arterial stenoses are most frequently associated with cerebrovascular symptoms such as stroke, TIA in the ipsilateral encephalic territories, and amaurosis fugax. People with asymptomatic carotid stenosis (ACS) are at risk not only of stroke or related symptoms but also of other cardiovascular episodes, such as myocardial infarction (heart attack) and peripheral artery disease ([Divya 2015](#); [Flumignan 2017](#)).

Asymptomatic carotid stenosis is a common condition in clinical practice, affecting about 3% to 7% of the general population. It

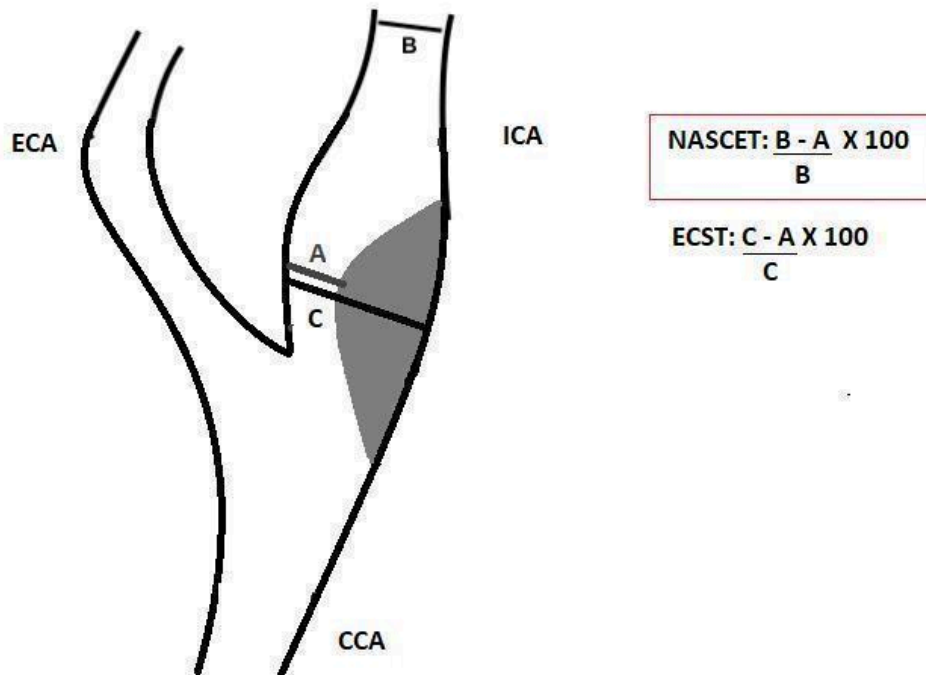
is more prevalent in older people (over 60 years of age), and can evolve into a stroke in 0.3% to 2% of patients each year ([De Weerd 2010](#); [Park 2019](#)). An atherosclerotic lesion, a diffuse and degenerative disease of the arteries, usually provokes ACS which narrows the vessel wall. A sudden rupture of atheromatous plaques from significant asymptomatic stenosis of the carotid artery can lead to thromboembolism, which causes 10% to 15% of all strokes ([Bulbulia 2017](#)). Thus, for people with extracranial carotid disease, it is important to identify risk factors, the degree of stenosis of the artery, and the characteristics of the plaque, such as ulcerations, intra-plaque haemorrhage, and lipid content, that may increase the likelihood of a cerebrovascular event ([De Waard 2017](#); [Derdeyn 2007](#); [Naylor 2018](#); [Ricotta 2011](#)).

The modifiable risk factors associated with ACS — such as hypertension, smoking, dyslipidaemia, diabetes, obesity, a sedentary lifestyle, alcoholism, inadequate diet quality, and psychosocial factors — can vary in importance according to region, ethnic group, gender, age, and family history. However, together these factors consistently contribute towards increasing the risk of cerebrovascular disease, making them targets for general approaches to preventing cerebrovascular events worldwide ([Arnett 2019](#); [Guzik 2017](#); [O'Donnel 2016](#)).

In order to diagnose and classify ACS there are some complementary imaging tests: duplex ultrasound (DUS) and angiography by magnetic resonance imaging (MRI), computed tomography angiography (CTA), or digital subtraction angiography (DSA). DSA was practically discontinued at the end of the 20th century as a diagnostic method, especially in asymptomatic patients, as it is associated with a 1.2% risk of neurological events ([ACAS 1995](#)). On the other hand, DUS is affordable, non-invasive, and inexpensive. It also does not bring the additional risks associated with DSA, MRA, and CTA, such as the use of iodinated or paramagnetic contrast, X-ray exposure, and embolisation risks. Thus, DUS is widely used as the first diagnostic method for detecting carotid stenosis in both symptomatic patients and those with risk factors for asymptomatic stenosis ([Cassola 2018](#); [Daolio 2019](#); [Naylor 2018](#); [Ricotta 2011](#); [Wardlaw 2006](#)).

The European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) applied different techniques to measure the percentage of stenosis in DSA ([Figure 1](#)), and identified those patients who would benefit from revascularisation. While ECST used residual lumen diameter as a denominator, NASCET used disease-free diameter in a segment of the carotid artery above the stenosis. Using NASCET measurement standards, other studies (namely the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial 1 (ACST-1)) have shown that surgical intervention would also benefit some asymptomatic patients with carotid stenosis greater than 60% of diameter on DSA ([ACAS 1995](#); [ECST 1998](#); [Halliday 2004](#); [NASCET 1991](#); [Naylor 2018](#); [Ricotta 2011](#)).

Figure 1. Longitudinal view of carotid bifurcation with methods of measuring carotid stenosis at angiography. A: narrowest ICA diameter
B: normal distal cervical ICA diameter
C: estimated original diameter at the site of the most stenosis
CCA: common carotid artery
ECA: external carotid artery
ECST: European Carotid Surgery Trial
ICA: internal carotid artery
NASCET: North American Symptomatic Carotid Endarterectomy Trial



Description of the intervention

It is important to ensure that people with ACS receive the best therapeutic option to avoid cerebral ischaemia, and this includes: the control of hypertension; use of lipid-lowering drugs to reduce cholesterol levels in order to regress plaque(s), decrease the risk of plaque accident, and for anti-inflammatory purposes; use of hypoglycaemic drugs; and the use of antiplatelet and anticoagulant agents.

Antihypertensive therapy

High blood pressure is one of the most powerful risk factors, and its decrease seems to be directly related to a lower incidence of stroke. A reduction of 5 mmHg to 10 mmHg blood pressure is associated with a 30% to 40% reduced risk of stroke compared with placebo. Despite a lack of randomised controlled trials (RCTs) assessing the effects of antihypertensives in people with ACS, the European Society for Vascular Surgery (ESVS) recommends a target blood pressure for people with ACS below 140/90 mmHg and, more radically, the American Heart Association (AHA) lowered these ideal blood pressure levels to close to 130/80 mmHg, with diastolic blood pressure less than 85 mmHg for people with diabetes in both guidelines (Arnett 2019; Brott 2013; Lawes 2004; Naylor 2018; Ricotta 2011).

Maintaining blood pressure may reduce stenosis and prevent lesion progression. Calcium channel blockers and angiotensin-converting enzyme inhibitors are associated with plaque reduction to a greater extent than diuretics and beta-blockers (Arnett 2019; Naylor 2018; Ricotta 2011).

Lipid-lowering drugs

At the end of the 20th century, less than 10% of people with carotid stenosis regularly used statins to treat dyslipidaemia. At the start of the 21st century there was an increase in statin use as studies showed a decrease in cardiovascular events in symptomatic patients by more than one-third when low-density lipoprotein (LDL) cholesterol levels were below 70 mg/dL. Systematic reviews observed a significant reduction in cardiovascular mortality (including stroke) when statins, mainly atorvastatin 80 mg daily, were used in primary prevention, for instance in people with ACS. However, ezetimibe or PCSK9 inhibitors may be an alternative treatment for high-risk patients who cannot tolerate statins (Amarenco 2006; Brott 2013; Herder 2012; Naylor 2018; Ricotta 2011; Taylor 2002; Taylor 2013; Wilson 2019; Zhan 2018).

Management of diabetes

Diabetes mellitus is an independent predictor of moderate and severe carotid stenosis and can contribute for doubling the

chances of stroke. Medications used for glycaemic control include oral hypoglycaemic agents (metformin or sulfonylureas, or both), insulin therapy, or the new glucose-lowering medications such as the analogue of human glucagon-like peptide 1, dipeptidyl peptidase 4 inhibitors, sodium glucose cotransporter 2 inhibitors, and thiazolidinediones. Strong control of glycaemic levels is not directly related to a decreased risk of stroke, but glycosylated haemoglobin levels lower than 7% may contribute to a reduction in other related events, such as microangiopathy. Meanwhile, systematic reviews indicated that strict control in people with a body mass index above 30 kg/m² was effective in reducing the risk of cerebrovascular disease (Chiquete 2014; De Weerd 2010; Holman 2014; Naylor 2018; Ricotta 2011; Zhang 2013).

Antiplatelet drugs

There is weak evidence for the use of antiplatelet drugs in people with ACS for reducing the risk of stroke, but there is more robust evidence for their use in secondary prevention. However, the use of aspirin at doses between 75 mg and 325 mg (or clopidogrel 75 mg when aspirin is intolerable) is recommended in asymptomatic patients to prevent other cardiovascular events (Murphy 2019; Naylor 2018; Ricotta 2011).

Anticoagulant agents

Anticoagulant therapy is known to prevent stroke in people with atrial fibrillation, but warfarin has not been shown to be more effective compared to antiplatelet therapy for secondary prevention in people without atrial fibrillation. However, recent studies have indicated that the use of low-dose rivaroxaban together with aspirin may decrease the risk of stroke in both symptomatic and asymptomatic patients (Ricotta 2011; Sharma 2019).

How the intervention might work

As carotid atherosclerosis is an important aspect in stroke pathophysiology, proper management of the diseases that lead to its increase may correspond to key targets for stroke prevention. The approaches discussed above work together to control the risk factors that increase atherosclerosis, avoiding irregular and ulcerated plaques, microembolic particles, and preventing carotid artery disease from progressing (Naylor 2018).

The ACAS and ACST-1 studies used an initial pharmacological therapy which has significantly changed in recent decades. For instance, only around 10% to 20% of ACAS and ACST-1 participants regularly used lipid-lowering drugs. There was a decline in annual stroke rates of approximately 60% between 1995 and 2004, which strongly correlates with improved pharmacological treatment associated with the increased use of aspirin, antihypertensive drugs, and statins, in that decade. Control of hypertension can reduce the risk of stroke by up to 30%, while control of cholesterol can reduce this risk by 15%. In addition, people with diabetes who, associated with glycaemic control, were taking statins, antiplatelet, and antihypertensive drugs, showed a 60% reduction in the risk of cardiovascular disease and death (ACAS 1995; Halliday 2004; Naylor 2018; Ricotta 2011).

Why it is important to do this review

Some randomised controlled trials (RCTs) have evaluated the use of pharmacological interventions, and topical guidelines

currently recommend triple medical therapy (e.g. antiplatelet agents, antihypertensive therapy, and statins) in addition to lifestyle interventions to reduce the risk of stroke. Routine carotid endarterectomy or stenting is not reasonable in asymptomatic patients, except in particular high-risk patients on medical therapy (Naylor 2018). However, the optimal therapeutic management strategy remains unclear (Raman 2013). Additionally, recent studies suggest that a more effective antithrombotic strategy (e.g. direct oral anticoagulants plus antiplatelet agents) may be more effective than antiplatelet agents alone for decreasing the risk of major vascular events (Abbott 2007; Sharma 2019).

Stroke continues to be the main cause of permanent disability and one of the most important causes of death in the world, and its impact leads to considerable socioeconomic impairment, not only to the patient and family, but also to society as a whole. In this context, pursuing the best pharmacological strategies may be useful to decrease ACS-related mortality and permanent neurological disability (Naylor 2018).

OBJECTIVES

To assess the effects of pharmacological interventions for the treatment of asymptomatic carotid stenosis, to prevent neurological impairment, stroke, disability, death, and other complications.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all RCTs with parallel (e.g. cluster or individual) or cross-over design. We will only use data from the first phase of cross-over studies to avoid the risk of carry-over effects, as described in Section 23.2.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a). We will include studies reported as full text, those published as abstract only, and unpublished data. Quasi-randomised trials (i.e. studies in which participants are allocated to intervention groups based on methods that are not truly random, such as hospital number or date of birth) will not be considered.

Types of participants

We will consider for inclusion participants of any gender and any age with ACS. Carotid stenosis will be defined as a narrowing of the internal or common carotid artery (or both), diagnosed by at least one valid objective test (e.g. DUS or angiography by tomography, magnetic resonance or digital subtraction). We will use the classification of carotid stenosis with the use of ultrasound as defined by Grant 2003 for the participant classification (Table 2). We will consider participants as asymptomatic if they were without ipsilateral neurological symptoms (e.g. amaurosis fugax, TIA or stroke) in the previous six months (Naylor 2018). All trials involving participants with ACS will be considered, irrespective of the degree of stenosis or the method of determining the degree of stenosis.

If we find studies with mixed populations, and only a subset of the participants meets our inclusion criteria, we will attempt to obtain data for the subgroup of interest from the trialists in order to include the study. For studies with mixed populations where we cannot obtain data on the subgroup of interest, but at least 50% of the

study population are of interest, we will include all participants in our analysis. Moreover, we will explore the effect of this decision in a sensitivity analysis. We will exclude studies in which less than 50% of the population are of interest and data on the subgroup of interest are not available.

Types of interventions

We will include trials comparing one pharmacological intervention (agent or drug) with placebo, no treatment, or another pharmacological intervention. We will include trials of any combination of interventions, providing co-treatments are balanced between the treatment and control arms for the ACS treatment. We will also include studies that compare different doses of drugs.

We will consider the following interventions:

- anticoagulants (unfractionated heparin (UFH) and low molecular weight heparins (LMWHs); vitamin K antagonists (VKA); direct oral anticoagulants (DOAC), factor Xa inhibitors and direct thrombin inhibitors; pentasaccharides);
- antiplatelet agents (e.g. aspirin, clopidogrel);
- antihypertensive drugs (e.g. angiotensin-converting enzyme inhibitors, beta blockers);
- glycaemic-lowering agents (e.g. biguanides, sulphonylureas);
- lipid-lowering agents (e.g. statins).

The possible comparisons are:

- anticoagulants plus antiplatelet agents versus antiplatelet agents;
- one class of antiplatelet versus a combination of antiplatelets from two classes;
- one class of antiplatelet versus another class of antiplatelet;
- anticoagulants versus antiplatelet agents;
- one class of lipid-lowering versus another class of lipid-lowering;
- one class of antihypertensive versus another class of antihypertensive;
- one class of glycaemic-lowering versus another class of glycaemic-lowering;
- any combination of the above treatments versus any combination, with or without placebo.

Types of outcome measures

Primary outcomes

- Neurological impairment, assessed using clinical outcome measures or any validated international scales (e.g. the National Institutes of Health Stroke Scale (NIHSS), the modified Rankin Scale (mRS), the Barthel Index (BI)). If we identify both dichotomous and continuous variables related to neurological impairment, we will report them separately as independently outcomes.
- Ipsilateral major or disabling stroke, related to the extracranial carotid stenosis and confirmed by any objective additional test (e.g. computerised tomography, angiography) other than only clinical examination.

Secondary outcomes

- Stroke-related mortality.

- Major bleeding: defined by a haemoglobin concentration decrease of 2 g/dL or more, a retroperitoneal or intracranial bleed, a transfusion of two or more units of blood, or fatal haemorrhagic events, as defined by the International Society on Thrombosis and Haemostasis (Schulman 2010). We will also consider the definition stipulated by the included study.
- Progression of carotid stenosis (any increase in extracranial carotid stenosis), evaluated by change in range of stenosis, i.e. less than 50%, 50% to 69%, 70% or more, near occlusion or occlusion. We will consider the carotid stenosis if it was evaluated by any valid objective method (e.g. duplex ultrasound (Grant 2003), or angiography by tomography, magnetic resonance or digital subtraction (NASCET 1991)).
- Adverse events, such as all-cause mortality, gastrointestinal, allergic reaction, renal failure, or minor bleeding.
- Quality of life, analysed by any validated questionnaire (e.g. SF-36 (Ware 1992)) or participant's subjective perception of improvement (yes or no) as reported by the study authors. If we are unable to pool data on quality of life due to the use of different measurements, we will attempt to extract data on improvement.

We will present the outcomes at the following two time points after the start of the intervention, if data are available:

- early outcomes (at six months or less after the start of the intervention);
- long-term outcomes (more than six months after the start of the intervention).

Search methods for identification of studies

See the methods for the Cochrane Stroke Group [Specialised register](#). We will search for trials in all languages and arrange for the translation of relevant articles where necessary.

Electronic searches

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

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library; latest issue);
- MEDLINE Ovid (from 1946) ([Appendix 1](#));
- Embase Ovid (from 1974);
- Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) (from 1982), via [Virtual Health Library](#);
- Índice Bibliográfico Español de Ciencias de la Salud (IBECS), via [Virtual Health Library](#).

We will model the subject strategies for databases on the search strategy designed for MEDLINE by the Cochrane Stroke Group's Information Specialist ([Appendix 1](#)). We have opted to write a highly-sensitive search strategy and have eliminated the pharmacological interventions component of the search entirely. The reasons for this are as follows. The problem component 'asymptomatic carotid stenosis' is already well defined and, when combined with Cochrane's verified RCT filter, retrieved a low number of results during test searches in MEDLINE Ovid. Pharmacological interventions search blocks can help improve recall when included in search strategies. However, because the initial test search recall is relatively low, as suggested above, we

elected not to include them in the enclosed search but we will select the relevant interventions manually. We will combine all search strategies deployed with subject strategy adaptations of the highly-sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019).

We will search the following ongoing trials registers:

- US National Institutes of Health Ongoing Trials Register, ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organization (WHO) International Clinical Trials Registry Platform (who.int/ictrp/en/);
- Stroke Trials Registry (www.strokecenter.org/trials/).

Searching other resources

In an effort to identify further published, unpublished and ongoing trials, we will:

- check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials, and search Google Scholar to forward-track relevant references (scholar.google.co.uk/);
- contact original trial authors for clarification and further data if trial reports are unclear;
- where necessary, contact experts/trialists/organisations in the field to obtain additional information on relevant trials, using a standard letter template (Appendix 2); and
- conduct a search of various grey literature sources, dissertation and theses databases, and databases of conference abstracts, including:
 - * [British Library EThOS](#) (UK E-Theses Online Service);
 - * [ProQuest Dissertation and Theses Global](#);
 - * [Repositório UNIFESP](#) (thesis repository of Universidade Federal de Sao Paulo, Brazil).

Data collection and analysis

Selection of studies

Two review authors (CNBC, NC) will independently screen titles and abstracts of the references obtained as a result of our searching activities and will exclude obviously irrelevant reports using the Covidence tool (Covidence). We will retrieve the full-text articles for the remaining references and two review authors (CNBC, NC) will independently screen these, identify studies for inclusion and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or, if required, we will consult a third review author (RLGF). We will collate multiple reports of the same study so that each study, not each reference, is the unit of interest in the review. We will record the selection process and complete a PRISMA flow diagram (Moher 2010).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which we will pilot on at least one study in the review. Two review authors (CNBC, NC) will independently extract data from the included studies. We will extract the following study characteristics.

- **Methods:** study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting and date of study.
- **Participants:** number randomised, number lost to follow-up/withdrawn, number analysed, number of interest, mean age, age range, gender, severity of condition, diagnostic criteria, smoking history, inclusion criteria, and exclusion criteria.
- **Interventions:** intervention, comparison, concomitant medications, and excluded medications.
- **Outcomes:** primary and secondary outcomes specified and collected, and time points reported.
- **Notes:** funding for trial, and notable conflicts of interest of trial authors.

We will resolve disagreements by consensus or by involving a third review author (RLGF). One review author (CNBC) will transfer data into Review Manager (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (NC) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (CNBC, NC) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will resolve any disagreements by discussion or by involving another review author (RLGF). We will assess the risk of bias according to the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- other bias.

In cluster-randomised trials, we will consider particular biases as recommended in section 8.15.1.1 of the *Cochrane Handbook for Systematic Reviews of Interventions*: 1) recruitment bias; 2) baseline imbalance; 3) loss of clusters; 4) incorrect analysis; and 5) comparability with individually randomised trials (Higgins 2017). We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report, together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We will analyse continuous data using the mean difference (MD) when the same scale/score is used, or standardised mean difference (SMD) when different scales/scores are used, with 95% CIs. We will enter data presented as a scale with a consistent direction of effect. We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

Individuals will be our unit of analysis. If trials include multiple intervention arms, we will consider only the arms relevant to the scope of our review. Where a study includes multiple intervention groups, we will combine groups to create a single pair-wise comparison. Where a study includes repeated observations, we will follow Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a).

Crossover trials

We do not anticipate identifying any cross-over RCTs. However, if we identify any such studies, we will only use data from the first phase to avoid the risk of carry-over effects, as described in Section 23.2.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a).

Cluster-randomised trials

We do not anticipate identifying any cluster-RCTs. However, if we identify any such studies, we will include them in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in Section 23.1.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we will synthesise the relevant information. We will consider it reasonable to combine the results from both types of trials if there is little heterogeneity between the study designs, and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where possible, we will use the Review Manager calculator to calculate missing standard deviations using other data from the trial, such as confidence intervals. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. For all outcomes, we will follow intention-to-treat (ITT) principles to the greatest degree possible, that is, we will analyse participants in their randomised group regardless of what intervention they actually received. We will use available-case data for the denominator if ITT data are not available.

We will present study-level data so that missing and unclear data are clearly indicated and to make available any unpublished data acquired from investigators.

Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis; we acknowledge that there is substantial uncertainty in the value of I^2 when there is only a small number of studies. If we identify substantial heterogeneity, we will report it and explore possible causes by pre-specified subgroup analysis.

As strict thresholds for interpretation of I^2 are not recommended, we will follow the guide to interpretation in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019):

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

When the I^2 value lies in an area of overlap between two categories (e.g. between 50% and 60%), we will consider differences in participants and interventions among the trials contributing data to the analysis (Deeks 2019).

Assessment of reporting biases

We will use funnel plots to investigate reporting biases if we identify 10 or more studies, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b).

Data synthesis

We will synthesise the data using Review Manager 5.3 (RevMan 2014). We will undertake meta-analysis only where this is meaningful, that is if the treatments, participants, and the underlying clinical question are similar enough for pooling to be appropriate.

If we are confident that trials are estimating the same underlying treatment effect, i.e. the included studies are homogenous (considering population, interventions, comparators, and outcome characteristics), we will use a fixed-effect meta-analysis. If clinical heterogeneity is sufficient to expect that underlying treatment effects differ between trials or if at least substantial heterogeneity is identified, we will use a random-effects meta-analysis. If there is substantial clinical, methodological, or statistical heterogeneity across trials that prevents the pooling of data, we will use a narrative approach to data synthesis (Deeks 2019).

We will address all outcomes listed in the [Types of outcome measures](#) section in the Results section of the review under the heading 'Effects of interventions', with outcomes addressed in the order in which they are shown in [Types of outcome measures](#). In addition, we will present one 'Summary of findings' table for each comparison, in which we will summarise the main outcomes. We will include the results of individual studies and any statistical summary of these in 'Data and analyses' tables in the review.

GRADE and 'Summary of findings' table

We will create 'Summary of findings' tables of comparisons that have included studies. In these tables, we will use the following outcomes:

- neurological impairment;
- ipsilateral major or disabling stroke;
- stroke-related mortality;
- major bleeding;
- progression of carotid stenosis;
- adverse events;
- quality of life.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We will use methods and recommendations described in Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019), and GRADEproGDT software (GRADEproGDT 2015). We will create a separate 'Summary of findings' table for each comparison, for example: 1) anticoagulants plus antiplatelet agents versus antiplatelet agents; 2) one class of antiplatelet versus another class of antiplatelet, etc. We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Two review authors (CNBC, NC), working independently, will make judgements about evidence quality, with disagreements resolved by discussion or involving a third review author (RLGF). We will justify, document, and incorporate judgements into the reporting of results for each outcome.

We plan to extract study data, format our comparisons in data tables, and prepare 'Summary of findings' tables before writing the results and conclusions of our review. A template 'Summary of findings' table is included as Table 3.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for the following factors, if sufficient data are available.

- Participant characteristics:
 - * age (e.g. adults (18 years to 74 years) and older people (75 years and over));
 - * race;
 - * comorbidities (e.g. tobacco addiction);
 - * degree of baseline stenosis as defined by Grant 2003 and available at Table 2.
- Intervention characteristics:
 - * doses of drugs;
 - * types of drugs (e.g. UFH, LMWH, VKA, DOAC among anticoagulants; aspirin, clopidogrel among antiplatelet agents);

- * route of administration (e.g. oral, intravenous, subcutaneous);
- * pre-specified target achieved (e.g. low-density lipoprotein level below 70 mg/dL).

We will use the following outcomes (i.e. the primary outcomes) in the subgroup analyses:

- neurological impairment;
- ipsilateral major or disabling stroke.

We will use the formal test for subgroup differences in Review Manager 5.3 (RevMan 2014) and base our interpretation on this.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main result. These analyses will be grouped according to study design (individual, cross-over, or cluster).

- Only including studies with a low risk of bias. We will consider a study to have a low risk of bias overall if there is no high-risk judgement in any of the four main domains, i.e. random sequence generation, allocation concealment, incomplete outcome data, and selective reporting.
- We will examine both the fixed-effect model and random-effects model meta-analyses, and we will explore the differences between the two estimates.
- If we identify studies with missing data that are unobtainable, we will repeat analyses excluding these studies to determine their impact on the primary analyses.

We will use the following outcomes (i.e. the primary outcomes) in the sensitivity analyses:

- neurological impairment;
- ipsilateral major or disabling stroke.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

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ADDITIONAL TABLES
Table 1. Glossary of terms

Term	Definition
Amaurosis fugax	Transient monocular visual loss associated with vascular thromboembolic events arising from the internal carotid arterial system
Anticoagulants	Drugs that suppress, delay, or prevent blood clots
Antiplatelet agents	Drugs which prevent blood clots by inhibiting platelet function
Atherosclerosis	A disease characterised by a build-up of abnormal fat, cholesterol and platelet deposits on the inner wall of the arteries
Atheromatous plaques	A fatty deposit in the inner lining (intima) of an artery, resulting from atherosclerosis
Atherosclerotic debris	Pieces of atheromatous plaque that can break off and be carried by the bloodstream
Body mass index (BMI)	Body mass divided by the square of the body height, universally expressed in units of kg/m ²
Computed tomography angiography (CTA)	Computed tomography scanning that uses an injection of contrast material into the blood vessels to help diagnose and evaluate blood vessel disease or related conditions
Digital subtraction angiography (DSA)	Fluoroscopy technique used in interventional radiology to clearly visualise blood vessels in a bony or dense soft tissue environment
Direct thrombin inhibitors	A drug that acts as anticoagulant by directly inhibiting the enzyme thrombin (factor IIa)
Duplex ultrasound	Non-invasive evaluation of blood flow through the arteries and veins by ultrasound devices
Dyslipidemia	Abnormal concentration of fats (lipids or lipoproteins) in the blood

Table 1. Glossary of terms (Continued)

Embolism	Obstruction of an artery or vein, typically by a clot of blood or an air bubble
Fator Xa inhibitors	A type of anticoagulant that works by selectively and reversibly blocking the activity of clotting factor Xa, preventing clot formation
Heparin	A drug which is used to prevent blood clotting (anticoagulant, blood thinner)
Ipsilateral encephalic territories	The same side of the brain
Low molecular weight heparin	A drug which is used to prevent blood clotting (anticoagulant)
Magnetic resonance angiography (MRA)	A group of techniques based on magnetic resonance imaging (MRI) to image blood vessels
Obesity	A condition where the amount of body fat is beyond healthy conditions (BMI greater than 30 kg/m ²)
Oedema	Excess watery fluid which collects in tissues of the body, causing swelling when fluid leaks out of the body's vessels
Overweight	Where body fat is over that of the average population, but less than unhealthy conditions (BMI between 25 kg/m ² and 30 kg/m ²)
Placebo	Substance or treatment with no active effect, like a sugar pill
Randomised controlled trial (RCT)	A study in which the participants are divided randomly into separate groups to compare different treatments
Stroke	Neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, persisting ≥ 24 hours or until death
Thrombosis	Local coagulation of blood (clot) in a part of the circulatory system
Transient ischaemic attack (TIA)	A transient episode (less than 24 hours) of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia without acute infarction
Unfractionated heparin (UFH)	A mixture of heparins obtained from animals which is used to prevent blood coagulation. Used to prevent and treat clotting disorders
Vascular	Relating to blood vessels (arteries and veins)
Vitamin K antagonists (VKAs)	Substances that reduce blood clotting by reducing the action of vitamin K

Table 2. DUS criteria for internal carotid stenosis

Consensus panel based on [Grant 2003](#)

Degree of stenosis (%)	Primary parameters		Additional parameters	
	ICA PSV (cm/sec)	Plaque estimate (%)*	ICA/CCA PSV ratio	ICA EDV (cm/sec)
Normal	< 125	None	< 2.0	< 40
< 50%	< 125	< 50	< 2.0	< 40

Table 2. DUS criteria for internal carotid stenosis (Continued)

50% to 69%	125 to 230	≥ 50	2.0 to 4.0	40 to 100
≥ 70% but less than near occlusion	> 230	≥ 50	> 4.0	> 100
Near occlusion	High, low or undetectable	Visible	Variable	Variable
Total occlusion	Undetectable	Visible, no detectable lumen	Not applicable	Not applicable

*Plaque estimate (diameter reduction) based on DUS B-mode and on additional colour mode ultrasound.

CCA: common carotid artery

DUS: duplex ultrasound

EDV: end diastolic velocity

ICA: internal carotid artery

PSV: peak systolic velocity

Table 3. Template for 'Summary of findings' table
Anticoagulants plus antiplatelet agents versus antiplatelet agents for asymptomatic carotid stenosis

Patient or population: adults with asymptomatic carotid stenosis

Settings: community

Intervention: anticoagulants plus antiplatelet agents

Comparison: antiplatelet agents

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with antiplatelet agents	Risk with anticoagulants plus antiplatelet agents				
	[control]	[experimental]				
Neurological impairment	[mean difference] (CI)	[mean difference] (CI)	–	[value] ([value])	⊕⊕⊕⊕ very low ⊕⊕⊕⊕ low ⊕⊕⊕⊕ moderate ⊕⊕⊕⊕ high	
Ipsilateral major or disabling stroke	[value] per 1000	[value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	⊕⊕⊕⊕ very low ⊕⊕⊕⊕ low ⊕⊕⊕⊕ moderate	

Pharmacological interventions for asymptomatic carotid stenosis (Protocol)

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Table 3. Template for 'Summary of findings' table *(Continued)*

					⊕⊕⊕⊕ high
Stroke-related mortality	[value] per 1000	[value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	⊕⊕⊕⊕ very low ⊕⊕⊕⊕ low ⊕⊕⊕⊕ moderate ⊕⊕⊕⊕ high
Major bleeding	[value] per 1000	[value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	⊕⊕⊕⊕ very low ⊕⊕⊕⊕ low ⊕⊕⊕⊕ moderate ⊕⊕⊕⊕ high
Progression of carotid stenosis	[value] per 1000	[value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	⊕⊕⊕⊕ very low ⊕⊕⊕⊕ low ⊕⊕⊕⊕ moderate ⊕⊕⊕⊕ high
Adverse events	[value] per 1000	[value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	⊕⊕⊕⊕ very low ⊕⊕⊕⊕ low ⊕⊕⊕⊕ moderate ⊕⊕⊕⊕ high
Quality of life	[value] per 1000	[value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	⊕⊕⊕⊕ very low ⊕⊕⊕⊕ low ⊕⊕⊕⊕ moderate ⊕⊕⊕⊕ high

Table 3. Template for 'Summary of findings' table (Continued)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

CI: confidence interval; **RR:** risk ratio

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. Further research is very unlikely to change our confidence in the estimate of 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. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

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. We are very uncertain about the estimate.

APPENDICES

Appendix 1. MEDLINE search strategy

1. carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/
2. carotid arteries/ or carotid artery, common/ or carotid artery, external/ or carotid artery, internal/
3. (carotid adj5 (stenosis or thrombo\$ or disease\$ or narrow\$ or plaque\$ or arterioscler\$ or atheroscler\$)).tw.
4. or/1-3
5. exp Asymptomatic Diseases/
6. asymptomatic.tw.
7. 5 or 6
8. 4 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. randomly.ab.
14. trial.ab.
15. groups.ab.
16. or/9-15
17. 8 and 16

Appendix 2. Enquiry letter

Dear Doctor

I am currently conducting a systematic review entitled 'Pharmacological interventions for asymptomatic carotid stenosis' with the Cochrane Stroke Group based in the University of Edinburgh. To ensure that the results are valid, it is essential that all relevant trials are included.

Cochrane was established to ensure all forms of health care will be subject to critical evaluation using standard criteria and specialised software.

As a [manufacturer/expert/trialist] of [drug/intervention name], it is possible that a trial of this or a similar agent has been conducted in patients with asymptomatic carotid stenosis. If so, we would be grateful if you could supply us with copies of any relevant protocols, reports or publications in the first instance; later it may become necessary to obtain the raw data. If the trial is eligible for inclusion in the review, [Pharmaceutical company/specialist name] will be cited in the final report which will be published electronically within the Cochrane Database of Systematic Reviews, and in standard medical journals

I would be grateful if you could fill in the accompanying form, and forward any information which you feel may be appropriate.

Thank you for your help.

Yours faithfully

Form for reply from Pharmaceutical Company/Trialist/Expert

Trials that fulfil the following criteria will be eligible for inclusion in the review:

- Types of participants:
- Treatment regimen:
- A valid randomisation method:

For example: a centralised scheme, e.g. by telephone or scheme controlled by pharmacy, e.g. pre-coded or numbered containers or on-site computer system where allocations are in a locked unreadable file or assignment envelopes - sequentially numbered, sealed and opaque or other combinations which provide assurance of adequate concealment.

Name of Pharmaceutical Company/Trialist/Expert

Name (person to whom any future correspondence should be addressed):

Trials fulfilling the above criteria:

Have not been conducted ()

Are currently underway * ()

Have been conducted in the past * ()

* Please enclose relevant protocols, citations, reports or other publications

Thank you for your valuable help.

Please complete and return to:

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CONTRIBUTIONS OF AUTHORS

CNBC drafted the protocol and is the guarantor of the review.

NC drafted the protocol.

CDQF drafted the protocol.

LCUN drafted the protocol.

VFMT drafted the protocol.

RLGF drafted the protocol.

All authors reviewed and approved the protocol content prior to submission.

DECLARATIONS OF INTEREST

CNBC: none known.

NC: none known.

CDQF: none known.

LCUN: none known.

VFMT: none known.

RLGF: none known.

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