Stroke FOUNDATION

# Clinical Guidelines for Stroke Management 2017

## Chapter 4 of 8:
## Secondary prevention

This is the fourth in a series of eight guideline chapters that provide evidence-based recommendations for recovery from stroke and TIA.

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**Disclaimer**

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# Summary of recommendations

## Introduction
## Methodology
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## Adherence to pharmacotherapy

Weak Recommendation

Interventions to promote adherence with medication regimens may be provided to all patients with stroke. Such regimens may include combinations of the following:

- reminders, self-monitoring, reinforcement, counselling, motivational interviewing, family therapy, telephone follow-up, supportive care and dose administration aids (Lawrence et al 2015 *[8]*; Mahtani et al 2011; Nieuwlaat et al 2014 *[14]*; Haynes et al 2008 *[13]*)
- development of self-management skills and modification of dysfunctional beliefs about medication (O'Carroll et al 2014 *[10]*; Kronish et al 2014 *[9]*)
- information and education in hospital and in the community (Lawrence et al 2015 *[8]*; Mahtani et al 2011 *[16]*; Nieuwlaat et al 2014 *[14]*).

## Blood pressure lowering therapy

### Acute blood pressure management

Practice Statement

Consensus-based recommendations

- All patients with acute stroke should have their blood pressure closely monitored in the first 48 hours after stroke onset.
- Patients with acute ischaemic stroke eligible for treatment with intravenous thrombolysis should have their blood pressure reduced to below 185/110 mmHg before treatment and in the first 24 hours after treatment.
- Patients with acute ischaemic stroke with blood pressure >220/120/mmHg should have their blood pressure cautiously reduced (e.g. by no more than 20%) over the first 24 hours.

Weak Recommendation Against

Intensive blood pressure lowering in the acute phase of care to a target SBP of <140mmHg is not recommended for any patient with stroke. (Bath and Krishnan 2014 *[40]*)

Weak Recommendation

In patients with intracerebral haemorrhage blood pressure may be acutely reduced to a target systolic blood pressure of around 140mmHg (but not substantially below). (Tsivgoulis et al 2014*[43]*; Qureshi et al 2016*[42]*)

Weak Recommendation

Pre-existing antihypertensive agents may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 *[40]*)

### Long term blood pressure management

Strong Recommendation

- All patients with stroke or TIA, with a clinic blood pressure of >140/90mmHg should have long term blood pressure lowering therapy initiated or intensified. (SPS3 2013 *[25]*; Thomopoulos et al 2016 *[30]*; Ettehad et al 2016 *[31]*; Lahkan and Sapko 2009 *[26]*)
- Blood pressure lowering therapy should be initiated or intensified before discharge for those with stroke or TIA, or soon after TIA if the patient is not admitted. (SPS3 2013 *[25]*; Thomopoulos et al 2016 *[30]*; Ettehad et al 2016 *[31]*; Lahkan and Sapko 2009 *[26]*)
- Any of the following drug classes are acceptable as blood pressure lowering therapy; angiotensin-converting-enzyme inhibitor, angiotensin II receptor antagonists, calcium channel blocker, thiazide diuretics. Beta-blockers should not be used as first-line agents unless the patient has ischaemic heart disease. (Lakhan and Sapko 2009 *[26]*; Mukete et al 2015 *[33]*)

Weak Recommendation

- In patients with a systolic blood pressure of 120-140mmHg who are not on treatment, initiation of antihypertensive treatment is reasonable, with best evidence for dual (ACEI/diuretic) therapy. (Ettehad et al 2016 *[31]*)
- The ideal long term blood pressure target is not well established. A target of <130mmHg systolic may achieve greater benefit than a target of 140mmHg systolic, especially in patients with stroke due to small vessel disease, provided there are no adverse effects from excessive blood pressure lowering. (SPS3 2013 *[25]*; Ettehad et al 2016 *[31]*)

## Antiplatelet therapy

Strong Recommendation

Long-term antiplatelet therapy (low-dose aspirin, clopidogrel or combined low-dose aspirin and modified release dipyridamole) should be prescribed to all patients with ischaemic stroke or TIA who are not prescribed anticoagulation therapy, taking into consideration patient co-morbidities. (Rothwell et al 2016 *[44]*; Niu et al 2016 *[45]*; Sandercock et al 2014 *[46]*)

Strong Recommendation

All ischaemic stroke and TIA patients should have antiplatelet therapy commenced as soon as possible once brain imaging has excluded haemorrhage unless thrombolysis has been administered, in which case antiplatelet therapy can commence after 24-hour brain imaging has excluded major haemorrhagic transformation. (see Antithrombotic therapy in Acute medical and surgical management)

Strong Recommendation

Aspirin plus clopidogrel should be commenced within 24 hours and used in the short term (first three weeks) in patients with minor ischaemic stroke or high-risk TIA to prevent stroke recurrence. (Hao et al. 2018 *[126]*)

Strong Recommendation Against

The combination of aspirin plus clopidogrel should not be used for the long-term secondary prevention of cerebrovascular disease in people who do not have acute coronary disease or recent coronary stent. (Zhang et al 2015 *[51]*)

Strong Recommendation Against

Antiplatelet agents should not be used for stroke prevention in patients with atrial fibrillation. (Connolly et al 2011 *[54]*)

## Anticoagulant therapy

Strong Recommendation

- For patients with ischaemic stroke or TIA, with atrial fibrillation (both paroxysmal and permanent), oral anticoagulation is recommended for long-term secondary prevention. (Saxena et al 2004 *[85]*; Saxena 2004 *[86]*; Ruff et al 2014 *[70]*)
- Direct oral anticoagulants (DOACs) should be initiated in preference to warfarin for patients with non-valvular atrial fibrillation and adequate renal function. (Ruff et al 2014 *[70]*)
- For patients with valvular atrial fibrillation or inadequate renal function, warfarin (target INR 2.5, range 2.0-3.0) should be used. Patients with mechanical heart valves or other indications for anticoagulation should be prescribed warfarin. (Tawfik et al 2016 *[99]*)

Practice Statement

**Consensus-based recommendation**
For patients with ischaemic stroke, the decision to begin anticoagulant therapy can be delayed for up to two weeks but should be made prior to discharge.

Recommendation Strength Not Set

**Practice points**

- Concurrent antiplatelet therapy should not be used for patients who are anticoagulated for atrial fibrillation unless there is clear indication (e.g. recent coronary stent). Addition of antiplatelet for stable coronary artery disease in the absence of stents should not be used.
- For patients with TIA, anticoagulant therapy should begin once CT or MRI has excluded intracranial haemorrhage as the cause of the current event.
- For patients with ischaemic stroke due to atrial fibrillation and a genuine contraindication to long-term anticoagulation, percutaneous left atrial appendage occlusion may be a reasonable treatment to reduce recurrent stroke risk.

## Cholesterol lowering therapy

Strong Recommendation

All patients with ischaemic stroke or TIA with possible atherosclerotic contribution and reasonable life expectancy should be prescribed a high-potency statin, regardless of baseline lipid levels. (Manktelow et al 2009 *[107]*; Tramacer et al 2019 *[118]*)

Strong Recommendation

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In patients with ischaemic stroke, cholesterol lowering therapy should target LDL cholesterol < 1.8 mmol/L for secondary prevention of atherosclerotic cardiovascular disease. (Amarenco et al 2020 *[112]*)

Weak Recommendation Against

Statins should not be used routinely for intracerebral haemorrhage. (Manktelow et al 2009 *[107]*; Amarenco et al 2006 *[108]*)

Weak Recommendation Against

Fibrates should not be used routinely for the secondary prevention of stroke. (Zhou et al 2013 *[104]*; Wang et al 2015 *[103]*)

## Carotid surgery

Strong Recommendation

- Carotid endarterectomy is recommended for patients with recent (<3 months) non-disabling carotid artery territory ischaemic stroke or TIA with ipsilateral carotid stenosis measured at 70-99% (NASCET criteria) if it can be performed by a specialist team with audited practice and a low rate (<6%) of perioperative stroke and death.
- Carotid endarterectomy can be considered in selected patients with recent (<3 months) non-disabling ischaemic stroke or TIA patients with symptomatic carotid stenosis of 50–69% (NASCET criteria) if it can be performed by a specialist team with audited practice and a very low rate (<3%) of perioperative stroke and death.
- Carotid endarterectomy should be performed as soon as possible (ideally within two weeks) after the ischaemic stroke or TIA.
- All patients with carotid stenosis should be treated with intensive vascular secondary prevention therapy.

(Bangalore et al 2011 *[137]*, Rerkasem & Rothwell 2011 *[152]*)

Weak Recommendation

- Carotid endarterectomy should be performed in preference to carotid stenting due to a lower perioperative stroke risk. However, in selected patients with unfavourable anatomy, symptomatic re-stenosis after endarterectomy or previous radiotherapy, stenting may be reasonable.
- In patients aged <70 years old, carotid stenting with an experienced proceduralist may be reasonable.

(Bangalore et al 2011 *[137]*)

Weak Recommendation Against

In patients with asymptomatic carotid stenosis, carotid endarterectomy or stenting should not be performed. (Rosenfield et al 2016 *[126]*; Raman et al 2013 *[133]*; Bangalore et al 2011 *[137]*)

Strong Recommendation Against

In patients with symptomatic carotid occlusion, extracranial/ intracranial bypass is not recommended. (Powers et al 2011 *[138]*; Fluri et al 2010 *[141]*)

## Cervical artery dissection

Strong Recommendation

Patients with acute ischaemic stroke due to cervical arterial dissection should be treated with antithrombotic therapy. There is no clear benefit of anticoagulation over antiplatelet therapy. (CADISS 2015 *[153]*)

## Cerebral venous sinus thrombosis

Strong Recommendation

Patients with cerebral venous sinus thrombosis (CVST) without contraindications to anticoagulation should be treated with either body weight-adjusted subcutaneous low molecular weight heparin or dose-adjusted intravenous heparin, followed by warfarin, regardless of the presence of intracerebral haemorrhage. (Coutinho et al 2011 *[162]*; Misra et al 2012 *[163]*; Afshari et al 2015 *[164]*)

Practice Statement

**Consensus-based recommendations**

- In patients with CVST, the optimal duration of oral anticoagulation after the acute phase is unclear and may be taken in consultation with a haematologist.
- In patients with CVST with an underlying thrombophilic disorder, or who have had a recurrent CVST, indefinite anticoagulation should be considered.
- In patients with CVST, there is insufficient evidence to support the use of either systemic or local thrombolysis.
- In patients with CVST and impending cerebral herniation, craniectomy can be used as a life-saving intervention.
- In patients with the clinical features of idiopathic intracranial hypertension, imaging of the cerebral venous system is recommended to exclude CVST.

## Diabetes management

Recommendation Strength Not Set

**Practice point**

Patients with glucose intolerance or diabetes should be managed in line with Diabetes Australia Best Practice Guidelines.

## Patent foramen ovale management

Strong Recommendation

Patients with ischaemic stroke or TIA and PFO should receive optimal medical therapy including antiplatelet therapy or anticoagulation if indicated. (Romoli et al 2020 *[187]*; Sagris et al 2019 *[186]*)

Strong Recommendation

In patients with ischaemic stroke aged <60 in whom a patent foramen ovale is considered the likely cause of stroke after thorough exclusion of other aetiologies, percutaneous closure of the PFO is recommended (Turc et al 2018 *[175]*, Saver et al 2018 *[177]*).

## Hormone replacement therapy

Practice Statement

**Consensus-based recommendation**
In patients with stroke or TIA, continuation or initiation of hormone replacement therapy is not recommended, but will depend on discussion with the patient and an individualised assessment of risk and benefit. (Boardman et al 2015 *[188]*; Yang et al 2013 *[189]*; Marjoribanks et al 2012 *[190]*; Nudy et al 2019 *[191]*)

## Oral contraception

Weak Recommendation

For women of child-bearing age who have had a stroke, non-hormonal methods of contraception should be considered. If systemic hormonal contraception is required, a non-oestrogen containing medication is preferred. (Roach et al 2015 *[192]*; Plu-Bureau 2013 *[193]*; Peragallo et al 2013 *[194]*; Li et al 2019 *[196]*)

Practice Statement

**Consensus-based recommendation**
For women of child bearing age with a history of stroke or TIA, the decision to initiate or continue oral contraception should be discussed with the patient and based on an overall assessment of individual risk and benefit.

## Lifestyle modifications

Recommendation Strength Not Set

**Practice point**
All patients with stroke or TIA (except those receiving palliative care) should be assessed and informed of their risk factors for recurrent stroke and strategies to modify identified risk factors. This should occur as soon as possible and prior to discharge from hospital.

## Smoking

Recommendation Strength Not Set

**Practice point**
Patients with stroke or TIA who smoke should be advised to stop and assisted to quit in line with existing guidelines, such as Supporting smoking cessation: a guide for health professionals. (RACGP 2014 *[202]*)

## Diet

Recommendation Strength Not Set

**Practice point**

- Patients with stroke or TIA should be advised to manage their dietary requirements in accordance with the Australian Dietary Guidelines. (NHMRC 2013 *[203]*)
- All patients with stroke should be referred to an Accredited Practising Dietitian who can provide individualised dietary advice.

## Physical activity

Recommendation Strength Not Set

**Practice point**

Patients with stroke or TIA should be advised and supported to undertake appropriate, regular physical activity as outlined in one of the following existing guidelines:

- Australia's Physical Activity & Sedentary Behaviour Guidelines for Adults (18-64 years) (Commonwealth of Australia 2014 *[207]*) OR
- Physical Activity Recommendations for Older Australians (65 years and older) (Commonwealth of Australia 2014 *[208]*).

## Obesity

Recommendation Strength Not Set

**Practice point**

Patients with stroke or TIA who are overweight or obese should be offered advice and support to aid weight loss as outlined in the Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults, Adolescents and Children in Australia (NHMRC 2013 *[211]*).

## Alcohol

Recommendation Strength Not Set

**Practice point**

People with stroke or TIA should be advised to avoid excessive alcohol consumption (>2 standard drinks per day) in line with the Australian Guidelines to Reduce Health Risks from Drinking Alcohol. (NHMRC 2009 *[215]*)

## Glossary and abbreviations

## Introduction

The Stroke Foundation is a national charity that partners with the community to prevent, treat and beat stroke. We stand alongside stroke survivors and their families, healthcare professionals and researchers. We build community awareness and foster new thinking and innovative treatments. We support survivors on their journey to live the best possible life after stroke.

We are the voice of stroke in Australia and we work to:
- Raise awareness of the risk factors, signs of stroke and promote healthy lifestyles.
- Improve treatment for stroke to save lives and reduce disability.
- Improve life after stroke for survivors.
- Encourage and facilitate stroke research.
- Advocate for initiatives to prevent, treat and beat stroke.
- Raise funds from the community, corporate sector and government to continue our mission.

The Stroke Foundation has been developing stroke guidelines since 2002 and in 2017 released the fourth edition. In order for the Australian Government to ensure up-to-date, best-practice clinical advice is provided and maintained to healthcare professionals, the NHMRC requires clinical guidelines be kept current and relevant by reviewing and updating them at least every five years. As a result, the Stroke Foundation, in partnership with Cochrane Australia, is testing a model of living guidelines, in which recommendations are continually reviewed and updated in response to new evidence. This project commenced in July 2018 and is currently being funded by the Australian Government via the Medical Research Future Fund.

This online version of the Clinical Guidelines for Stroke Management updates and supersedes the Clinical Guidelines for Stroke Management 2017. The Clinical Guidelines have been updated in accordance with the 2011 NHMRC Standard for clinical practice guidelines and therefore recommendations are based on the best evidence available. The Clinical Guidelines cover the whole continuum of stroke care, across 8 chapters.

Review of the Clinical Guidelines used an internationally recognised guideline development approach, known as GRADE (**G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation), and an innovative guideline development and publishing platform, known as MAGICapp (**Ma**king **G**rade the **I**rresistible **C**hoice). GRADE ensures a systematic process is used to develop recommendations that are based on the balance of benefits and harms, patient values, and resource considerations. MAGICapp enables transparent display of this process and access to additional practical information useful for guideline recommendation implementation.

**Purpose**
The *Clinical Guidelines for Stroke Management* provides a series of best-practice recommendations to assist decision-making in the management of stroke and transient ischaemic attack (TIA) in adults, using the best available evidence. The Clinical Guidelines should not be seen as an inflexible recipe for stroke management; rather, they provide a guide to appropriate practice to be followed subject to clinical judgment and patient preferences.

**Scope**
The Clinical Guidelines cover the most critical topics for effective management of stroke, relevant to the Australian context, and include aspects of stroke management across the continuum of care including pre-hospital, assessment and diagnosis, acute medical and surgical management, secondary prevention, rehabilitation, discharge planning, community participation, and management of TIA. Some issues are dealt with in more detail, particularly where current management is at variance with best practice, or where the evidence needs translation into practice.

The Clinical Guidelines do not cover:
- Subarachnoid haemorrhage;
- Stroke in infants, children and youth, i.e. <18 years old (refer to Australian Childhood Stroke Advisory Committee, Guideline for the diagnosis and acute management of childhood stroke – 2017, and Victorian Subacute Childhood Stroke Advisory Committee, Guideline for the subacute management of childhood stroke – 2019, https://informme.org.au/Guidelines/Childhood-stroke-guidelines); or
- Primary prevention of stroke. (Refer to *Guidelines for the management of absolute cardiovascular disease risk 2012* (National Vascular Disease Prevention Alliance *[5]*) - https://informme.org.au/en/Guidelines/Guidelines-for-the-assessment-and-management-of-absolute-CVD-risk, and *Guideline for the diagnosis and management of hypertension in adults 2016* (Heart Foundation *[6]*) - https://www.heartfoundation.org.au/for-professionals/clinical-information/hypertension).

**Target audience**
The Clinical Guidelines are intended for use by healthcare professionals, administrators, funders and policy makers who plan, organise and deliver care for people with stroke or TIA during all phases of recovery.

**Development**
The Guidelines are published in eight separate chapters:
Pre-hospital care
Early assessment and diagnosis

Acute medical and surgical management
Secondary prevention
Rehabilitation
Managing complications
Discharge planning and transfer of care
Community participation and long-term care

The Clinical Guidelines have been developed according to processes prescribed by the National Health and Medical Research Council (NHMRC) under the direction of an interdisciplinary working group. Refer to the document on InformMe that details the Interdisciplinary Working Group Membership and Terms of Reference.

**Use**
The primary goal of the Clinical Guidelines is to help healthcare professionals improve the quality of the stroke care they provide. Refer to documents on InformMe that provide 2-page summaries of the Clinical Guidelines – one for healthcare professionals, and one for consumers.

Guidelines differ from clinical or care pathways (also referred to as critical pathways, care paths, integrated care pathways, case management plans, clinical care pathways or care maps). Guidelines are an overview of the current best evidence translated into clinically relevant statements. Care pathways are based on best practice guidelines but provide a local link between the guidelines and their use.

In considering implementation of the Guidelines at a local level, healthcare professionals are encouraged to identify the barriers, enablers and facilitators to evidence-based practice within their own environment and determine the best strategy for local needs. Where change is required, initial and ongoing education is essential and is relevant to all recommendations in the Guidelines.

Refer to the document on InformMe that summarises all the Clinical Guidelines recommendations.

**Aboriginal and Torres Strait Islander People**
Refer to the document on InformMe for information regarding Aboriginal and Torres Strait Islander people.

**Decision-making**
Stroke survivors should be treated in accordance with the principles of shared decision-making contained within the *Acute Stroke Care Clinical Standard*, *Acute Stroke Services Framework 2019* and *Rehabilitation Stroke Services Framework 2013*, which include, among other things, that treatment should be patient-centred. Therefore, stroke survivors should be involved in decisions about their care at all times; but where they do not have capacity, or have limited capacity, family members should be involved in the decision-making.

**Consent**
The principles of informed consent underpin these Clinical Guidelines and therefore the wording of the recommendations are directed at the healthcare professional; that is, the intervention should/may be used, rather than offered, for the stroke patient. For patients with aphasia and/or cognitive disorders requiring formal consent, easy English or aphasia-friendly written versions of an information sheet and consent form should be offered and clearly explained to patients and their families in order to assist understanding and agreement.

**Endorsement**
The Clinical Guidelines have been endorsed (based on the 2017 version) by a number of organisations and associations. Refer to the document on InformMe that details the organisations formally endorsing the Clinical Guidelines.

**Evidence gaps**
Refer to the document on InformMe that details the gaps in evidence identified, noting areas for futher research.

**Reports**
Refer to documents on InformMe - Technical Report, Administrative Report and Dissemination and Implementation Report.

**Resources**
Refer to documents on InformMe that provide supporting resources to assist with implementation of the Clinical Guidelines.

**Publication Approval**

**Australian Government**
**National Health and Medical Research Council**

These guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 25 July 2017, with subsequent amendments approved on 22 November 2017, 9 July 2018 (updated recommendations for Neurointervention), and 7 November 2019 (updated recommendations for Thrombolysis, Acute antiplatelet therapy, and Patent foramen ovale management) under Section 14A of the National Health and Medical Research Council Act 1992. In approving the guidelines recommendations the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that the guideline recommendations are systematically derived, based on identification and synthesis of the best available scientific evidence and are developed for health professionals practising in an Australian health care setting.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

Disclaimer
These Clinical Guidelines are a general guide to appropriate practice, to be followed subject to the clinician's judgment and the patient's preference in each individual case. The Clinical Guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of development.

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## Methodology

# Brief summary of GRADE

The Clinical Guidelines were developed following the GRADE methodology (Grading of Recommendations, Assessment, Development and Evaluation).

GRADE methodology includes four factors to guide the development of a recommendation and determine the strength of that recommendation:
1. The balance between desirable and undesirable consequences.
2. Confidence in the estimates of effect (quality of evidence).
3. Confidence in values and preferences and their variability (clinical and consumer preferences).
4. Resource use (cost and implementation considerations).

For full details of how GRADE is used for developing clinical recommendations, refer to the GRADE handbook, available at: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html.

# Strength of recommendations

The GRADE process uses only two categories for the strength of recommendations, based on how confident the guideline panel is that the "desirable effects of an intervention outweigh undesirable effects [...] across the range of patients for whom the recommendation is intended" (GRADE Handbook):

- **Strong** recommendations: where guideline authors are certain that the evidence supports a clear balance towards either desirable or undesirable effects; or
- **Weak** recommendations: where the guideline panel is uncertain about the balance between desirable and undesirable effects.

These strong or weak recommendations can either be for or against an intervention. If the recommendation is against an intervention this means it is recommended NOT to do that intervention. There are a number of recommendations where we have stated that the intervention may only be used in the context of research. We have done this because these are guidelines for clinical practice, and while the intervention cannot be recommended as standard practice at the current time, we recognise there is good rationale to continue further research.

The implications of a strong or weak recommendation for a particular treatment are summarised in the GRADE handbook as follows:
*Table 1: Implications of GRADE recommendation categories (for a positive recommendation) for patients, clinicians and policy makers. Source: GRADE Handbook (http://gdt.guidelinedevelopment.org/app/handbook/handbook.html)*

| | Strong Recommendation | Weak Recommendation |
|---|---|---|
| **For patients** | Most individuals in this situation would want the recommended course of action and only a small proportion would not. | The majority of individuals in this situat the suggested course of action, but ma |
| **For clinicians** | Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. | Recognise that different choices will be different patients, and that you must he arrive at a management decision consis his values and preferences. Decision aid useful helping individuals making decisi with their values and preferences. Clini expect to spend more time with patien towards a decision. |
| **For policy makers** | The recommendation can be adapted as policy in most situations including for the use as performance indicators. | Policy making will require substantial d involvement of many stakeholders. Poli more likely to vary between regions. Pe indicators would have to focus on the f adequate deliberation about the manag has taken place. |

For topics where there is either a lack of evidence or insufficient quality of evidence on which to base a recommendation but the guideline panel believed advice should be made, statements were developed based on consensus and expert opinion (guided by any underlying or indirect evidence). These statements are labelled as 'Practice statements' and correspond to 'consensus-based recommendations' outlined in the NHMRC procedures and requirements.

For topics outside the search strategy (i.e. where no systematic literature search was conducted), additional considerations are provided. These are labelled 'Info Box' and correspond to 'practice points' outlined in the NHMRC procedures and requirements.

**Explanation of absolute effect estimates used**
The standardised evidence profile tables presented in the Clinical Guidelines include "Absolute effect estimates" for dichotomous outcomes. These represent the number of people per 1000 people expected to have the outcome in the control and intervention groups. This estimated risk in people receiving the intervention is based on a relative effect estimate which might be adjusted, e.g. to account for baseline differences between participants or when effect estimates have been pooled from different studies in a systematic review and adjusted to account for the variance of each individual estimate. Therefore, this estimated risk in the intervention group may differ from the raw estimate of the intervention group risk from the corresponding study. The estimated risk reflects the best estimate of the risk in the relevant population, relative to the risk observed among patients receiving the control or comparator intervention.

Wherever possible (i.e. when the relevant study reported enough information to allow the calculation to be done), these estimates were calculated using the following procedure:
1. Obtain the relative effect estimate (odds ratio or relative risk) and confidence interval from the best available study (systematic review or primary study) providing evidence about the effects of the intervention.
2. Use the observed number of events in the control group of the same study to calculate a baseline risk per 1000 people (or "assumed control risk").
3. Calculate an estimate of the corresponding risk per 1000 in people receiving the intervention using the relative effect estimate. This can be done using methods based on the formulas for calculating absolute risk reductions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (http://handbook.cochrane.org/). Applying the same calculations to the upper and lower bounds of the confidence interval for the relative effect estimate gives a confidence interval for the risk in the intervention group, which is then used to calculate the confidence interval for the difference per 1000 people, reported in the evidence tables.

**Cost effectiveness summaries**
There are several important points to consider when interpreting the cost-effectiveness information provided in the *Resources and Other Considerations* sections of the Clinical Guidelines.

Firstly, an intervention can be cost-effective without being cost-saving. This means that although there is an additional cost for the health benefits gained from the intervention, the intervention is still considered worthwhile. The incremental cost-effectiveness ratios (ICER) presented (e.g. cost per quality adjusted life year gained) are an indication of the cost-effectiveness or "value-for-money", with lower ICERs indicating better cost-effectiveness of an intervention.

Secondly, whether or not the intervention is cost-effective is a judgment call; and should reflect a society's willingness-to-pay to have the intervention for the potential outcomes achieved. An ICER that is approximately or equivalent to US$50,000 has been commonly used by researchers in the past as a threshold for judging an intervention as being cost-effective (http://www.nejm.org/doi/full/10.1056/NEJMp1405158#t=article). However, no scientific basis for this threshold exists and actual willingness-to-pay may differ. For example, in a survey of 1000 Australian respondents conducted in 2007, the willingness-to-pay for an additional quality adjusted life year in Australia was estimated to be $64,000 (https://www.ncbi.nlm.nih.gov/pubmed/19382128).

Thirdly, there is no absolute threshold for determining whether an intervention should be funded based on the ICER (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5153921/). ICERs are only one of the major factors considered in priority setting (the process to decide which interventions should be funded within a given resource constraint). Other considerations include affordability, budget impact, fairness, feasibility and other factors that are important in the local context (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5153921/).

Lastly, in areas where there are no data from economic evaluations that support the recommendations or practice statements, it remains unclear whether the additional costs of providing the intervention above usual care for the additional potential benefits obtained is justified. However, this should not detract from implementing the Clinical Guideline recommendations.

**Use of language related to timing of interventions**
***Immediate*:** without delay, or within minutes, not hours (life critical action required).
***Urgent*:** minutes to several hours (immediate action but not life critical).
***Very early:*** within hours and up to 24 hours.
***Early*:** within 48 hours.

For all Clinical Guideline recommendations we make the assumption that healthcare professionals will be appropriately qualified and skilled to carry out the intervention.

## Clinical questions

4.1 What strategies improve concordance with medication to improve outcomes for people with stroke?

4.2 What blood pressure lowering interventions lower the risk of strokes after stroke or TIA?

4.3 What antiplatelet therapies lower the risk of stroke after stroke or TIA?

4.4 What interventions improve outcomes for people with atrial fibrillation after stroke or TIA?

4.5 What cholesterol lowering therapies lower the risk of strokes after stroke or TIA?

4.6 What interventions improve the outcomes for patients with carotid stenosis after stroke or TIA?

4.7 What interventions improve outcomes for people with cervical artery dissection?

4.8 What interventions improve outcomes for those with venous sinus thrombosis?

4.9 What interventions in patent foramen ovale management lower the risk of further strokes in stroke survivors?

4.10 Does hormone replacement therapy increase the risk of subsequent stroke in stroke survivors?

4.11 Does oral contraception increase the risk of subsequent stroke in stroke survivors?

## Secondary prevention - overview

A patient with stroke has an accumulated risk of subsequent stroke of 43% over 10 years, with an annual rate of approximately 4% (Hardie et al. 2004 *[7]*). Secondary prevention strategies should be considered for all patientswith stroke or TIA who are not receiving palliative care. Long-term management of risk factors, particularly medication adherence, is the primary role of GPs with support from primary care-based allied health practitioners (e.g. practice nurses, community pharmacists). Good communication between secondary and primary carers is essential.

## Adherence to pharmacotherapy

Failure to adhere to prescribed medication continues to be a major barrier to the secondary prevention of stroke. In one large Swedish cohort, the proportion of patients who continued using hospital-prescribed medication after two years was 74.2% for antihypertensives, 56.1% for statins, 63.7% for antiplatelet agents, and 45.0% for warfarin (Glader et al 2010 *[19]*). A systematic review reported that, in Europe, as much as 9% of all cardiovascular events are directly attributable to poor adherence to vascular medications (Jamison et al 2016 *[20]*). Specific data regarding medication adherence in Australian patients with stroke is lacking, however, a meta-analysis of local studies highlights that non-adherence to cardiovascular medications, in general, is high; in the older population, the overall prevalence of non-adherence is 14 to 43% (McKenzie et al 2015 *[21]*).

Information about the specific barriers to medication adherence among patients with stroke is also relatively scarce. However, beliefs about medication, concerns about side-effects, limited knowledge of stroke prevention therapies, inadequate provision of information, inability to self-care, difficulties taking medication, the tendency of the patient with stroke to trivialise stroke, and burden of treatment, have all been cited as key barriers to medication adherence (Kronish et al 2014 *[9]*).

Weak Recommendation

Interventions to promote adherence with medication regimens may be provided to all patients with stroke. Such regimens may include combinations of the following:

- reminders, self-monitoring, reinforcement, counselling, motivational interviewing, family therapy, telephone follow-up, supportive care and dose administration aids (Lawrence et al 2015 *[8]*; Mahtani et al 2011; Nieuwlaat et al 2014 *[14]*; Haynes et al 2008 *[13]*)
- development of self-management skills and modification of dysfunctional beliefs about medication (O'Carroll et al 2014 *[10]*; Kronish et al 2014 *[9]*)
- information and education in hospital and in the community (Lawrence et al 2015 *[8]*; Mahtani et al 2011 *[16]*; Nieuwlaat et al 2014 *[14]*).

### Key Info

**Benefits and harms**

Substantial net benefits of the recommended alternative

A review of 23 studies demonstrated that behavioural interventions improved medication adherence to antithrombotic medications (OR 1.45, 95% CI 1.21 to 1.75), and statins (OR 2.53, 95% CI 2.15 to 2.97) (Lawrence et al 2015 *[8]*). There was no significant difference in antihypertensive adherence (OR 0.93, 95% CI 0.76 to 1.13). There were no harms reported.

**Certainty of the Evidence**

Moderate

The quality of the evidence was low for overall medication adherence but moderate for adherence to antithrombotics, statins and antihypertensive medication. This was due to serious risk if bias resulting from poor allocation concealment, lack of allocation blinding and selective outcome reporting in many trials.

**Preference and values**

No substantial variability expected

Marshall et al (2012) *[22]* synthesised findings from qualitative studies of patient's understanding and experience of hypertension and drug taking to investigate whether there were cultural or ethnic differences that needed to be considered in the development of interventions that could improve adherence. They conducted a systematic review and narrative syntheses of 59 papers reporting 53 qualitative studies from 16 countries using the 2006 UK Economic and Social Research Council research methods as a guide. Of the 59 papers that met the inclusion criteria forty used one to one qualitative interviews, 11 used focus groups, and two used a mixture of these methods. Twenty four of the 53 studies included people from ethnic minority groups. The areas covered included, patient's understanding of causes, effects, exacerbating factors, and consequences of hypertension; attitudes to drugs and perceived influences of stress, diet and racism. The studies included were assessed as generally of high quality (mean quality score of 9.8 out of 11) and were limited to peer reviewed publications. In addition sensitivity analysis was undertaken for the key themes of connecting hypertension with stress, having symptoms, using symptoms to judge blood pressure levels, and taking drugs only when symptoms are present. This review methodology has features suggesting that the results can be regarded as robust. The key findings are that patient's perspectives differ from medical viewpoints but do not differ across cultural and ethnic groups, although there was some bias toward US ethnic minorities. The commonly held beliefs reported were that: hypertension is principally a stress related condition with symptoms

and; a fear of addiction and dependence on drugs often leads to intentional non-adherence.

Horne et al (2013) *[23]* reports the findings of a systematic review and meta analysis of 94 studies selected from 3,777 studies that used the validated Beliefs about Medicines Questionnaire (BMQ). This meta analysis was undertaken to consolidate results from these studies to examine the usefulness of grouping patient's beliefs under two categories; perceptions of personal need for treatment (Necessity beliefs) and Concerns about a range of adverse consequences. They assess whether the Necessity Concerns Framework is predictive of adherence to medication for long term medical conditions. The total sample size across the included studies was 25,072, encompassing patients from a broad range of long term illnesses including chronic diseases, mental health and a small number related to stroke patients. The majority of studies were cross sectional (81.9%) with few studies using longitudinal or prospective designs. Eighty three studies (88.3%) measured adherence using self report and most studies were conducted outside the UK (66%). Substantial and significant heterogeneity was present in all analyses. The authors acknowledge the limitations of the research design of the primary studies in their analysis but found when they conducted a number of sensitivity analyses that the associations they report were robust. The key findings of this meta analysis was that across the studies there was a strong association to adherence and the perceptions by the patient of the necessity for treatment, OR=1.742,95% CI (1.596, 1.934) and fewer concerns about treatment, OR=0.504, 95% CI (0.450,0.564). The association between Necessity and Concerns with adherence to medication remained significant across study size, country and type of adherence measure used.

Chee et al (2014) *[24]* presents a literature review of 58 studies of 122 identified that aimed to determine patient's perceptions of statins and the impact of these perceptions on statin use and adherence. The studies included original research of patient's perceptions of factors that influenced their use of statins and intervention based studies, randomised and non randomised controlled trials and meta analyses. The interventions included patient education, medication reminders, medication cost management and enhancement of patient –physician communication. The analysis was undertaken by categorising the results of the literature review to the key components of the Health Belief Model (HBM) that has shown that patient's health related decisions are likely to be based of the following factors a) perceived susceptibility to a serious health problem, b) perceived severity of the illness, c) perceived benefits of the treatment in reducing susceptibility to a serious health problem, and d) perceived barriers restricting patient's use of treatment. The findings of their literature review confirmed an association with the categories in the HBM that are then discussed along with possible strategies to overcome these patient related factors. They conclude that a patient centric approach that addressed perceived severity and susceptibility of the health problem and the perceived benefits and barriers of taking preventive medication, in this case statins, could be achieved through education initiatives and stronger health care partnerships and shared decision making between physicians and patients.

**Resources and other considerations**

No important issues with the recommended alternative

<u>Resources considerations</u>

There is no direct evidence of cost-effectiveness of adherence interventions in the Australian stroke population. However, Chung et al (2014) *[18]* found, using Markov decision analytic modelling, that therapeutic drug monitoring to address medication non-adherence was a cost-effective healthcare intervention in patients diagnosed with resistant hypertension in a European setting. Compared to control, therapeutic drug monitoring cost at an additional cost of €3,602 per QALY in men and €4,043 per QALY in women (cost reference year 2014)

## Rationale

There is evidence that 'multimodal' behavioural interventions improve medication adherence overall and there was significant improvement for antithrombotics and statins but not for antihypertensives (Lawrence et al 2015 *[8]*). The quality of evidence is low to moderate due to risk of bias due to poor allocation concealment, lack of allocation blinding and selective outcome reporting present in many trials. No harms were reported with any of the interventions.

## Clinical Question/ PICO

**Population:** Adults with stroke

**Intervention:** Behavioural, educational or organisations interventions designed to improve medication adherence/ concordance

**Comparator:** Usual care or modified usual care

## Summary

Lawrence et al (2015) *[8]* conducted a systematic review and meta-analysis of 'multimodal' behavioural interventions for secondary stroke preventions. These multimodal interventions included medication and/or medication adherence education, education about stroke and stroke risk factors, and attempted to address lifestyle behaviours such as smoking or physical activity or medication adherence and stress management behaviours. Twenty-three studies reporting results from 20 RCTs were included, generally comparing behavioural interventions to 'usual care'. The overall risk of bias for the included RCTs was judged as being high or unclear, with poor allocation concealment, lack of allocation blinding and selective outcome reporting present in many trials. Meta-analysis found significantly lower systolic and diastolic blood pressure in intervention groups, but no significant differences in other physiological outcomes such as HDL, LDL and total cholesterol, blood glucose or BMI. In terms of medication adherence, adherence with antithrombotic medications showed a significant increase (OR 1.45, 95% CI 1.21 to 1.75), as did statins (OR 2.53, 95% CI 2.15 to 2.97). There was no significant difference in antihypertensive adherence, (OR 0.93, 95% CI 0.76 to 1.13). The interventions in included studies varied considerably in format, duration and length of follow-up, and the lack of consistency in outcome measures meant that results could generally only be pooled across small numbers of trials.

Other recent trials assessing interventions to promote medication adherence and stroke prevention include:

Kronish et al (2014) *[9]* conducted a randomised clinical trial (N = 600) of a peer-led, community-based stroke prevention self-management group workshop for preventing secondary stroke. The workshop was a 6-week peer-led community-based education program, comprising weekly group workshops focusing on development of self-management skills for those with a prior stroke / TIA in low-income minority groups. It provided education about stroke biology, emphasised adherence to preventative medication and suggested ways to optimise adherence. The wait-list control group received written stroke education materials and a list of healthcare providers. The primary outcome was a composite outcome requiring patients to have blood pressure < 140/90 mmHg, LDL cholesterol < 100mg/dL and use of antithrombotics. At both 3 and 6 month follow-ups, there was no difference between intervention and control groups on this composite outcome (6 month RR 1.00, 95% CI 0.80 to 1.25). Analysing the individual components of this outcome, there were no differences in controlled LDL cholesterol or the proportion of participants taking antithrombotic medications at either follow-up. However, the intervention group showed a slight but significant increase in controlled blood pressure at 6 months (RR 1.13, 95% CI 1.02-1.25). The study sample (recruited in the Upper Manhattan and South Bronx neighbourhoods in New York City) contained high proportions of nonwhite (86%) and low-income participants, and the intervention was specifically aimed at reducing recurrent stroke in Black and Latino stroke survivors. Therefore, the results of the study may not generalise to Australian populations. There was also substantial loss to follow-up, with only 85% completing the 6-month follow-up assessments, and loss to follow-up appeared to be higher in the intervention group (59/301 lost) than the control group (33/299 lost).

MacKenzie et al (2013) *[11]* assessed a cluster of nurse-led case management interventions for improving blood pressure management and medication adherence in a multicentre randomised controlled trial (N = 56). The intervention included specialist assessment, monthly telephone calls from advanced practice nurses employing motivational interviewing techniques to encourage risk factor reduction, home blood pressure monitoring and medication administration aids including dosette boxes. The usual care control group received adherence and risk factor counselling during clinic visits and follow-up contact from family physicians. The primary outcome was lowered blood pressure, with a target reduction of >= 6mmHg systolic at 6 month follow-up. The intervention group showed a higher proportion of patients meeting blood pressure targets at 6 months (59% vs 37%) but the difference was non-significant. The difference in systolic blood pressure reduction was also non-significant. Medication adherence was assessed both through the self-reported number of missed pills and by a community pharmacist who reviewed participants' prescription renewals and judged whether they were adherent >= 80% of the time. Neither measure showed significant between-group differences at 6 months.

The study focussed on patients with psychosocial or cognitive deficits, and had inclusion criteria including a score < 26 on the Montreal Cognitive Assessment (MoCA). The effects of adherence interventions may be different in patients without cognitive deficits. There was also a suggestion of baseline imbalance, with participants in the usual care group showing significantly lower MoCA scores. The sample size for the study was small, with wide confidence intervals around effect estimates, meaning there is a large degree of uncertainty about the results obtained.

O'Carroll et al (2013) *[10]* reported on a pilot randomised controlled trial (N = 62) of an intervention that emphasised 'implementation intentions' (medication-taking behaviour) and 'modifying dysfunctional beliefs' (medication beliefs). The aim was to increase medication adherence, for antihypertensives specifically, in patients at risk of a secondary stroke. The intervention was delivered in two sessions where a research fellow first helped patients establish a medication routine based around a specific time, place and situation, and then addressed and challenged mistaken beliefs about the patients' illness and medication in the second session. The control group also received two visits from a research fellow but were

engaged in non-medication-related conversation. The primary outcomes were medication adherence outcomes, measured using an electronic pill bottle (MEMS) that recorded pills used and recorded at 1, 2 and 3 months. The intervention group showed a higher percentage of doses taken, percentage of days where the correct dose was taken, and percentage of doses taken on schedule, but only the difference in doses taken on schedule was significant (MD: 9.8%, 95% 0.2 to 16.2%). The intervention group also showed significantly greater self-reported medication adherence (Medication Adherence Report Scale). There were no between-group differences in systolic or diastolic blood pressure. Assessment of beliefs about illness and medication showed that the intervention group showed a greater decrease in concerns about medication as assessed by the Beliefs about Medication Questionnaire.

The sample size for the study was small, and all participants were 'white caucasian', generally from higher socioeconomic groups with higher baseline medication adherence than in other trials. The participants in the RCT also had significantly higher socioeconomic status than people who had completed the same initial survey but did not participate.

An earlier Cochrane review by Haynes et al (2008) *[13]* assessed randomised trials promoting medication adherence, but was not restricted to patients with stroke. Due to the heterogeneity in patient populations, interventions and outcome measures in studies, the review authors carried out a qualitative analysis. 10 RCTs were found investigating short term treatments, with 5 showing significantly greater adherence and 4 showing both greater adherence and at least one improved clinical outcome. Out of 83 long term interventions reported in 70 RCTs, less than half (36/83) showed improved adherence, and only 25/83 showed improvement in clinical outcomes. The long term treatments that were effective were generally intensive and complex and involved multiple different factors, including information, reminders, counselling, telephone follow-up and supportive care. Even these effective treatments generally did not show large improvements in adherence or clinical outcomes. These results suggest the effectiveness of complex multimodal interventions of the kinds used in the above trials, but also the potential to improve adherence interventions through innovations in treatment methods and better methods of addressing barriers to adherence.

This review was updated by Nieuwlaat et al (2014) *[14]*, who found 109 additional RCTs, but found that their conclusions only changed slightly. Assessing trials according to their risk of bias, there was a lack of convincing evidence in trials with low risk of bias, with only a minority reporting improved adherence and clinical outcomes. These trials generally involved complex interventions that may not be suitable for implementation on a broad scale.

Mahtani et al (2011) *[16]* conducted a Cochrane review of medication packaging that updated an earlier review by Heneghan et al (2006) *[15]* , including 12 RCTs of which 4 were newly included. This review was again not specific to the stroke population. Reminder packaging included pill boxes divided by day of the week or calendar blister packaging. Adherence, assessed in terms of the percentage of pills taken, increased significantly in intervention groups (MD 11%, 95% CI 6 to 17%). Blood pressure outcomes were only available in 2 trials, with meta-analysis showing a non-significant decrease in systolic blood pressure but significantly reduced diastolic blood pressure. The review authors judged that only 2 included trials were of high quality, highlighting issues with randomisation, confounding and follow-up that create serious risks of bias.

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Usual care or modified usual care | Behavioural/ educational/ organisational interventions | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Medication adherence - statins** Post-treatment | Odds Ratio 2.53 (CI 95% 2.15 - 2.97) Based on data from 2,636 patients in 3 studies. (Randomized controlled) Follow up 3 to 12 months, 1 unknown | 352 per 1000 | 579 per 1000 Difference: 227 more per 1000 ( CI 95% 187 more - 265 more ) | **Moderate** Due to serious risk of bias [1] | Behavioural interventions probably improve medication adherence for statins |
| **Medication adherence - overall** | Odds Ratio 1.1 (CI 95% 0.71 - 1.71) Based on data from 456 | 773 per 1000 | 789 per 1000 | **Low** Due to serious inconsistency, | Behavioural interventions may improve medication |

| | | | | |
|---|---|---|---|---|
| Post-treatment | patients in 2 studies. (Randomized controlled) Follow up 3 to 6 months of treatment | Difference: **16 more** per 1000 ( CI 95% 66 fewer - 80 more ) | Due to serious imprecision [2] | adherence slightly |
| **Medication adherence - antithrombotics** Post-treatment | Odds Ratio 1.45 (CI 95% 1.21 - 1.75) Based on data from 2,756 patients in 2 studies. (Randomized controlled) Follow up 3 months, unknown | **753** per 1000 **816** per 1000 Difference: **63 more** per 1000 ( CI 95% 34 more - 89 more ) | **Moderate** Due to serious risk of bias [3] | Behavioural interventions probably improve medication adherence for antithrombotics |
| **Medication adherence - antihypertensives** Post-treatment | Odds Ratio 0.93 (CI 95% 0.76 - 1.13) Based on data from 2,028 patients in 3 studies. (Randomized controlled) Follow up 3 to 10 months, 1 unknown | **729** per 1000 **714** per 1000 Difference: **15 fewer** per 1000 ( CI 95% 57 fewer - 23 more ) | **Moderate** Due to serious risk of bias [4] | Behavioural interventions probably have little or no difference on medication adherence for antihypertensives |

1. **Risk of bias: Serious.** High or unclear risk of bias for most problem areas for 2 of the 3 studies, including the largest study. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
2. **Risk of bias: No serious.** Inadequate/lack of blinding of outcome assessors in 1 study, resulting in potential for detection bias. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 73%.. **Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
3. **Risk of bias: Serious.** Unclear or high risk of bias for most problem areas in the largest study. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
4. **Risk of bias: Serious.** Unclear or high risk of bias in the largest study, some risk of bias in others. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

## Clinical Question/ PICO

**Population:** Adults with stroke
**Intervention:** Organisational interventions
**Comparator:** Usual care


### Summary

A Cochrane review by Lager et al (2014) *[17]* included 15 randomised trials of organisational interventions for improving risk factor control in secondary stroke prevention. The organisational interventions involved integrated care services and multidisciplinary collaboration, as well as some education for patients and service providers. There non-significant increases in blood pressure target achievement and reductions in secondary stroke and TIA. Confidence intervals were wide and there was moderate to large heterogeneity for many outcomes.


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Usual care | Organisational interventions | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Blood pressure target achievement** | Odds Ratio 1.24 (CI 95% 0.94 - 1.64) Based on data from 1,346 patients in 7 studies. [1] (Randomized controlled) | 496 per 1000 549 per 1000 Difference: 54 more per 1000 ( CI 95% 15 fewer - 121 more ) | **Low** Due to serious risk of bias, Due to serious inconsistency, Due to very serious indirectness, Due to serious imprecision [2] | We are uncertain whether organisational interventions increase or decrease blood pressure target achievement |
| **Proportion of participants with secondary stroke or TIA** | Odds Ratio 0.66 (CI 95% 0.23 - 1.86) Based on data from 791 patients in 4 studies. [3] (Randomized controlled) | 175 per 1000 122 per 1000 Difference: 52 fewer per 1000 ( CI 95% 128 fewer - 108 more ) | **Low** Due to serious indirectness, Due to serious imprecision, Due to very serious inconsistency, Due to serious risk of bias [4] | We are uncertain whether organisatiional interventions increase or decrease the proportion of participants with secondary stroke or TIA |
| **Proportion of participants with vascular death** End of follow-up - 3 years | Odds Ratio 1.75 (CI 95% 0.41 - 7.46) Based on data from 324 patients in 1 studies. [5] (Randomized controlled) Follow up 3 years | 18 per 1000 31 per 1000 Difference: 13 more per 1000 ( CI 95% 11 fewer - 102 more ) | **Low** Due to very serious imprecision, Due to serious risk of bias, Due to serious indirectness [6] | We are uncertain whether organisational interventions increase or decrease vascular death |
| **Number of vascular deaths** End of follow-up - 2 years | Odds Ratio 0.75 (CI 95% 0.17 - 3.35) Based on data from 314 patients in 1 studies. (Randomized controlled) Follow up 2 years | | **Low** Due to very serious imprecision, Due to serious risk of bias, Due to serious indirectness [7] | We are uncertain whether organisational interventions increase or decrease vascular death |

1. Systematic review [17] with included studies: Hornnes 2011, Brotons 2011, Allen 2009, Flemming 2013, Wang 2005, Johnston 2010, Joubert 2009. **Baseline/comparator:** Systematic review.
2. **Risk of bias: Serious.** Selective outcome reporting; data for subgroups only reported in some studies. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was moderate to high across the studies.. **Indirectness: Very Serious.** Differences between the outcomes of interest and those reported (differences in BP targets), Differences between the population of interest and those studied (particularly in relation to presence of comorbidities). **Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
3. Systematic review [17] with included studies: Welin 2010, Allen 2002, Wang 2005, Kerry 2013. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors in at least two studies, resulting in potential for detection bias. **Inconsistency: Very Serious.** The magnitude of statistical heterogeneity was high, up to I^2:77 %.. **Indirectness: Serious.** Inconsistency in methods used to verify outcomes (review of clinical records versus patient interview); no objective verification. **Imprecision: Serious.** Low number of patients; few experiencing outcome during the available follow-up periods in the included studies. **Publication bias: No serious.**
5. Systematic review [17] with included studies: Brotons 2011. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: No serious. Indirectness: Serious.** The outcome time frame in studies were insufficient. **Imprecision: Very Serious.** Low number of patients; only 2 studies (both organisational interventions). **Publication bias: No serious.**
7. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: No serious. Indirectness: Serious.** The outcome time frame in studies were insufficient. **Imprecision: Very Serious.** Low number of patients; only 2 studies (both organisational interventions). **Publication bias: No serious.**

## Blood pressure lowering therapy

Blood pressure (BP) is a leading modifiable risk factor for stroke. Commencement of secondary prevention medications, including BP lowering therapy, prior to hospital discharge is the most important for improving rates of adherence long-term after stroke. (Thrift et al 2014 *[35]*). Yet only 73% of eligible patients discharged from acute services, and 78% from in-patient rehabilitation services are prescribed with BP lowering therapy (Stroke Foundation 2015 *[197]* 2016 *[198]*). Lifestyle change including diet and exercise, either alone or in conjunction with pharmacotherapy, can also be used to reduce BP (see Lifestyle modification section).

The timing of commencing therapy remains unclear. Blood pressure therapy in acute care is further discussed (see Acute-phase blood pressure lowering therapy section in Acute medical and surgical management).

### Acute blood pressure management

Practice Statement

**Consensus-based recommendations**

- All patients with acute stroke should have their blood pressure closely monitored in the first 48 hours after stroke onset.
- Patients with acute ischaemic stroke eligible for treatment with intravenous thrombolysis should have their blood pressure reduced to below 185/110 mmHg before treatment and in the first 24 hours after treatment.
- Patients with acute ischaemic stroke with blood pressure >220/120/mmHg should have their blood pressure cautiously reduced (e.g. by no more than 20%) over the first 24 hours.

#### Rationale

Available evidence suggests high blood pressure in acute stroke is associated with poor outcome. Studies in blood pressure lowering therapy in acute stroke however, have failed to show a benefit. Results from ongoing studies targeting the hyper-acute phase may answer this important clinical question. Blood pressure lowering therapy, except for patients being considered for intravenous thrombolysis and in the case of extreme hypertension, cannot be recommended.

Weak Recommendation Against

Intensive blood pressure lowering in the acute phase of care to a target SBP of <140mmHg is not recommended for any patient with stroke. (Bath and Krishnan 2014 *[40]*)

#### Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

No benefits were found in a robust Cochrane systematic review of acute blood pressure lowering to SBP<140mmHg (Bath and Krishnan 2014 *[40]*).

**Certainty of the Evidence** — High

The evidence has multiple high quality randomised controlled trials (Bath and Krishnan 2014 *[40]*).

**Preference and values** — No substantial variability expected

No substantial variability was identified or expected

#### Rationale

High-quality evidence showed that there was no overall effect of acute blood pressure lowering to <140mHg on death or functional

outcome.

## Clinical Question/ PICO

**Population:** Adults with ICH
**Intervention:** Blood pressure lowering
**Comparator:** Control

### Summary

Systematic review by Bath et al (2014 *[40]*) , which primarily comes from two large, well-designed RCTs, examined the effect of acute blood pressure lowering in ICH over the last 5 years. One of them is INTERACT2, which suggested that a systolic target of 140mmHg probably improves outcomes, while another recent trial ATACH-II published after this systematic review did not support lowering the SBP to less than 140mmHg (Qureshi et al 2016 *[42]*).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Blood pressure lowering | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Death and dependency** [1] 9 Critical | Odds Ratio 1.01 (CI 95% 0.84 - 1.21) Based on data from 4,209 patients in 7 studies. (Randomized controlled) | 543 per 1000 | 545 per 1000 Difference: 2 more per 1000 ( CI 95% 43 fewer - 47 more ) | High | In patients with mild to moderate size ICH, a treatment target of SBP 140 has little or no difference on death and dependency. |

1. mRS > 1 or > 2 depending on trial definition

## Clinical Question/ PICO

**Population:** Adults with ischaemic stroke
**Intervention:** Blood pressure lowering
**Comparator:** Control

### Summary

Two systematic reviews from Lee et al (2015) *[39]* and Bath et al (2014) *[40]* showed that there was no overall effect of treatment on death as an outcome in the studies analysed. No differences were observed when analysed by the subgroup of ischaemic stroke either .

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Blood pressure lowering | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Death and dependency** [1] | Odds Ratio 1 (CI 95% 0.92 - 1.08) Based on data from 11,015 patients in 8 studies. (Randomized | 409 per 1000 | 409 per 1000 Difference: 0 fewer per 1000 | High | blood pressure lowering has little or no difference on death and dependency |

| | | | |
|---|---|---|---|
| 9 Critical | controlled) | ( CI 95% 20 fewer - 19 more ) | |

1. mRS > 1 or > 2 depending on definition in individual trials

Weak Recommendation

In patients with intracerebral haemorrhage blood pressure may be acutely reduced to a target systolic blood pressure of around 140mmHg (but not substantially below). (Tsivgoulis et al 2014*[43]*; Qureshi et al 2016*[42]*)

## Key Info

**Benefits and harms**

Small net benefit, or little difference between alternatives

The evidence of this recommendation is based on the Cochrane review by Bath et al. *[104]*, incorporating results from a large randomised controlled trial INTERACT2 (N = 2794). In INTERACT2, The primary end point of death or major disability at 3 months between the intensive treatment group and the control group fell just short of statistical significance (OR 0.87, 95% CI 0.75-1.01) (Anderson et al 2013 *[106]*). An ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of blood pressure (OR 0.87, 95%CI 0.77 - 1.00) (Bath and Krishnan 2014 *[104]*). Results from ATACH-II did not support lowering the SBP to less than 140mmHg - there was no difference in death or disability but a higher rate of serious adverse events (Qureshi et al 2016 *[105]*).

**Certainty of the Evidence**

High

Multiple high quality randomised controlled trials

**Preference and values**

No substantial variability expected

None identified or expected

**Resources and other considerations**

Resources considerations

No literature to understand or describe the potential economic implications of this recommendation was identified.

## Rationale

High-quality evidence suggests that in patients with mild to moderate intracerebral haemorrhage, a systolic blood pressure (SBP) target of 140mmHg (but not lower), is probably safe and associated with better patient outcomes as demonstrated by a shift in modified Rankin Scale scores at 90 days.

## Clinical Question/ PICO

**Population:** Adults with ICH
**Intervention:** Blood pressure lowering
**Comparator:** Control

## Summary

Systematic review by Bath et al (2014 *[40]*) , which primarily comes from two large, well-designed RCTs, examined the effect of acute blood pressure lowering in ICH over the last 5 years. One of them is INTERACT2, which suggested that a systolic target of 140mmHg probably improves outcomes, while another recent trial ATACH-II published after this systematic review did not support lowering the SBP to less than 140mmHg (Qureshi et al 2016 *[42]*).


| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Control | <br>Blood pressure lowering | Certainty of the Evidence<br>(Quality of evidence) | Plain text summary |
|---|---|---|---|---|---|
| Death and dependency [1]<br><br>9 Critical | Odds Ratio 1.01 (CI 95% 0.84 - 1.21) Based on data from 4,209 patients in 7 studies. (Randomized controlled) | 543<br>per 1000 | 545<br>per 1000<br><br>Difference: 2 more per 1000<br>( CI 95% 43 fewer - 47 more ) | High | In patients with mild to moderate size ICH, a treatment target of SBP 140 has little or no difference on death and dependency. |

1. mRS > 1 or > 2 depending on trial definition

Weak Recommendation

Pre-existing antihypertensive agents may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 *[40]*)

## Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

In the meta-analysis incorporating the ENOS study, continuing pre-stroke anti-hypertensives did not affect the primary outcome but was associated with worse Barthel Index at 90 days (Bath and Krishnan 2014 *[40]*). The exact reason for this is uncertain.

**Certainty of the Evidence** — High

High quality randomised controlled trial data mainly from one study

**Preference and values** — No substantial variability expected

Not identified and no variation in preference and values expected.

**Resources and other considerations** — Important issues, or potential issues not investigated

Resources considerations
No literature to understand or describe the potential economic implications of this recommendation was identified.

## Rationale

Based on limited available evidence, there appears to be no urgency in resuming pre-stroke anti-hypertensive therapy in acute

stroke patients. Doing so may be associated with worsening functional outcome and it is advisable to wait until a safe route of administration is established.

### Clinical Question/ PICO

**Population:** Adults with acute stroke
**Intervention:** Continue pre-stroke antihypertensives
**Comparator:** Stop pre-stroke antihypertensives

### Summary

Bath et al (2014) *[40]* conducted a systematic review of the effectiveness of altering blood pressure in patients with acute stroke. In a total of 2860 patients, they did not find a significant difference of death or dependency between patients who continued pre-stroke anti-hypertensive treatment and whose who stopped. However, better functional outcomes measured by Barthel Index were associated with discontinuation of antihypertensives.

| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Stop pre-stroke antihypertensives | <br>Continue pre-stroke antihypertensives | Certainty of the Evidence<br>(Quality of evidence) | Plain text summary |
|---|---|---|---|---|---|
| Death or dependency [1]<br>9 Critical | Odds Ratio 1.06 (CI 95% 0.91 - 1.24) Based on data from 2,860 patients in 2 studies. (Randomized controlled) | 567<br>per 1000 | 581<br>per 1000<br>Difference: 14 more per 1000<br>( CI 95% 23 fewer - 52 more ) | High | continue pre-stroke antihypertensives has little or no difference on death or dependency |

1. mRS > 1 or > 2 depending on definition in individual trials

## Long term blood pressure management

Strong Recommendation

- All patients with stroke or TIA, with a clinic blood pressure of >140/90mmHg should have long term blood pressure lowering therapy initiated or intensified. (SPS3 2013 *[25]*; Thomopoulos et al 2016 *[30]*; Ettehad et al 2016 *[31]*; Lahkan and Sapko 2009 *[26]*)
- Blood pressure lowering therapy should be initiated or intensified before discharge for those with stroke or TIA, or soon after TIA if the patient is not admitted. (SPS3 2013 *[25]*; Thomopoulos et al 2016 *[30]*; Ettehad et al 2016 *[31]*; Lahkan and Sapko 2009 *[26]*)
- Any of the following drug classes are acceptable as blood pressure lowering therapy; angiotensin-converting-enzyme inhibitor, angiotensin II receptor antagonists, calcium channel blocker, thiazide diuretics. Beta-blockers should not be used as first-line agents unless the patient has ischaemic heart disease. (Lakhan and Sapko 2009 *[26]*; Mukete et al 2015 *[33]*)

### Practical Info

The recommendation for treatment based on clinic blood pressure assumes that the individual's clinic BP is similar to that measured outside the clinic. If the BP outside the clinic (e.g. home BP or 24hr ambulatory BP) is substantially lower than BP inside the clinic, BP measured outside the clinic should be used for treatment decisions. In these patients a BP of > 135/85 mmHg is recommended as the decision point in general secondary prevention.There is no agreed blood pressure treatment target after stroke and the intensity of blood pressure lowering should reflect the overall vascular risk of the individual (which is high in people with a history of

stroke). Subanalysis of the PROGRESS trial did not find heterogeneity in the benefit of blood pressure lowering treatment across the range of baseline BP (noting that few patients had baseline BP<120mmHg) (Arima et al 2006 *[29]*). There did appear to be benefit in starting treatment for intracerebral haemorrhage patients if BP was >120mmHg. Treatment to at least 130 mmHg was not harmful in SPS3 (SPS3 2013 *[25]*). Observational studies vary in whether there is an increase in stroke risk in people with low-normal BP (ie a "J-curve") and some have found a higher risk of poor outcome in patients with systolic BP <120mmHg. However this effect was not seen in meta-analyses of primary and secondary prevention trials including the SPRINT trial (which did not include patients with stroke due to other ongoing research). Patient outcomes were improved by more intense blood pressure lowering to a target of <120mmHg systolic, irrespective of baseline levels (Thomopoulos et al 2016 *[30]*, Ettehad 2016 *[31]*). The ongoing SHOT trial (NCT01563731) is testing BP lowering in stroke patients to a target of <125mmHg vs 125-135mmHg vs 135-145mmHg. **We would suggest initiation or intensification of blood pressure lowering treatment to achieve systolic BP between 120-140mmHg, provided there are no adverse effects from excessive BP lowering**.

## Key Info

**Benefits and harms** — Substantial net benefits of the recommended alternative

Consistent benefits of blood pressure lowering to reduce stroke risk by 25-30% (SPS3 2014 *[25]*; Lakhan and Sapko 2009 *[26]*; Arima et al 2006 *[29]*; Thomopoulos et al 2016 *[30]*; Ettehad et al 2016 *[31]*).

**Certainty of the Evidence** — High

Mutiple large trials and meta-analysis

**Preference and values** — No substantial variability expected

Selection of an antihypertensive agent will depend on patient co-morbidities and tolerability according to side effect profile.

**Resources and other considerations** — No important issues with the recommended alternative

Resources considerations

There is evidence that blood pressure lowering therapy is cost effective. In patients at a high risk of heart disease and stroke in Australia, it was found that blood pressure lowering with ramipril was cost-effective at an additional cost of AU$17,214 per life year gained compared to placebo (cost reference year not reported) (Smith et al 2003 *[36]*). In patients with previous stroke or TIA, in a European setting, it was found that blood pressure lowering with perindopril would be cost-effective at an additional cost of £6,927 per QALY gained compared to placebo (cost reference year 2005) (Tavakoli et al 2009 *[37]*; PROGRESS Collaborative Group 2001 *[38]*). In a more recent evaluation, it was found that organised blood pressure control programs were cost-effective for secondary prevention of stroke in Australia, costing AU$1,811 to 4,704 per quality adjusted life year gained compared to usual practice (cost reference year 2004) (Cadilhac et al 2012 *[27]*).

Implementation considerations

There is a clinical indicator collected on blood pressure therapy in the National Stroke Audit. Blood pressure therapy is included in the Acute Stroke Clinical Care Standard specifically for patients with intracerebral haemorrhage or as a bundle approach with blood pressure lowering, cholesterol lowering and antiplatelet medication for patients with ischaemic stroke.

## Rationale

Blood pressure lowering is consistently found to reduce stroke risk by about 25%. The benefits are found irrespective of baseline blood pressure. Observational data consistently finds higher adherence by patients if medication is commenced prior to discharge from hospital rather than delaying commencement until patient is back in the community, therefore treatment should commence while in hospital for people admitted for stroke. There is less clear evidence about optimal timing following TIA but initiation of all medical therapy soon after TIA has been found to reduce risk.

## Clinical Question/ PICO

**Population:** Adults with recent stroke
**Intervention:** Lower target of blood pressure (less than 130 mmHg)
**Comparator:** Higher target of blood pressure (130-149 mm Hg)

## Summary

The SPS3 trial randomised 3020 patients with recent lacunar stroke (SPS3 group 2013 *[25]*). A systolic blood pressure target of 130mmHg compared with that of 130-140mmHg was associated with a non-significant reduction in recurrent stroke.

Post hoc analysis of the PROGRESS trial, an RCT of blood pressure lowering with perindopril in 6105 patients with previous cerebrovascular disease, showed that greater risk reduction was associated with more intensive BP lowering therapy. Despite 52% of participants being classified as normotensive at baseline, PROGRESS showed consistently reduced stroke risk irrespective of initial BP levels with no evidence of increased risk at very low BP levels (Arima et al 2006 *[29]*).

A recent updated meta-analysis reported better outcomes for patients with more intense BP lowering irrespective of baseline levels (Thomopoulos et al 2016 *[30]*). Another recent meta-analysis including 123 studies and 613,815 subjects (with and without preceding stroke) confirmed treatment significantly reduced cardiovascular events and death in proportion to the magnitude of BP with every 10mm Hg reduction in SBP reducing risk of cardiovascular disease by 20% and stroke in particular by 27%. (Ettehad et al 2016 *[31]*).

Overall, lower blood pressure is likely to be associated with better outcomes in patients with stroke.


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Higher target of blood pressure (130-149 mm Hg) | Lower target of blood pressure (less than 130 mmHg) | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Death** 9 Critical | Hazard Ratio 1.03 (CI 95% 0.79 - 1.35) Based on data from 3,020 patients in 1 studies. (Randomized controlled) Follow up Mean follow-up of 3.7 years | | | **Low** Due to serious imprecision, Due to serious risk of bias [1] | Blood pressure target of less than 130 mm hg may have little or no difference on death in patients with recent lacunar stroke |
| **Recurrent stroke** 8 Critical | Hazard Ratio 0.81 (CI 95% 0.64 - 1.03) Based on data from 3,020 patients in 1 studies. (Randomized controlled) Follow up Mean follow-up of 3.7 years. | | | **Low** Due to serious imprecision, Due to serious risk of bias [2] | Blood pressure target of less than 130 mm hg may decrease recurrent stroke in patients with recent lacunar stroke |
| **Recurrent ischaemic stroke** 8 Critical | Hazard Ratio 0.84 (CI 95% 0.66 - 1.09) Based on data from 3,020 patients in 1 studies. (Randomized controlled) Follow up Mean follow-up of 3.7 years | | | **Low** Due to serious imprecision, Due to serious risk of bias [3] | Blood pressure target of less than 130 mm hg may decrease recurrent ischaemic stroke in patients with recent lacunar stroke |
| **Recurrent intracerebral haemorrhage** | Hazard Ratio 0.61 (CI 95% 0.31 - 1.22) Based on data from 3,020 patients in 1 studies. (Randomized | | | **Low** Due to serious imprecision, Due to serious risk of bias [4] | Blood pressure target of less than 130 mm hg may decrease recurrent haemorrhagic stroke in patients with recent |

| | | | | |
|---|---|---|---|---|
| 8 Critical | controlled)<br>Follow up Mean follow-up of 3.7 years | | | lacunar stroke |
| Adverse events [5]<br>7 Critical | Hazard Ratio 1.53 (CI 95% 0.8 - 2.93)<br>Based on data from 3,020 patients in 1 studies. (Randomized controlled)<br>Follow up Mean follow-up of 3.7 years | | Moderate<br>Due to serious imprecision [6] | Blood pressure target of less than 130 mm hg may have little or no difference on adverse events in patients with recent lacunar stroke |

1. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious.** Subgroup analyses within the study showed no heterogeneity between subgroups. **Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Only data from one study, confidence intervals (for hazard ratio) cross 1, Wide confidence intervals, Only data from one study. **Publication bias: No serious.**
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Single study but similar results to prior studies and large numbers. **Publication bias: No serious.**
3. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Wide confidence intervals, Only data from one study. Similar results to prior studies and large numbers. **Publication bias: No serious.**
5. Serious adverse events related to hypotension
6. **Inconsistency: No serious. Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**

## Clinical Question/ PICO

**Population:** Adults with previous stroke or TIA
**Intervention:** Blood pressure reduction medication
**Comparator:** Control/placebo

### Summary

Blood pressure (BP) lowering has consistently been reported to reduce recurrent stroke in patients with/without previous stroke/TIA. Specific to secondary stroke prevention a systematic review (10 RCTs) found that therapy to lower BP, even when initial BP was within normal range, reduced recurrent stroke (OR 0.71, 95% CI 0.59–0.86) and cardiovascular events (OR 0.69, 95% CI 0.57–0.85) in patients with a previous stroke or TIA. (Lakhan and Sapko 2009 *[26]*). It, however, did not lower all-cause mortality (OR 0.95, 95% CI 0.83–1.07).

In terms of specific medication effective in reducing recurrent stroke, the most direct evidence of benefit is for the use of an ACE inhibitor (alone or in combination with a diuretic) based on the PROGRESS trial. However, most antihypertensive agents have been found to be effective with the exception being beta blockers (Rashid et al 2003 *[28]*). A recent meta-analysis of 39,329 patients with previous stroke supported the use of diuretic-based treatment, especially when combined with ACE inhibitor (Wang et al 2016 *[32]*). Another meta-analysis of 251,853 patients showed that all classes of blood pressure lowering medication reduce stroke (except beta blockers), including primary and secondary, with the most effective

reported to be calcium channel blockers (Mukete et al 2015 *[33]*).

| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Control/placebo | <br>Blood pressure lowering | Certainty of the Evidence<br>(Quality of evidence) | Plain text summary |
|---|---|---|---|---|---|
| **Death (all-cause)**<br>End of follow-up<br><br>9 Critical | Odds Ratio 0.95<br>(CI 95% 0.83 - 1.07)<br>Based on data from 30,866 patients in 7 studies. [1] (Randomized controlled)<br>Follow up 1 to 4 years | 83<br>per 1000 | 79<br>per 1000<br><br>Difference: **4 fewer** per 1000<br>( CI 95% 13 fewer - 5 more ) | **High**<br>[2] | Blood pressure lowering medications have little or no difference on all-cause death |
| **Recurrent stroke** [3]<br>End of follow-up<br><br>8 Critical | Odds Ratio 0.71<br>(CI 95% 0.59 - 0.86)<br>Based on data from 37,737 patients in 10 studies. [4] (Randomized controlled)<br>Follow up 1 to 5 years | 106<br>per 1000 | 78<br>per 1000<br><br>Difference: **28 fewer** per 1000<br>( CI 95% 41 fewer - 13 fewer ) | **Moderate**<br>Due to serious inconsistency (heterogeneity) and possible publication bias [5] | Blood pressure lowering medications probably decrease recurrent stroke |

1. Systematic review [26] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Risk of bias not really reported in systematic review but mostly placebo controlled. One smaller trial was open-label but rest were placebo controlled. . **Inconsistency: No serious.** Low statistical heterogeneity: I^2 29%. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. Includes both fatal and non-fatal stroke, and includes ischaemic stroke and intracerebral haemorrhage
4. Systematic review [26] . **Baseline/comparator:** Control arm of reference used for intervention.
5. **Risk of bias: No serious.** Risk of bias not really reported in systematic review but mostly placebo controlled. One smaller trial was open-label but rest were placebo controlled. . **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 78%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** Asymmetrical funnel plot: funnel plot analysis showed one trial with a strong reduction in stroke (OR = 0.4) fell outside the 95% CI. Excluding this study from meta-analysis led to a less pronounced but still significant overall effect (OR 0.77, 95% CI 0.66-0.90, P = 0.0009).

## Clinical Question/ PICO

**Population:** People with hypertension
**Intervention:** Intensive blood pressure lowering therapy
**Comparator:** Lower intensity blood pressure lowering therapy

| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Lower intensity blood pressure lowering therapy | <br>Intensive blood pressure lowering therapy | Certainty of the Evidence<br>(Quality of evidence) | Plain text summary |
|---|---|---|---|---|---|
| **All cause death**<br>mean 3.7 years | Relative risk 0.83<br>(CI 95% 0.69 - 1.03)<br>Based on data from | 41 | 34 | **Moderate**<br>Due to serious inconsistency [1] | Intensive blood pressure lowering therapy probably decreases all |

| | | | | |
|---|---|---|---|---|
| 9 Critical | 52,235 patients in 16 studies. (Randomized controlled) Follow up mean 3.7 years | per 1000 per 1000<br>Difference: 7 fewer per 1000 ( CI 95% 13 fewer - 1 more ) | | cause death |
| **Stroke Event** mean 3.7 years<br>9 Critical | Relative risk 0.71 (CI 95% 0.6 - 0.84) Based on data from 49,952 patients in 13 studies. (Randomized controlled) Follow up mean 3.7 years | 24 per 1000 17 per 1000<br>Difference: 7 fewer per 1000 ( CI 95% 10 fewer - 4 fewer ) | **High** | Intensive blood pressure lowering therapy prevents stroke |

1. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

## Clinical Question/ PICO

**Population:** Adults
**Intervention:** Blood pressure lowering therapy
**Comparator:** Placebo or alternative blood pressure lowering therapy

### Summary

The large meta-analysis by Ettehad et al 2016 *[31]* synthesised results from 123 studies involving 613, 815 participants in which blood pressure (BP) lowering therapy was compared to placebo or other BP lowering therapy in adults with a range of comorbidities and baseline BP. A meta-regression analysis was conducted to examine proportional risk reductions relatived to the magnitude of BP reductions achieved. The results found significant risk reductions associated with every 10mmHg reduction in systolic BP for a range of outcomes including all-cause mortality and stroke events. The results were consistent for participants with differing baseline BP and comorbidities.

Mukete et al 2015 *[33]* synthesised 17 studies involving 251,853 participants and compared different classes of BP lowering drugs to all other classes. This included angiotensin-converting-enzyme-inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers, thiazide diuretics and beta blockers. Calcium channel blockers were most effective and reducing risk of stroke and beta blo ckers increased risk of stroke. There were insufficient data reported in this paper to calculate absolute effect estimates.

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Blood pressure lowering therapy | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **All cause mortality for 10mmHg reduction in systolic BP**<br>9 Critical | Relative risk 0.8 (CI 95% 0.77 - 0.83) Based on data from 265,576 patients in 55 studies. (Randomized controlled) Follow up minimum of 1000 patient-years follow-up | 110 per 1000 | 88 per 1000<br>Difference: 22 fewer per 1000 ( CI 95% 25 fewer - 19 fewer ) | **High** | Blood pressure lowering therapy achieving 10mmHg reduction in systolic BP reduces all cause mortality |

| | | | | |
|---|---|---|---|---|
| **Stroke event**<br>9 Critical | Relative risk 0.73 (CI 95% 0.68 - 0.77)<br>Based on data from 265,322 patients in 54 studies. (Randomized controlled)<br>Follow up minimum of 1000 patient-years follow-up | **42** per 1000 **31** per 1000<br>Difference: **11 fewer** per 1000<br>( CI 95% 13 fewer - 10 fewer ) | **High** | Blood pressure lowering therapy achieving 10mmHg in systolic BP reduces stroke events |
| **Stroke event - ACEI drugs**<br>9 Critical | Relative risk 1.01 (CI 95% 0.81 - 1.27)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | **Moderate**<br>Due to serious inconsistency [1] | ACEI drugs probably have similar effects to other drug classes in preventing stroke events |
| **Stroke event - ARB drugs**<br>9 Critical | Relative risk 0.83 (CI 95% 0.59 - 1.18)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | **Moderate**<br>Due to serious inconsistency [2] | ARB drugs probably have similar effects to other drug classes in preventing stroke events |
| **Stroke events - beta blockers**<br>9 Critical | Relative risk 1.42 (CI 95% 1.26 - 1.61)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | **High** | Beta blockers increase the risk of stroke |
| **Stroke event - calcium channel blockers**<br>9 Critical | Relative risk 0.83 (CI 95% 0.79 - 0.89)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | **High** | Calcium channel blockers decrease the risk of stroke |
| **Stroke event - thiazide diuretics**<br>9 Critical | Relative risk 0.9 (CI 95% 0.75 - 1.08)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | **Moderate**<br>Due to serious inconsistency [3] | Thiazide diuretics probably have similar effects to other drug classes in preventing stroke events |

1. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2 = 94%. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

2. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2=51%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2=79%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Weak Recommendation

- In patients with a systolic blood pressure of 120-140mmHg who are not on treatment, initiation of antihypertensive treatment is reasonable, with best evidence for dual (ACEI/diuretic) therapy. (Ettehad et al 2016 *[31]*)
- The ideal long term blood pressure target is not well established. A target of <130mmHg systolic may achieve greater benefit than a target of 140mmHg systolic, especially in patients with stroke due to small vessel disease, provided there are no adverse effects from excessive blood pressure lowering. (SPS3 2013 *[25]*; Ettehad et al 2016 *[31]*)

## Key Info

**Benefits and harms**

Substantial net benefits of the recommended alternative

Consistent benefits of blood pressure lowering to reduce stroke risk by 25-30% (SPS3 2014 *[25]*; Lakhan and Sapko 2009 *[26]*; Arima et al 2006 *[29]*; Thomopoulos et al 2016 *[30]*; Ettehad et al 2016 *[31]*).

**Certainty of the Evidence**

Low

Multiple large trials and meta-analyses have been performed but these relate to a general vascular disease patient group rather than specifically secondary stroke prevention. Some evidence is also from post-hoc subanalyses of randomized trials.

**Preference and values**

No substantial variability expected

Selection of an antihypertensive agent will depend on patient co-morbidities and tolerability according to side effect profile.

**Resources and other considerations**

No important issues with the recommended alternative

<u>Resources considerations</u>
There is evidence that blood pressure lowering therapy is cost effective. In patients at a high risk of heart disease and stroke in Australia, it was found that blood pressure lowering with ramipril was cost-effective at an additional cost of AU$17,214 per life year gained compared to placebo (cost reference year not reported) (Smith et al 2003 *[36]*). In patients with previous stroke or TIA, in a European setting, it was found that blood pressure lowering with perindopril would be cost-effective at an additional cost of £6,927 per QALY gained compared to placebo (cost reference year 2005) (Tavakoli et al 2009 *[37]*; PROGRESS Collaborative Group 2001 *[38]*). In a more recent evaluation, it was found that organised blood pressure control programs were cost-effective for secondary prevention of stroke in Australia, costing AU$1,811 to 4,704 per quality adjusted life year gained compared to usual practice (cost reference year 2004) (Cadilhac et al 2012 *[27]*).

<u>Implementation considerations</u>
There is a clinical indicator collected on blood pressure therapy in the National Stroke Audit. Blood pressure therapy is included in the Acute Stroke Clinical Care Standard specifically for patients with intracerebral haemorrhage or as a bundle approach with blood pressure lowering, cholesterol lowering and antiplatelet medication for patients with ischaemic stroke.

## Rationale

There is no agreed blood pressure treatment target and the intensity of blood pressure lowering should reflect the overall vascular risk of the individual (which is high in patientswith a history of stroke). Subanalysis of the PROGRESS trial did not find heterogeneity

in the benefit of blood pressure lowering treatment across the range of baseline BP (noting that few patients had baseline BP<120mmHg) (Arima et al 2006 *[29]*). There did appear to be benefit in starting treatment for patients with intracerebral haemorrhage if BP was >120mmHg. Treatment to at least 130 mmHg was not harmful in SPS3 (SPS3 2013 *[25]*). Observational studies vary in whether there is an increase in stroke risk in people with low-normal BP (ie a "J-curve") and some have found a higher risk of poor outcome in patients with systolic BP <120mmHg. However this effect was not seen in meta-analyses of primary and secondary prevention trials including the SPRINT trial (which did not include patients with stroke due to other ongoing research). Patient outcomes were improved by more intense blood pressure lowering to a target of <120mmHg systolic, irrespective of baseline levels (Thomopoulos et al 2016 *[30]*, Ettehad 2016 *[31]*). The ongoing SHOT trial (NCT01563731) is testing BP lowering in stroke patients to a target of <125mmHg vs 125-135mmHg vs 135-145mmHg. **We would suggest initiation or intensification of blood pressure lowering treatment to achieve systolic BP between 120-140mmHg, provided there are no adverse effects from excessive blood pressure lowering**. The use of ambulatory BP monitoring may be useful if the consistency of BP control is uncertain.

## Clinical Question/ PICO

**Population:** Adults with recent stroke
**Intervention:** Lower target of blood pressure (less than 130 mmHg)
**Comparator:** Higher target of blood pressure (130-149 mm Hg)

### Summary

The SPS3 trial randomised 3020 patients with recent lacunar stroke (SPS3 group 2013 *[25]*). A systolic blood pressure target of 130mmHg compared with that of 130-140mmHg was associated with a non-significant reduction in recurrent stroke.

Post hoc analysis of the PROGRESS trial, an RCT of blood pressure lowering with perindopril in 6105 patients with previous cerebrovascular disease, showed that greater risk reduction was associated with more intensive BP lowering therapy. Despite 52% of participants being classified as normotensive at baseline, PROGRESS showed consistently reduced stroke risk irrespective of initial BP levels with no evidence of increased risk at very low BP levels (Arima et al 2006 *[29]*).

A recent updated meta-analysis reported better outcomes for patients with more intense BP lowering irrespective of baseline levels (Thomopoulos et al 2016 *[30]*). Another recent meta-analysis including 123 studies and 613,815 subjects (with and without preceding stroke) confirmed treatment significantly reduced cardiovascular events and death in proportion to the magnitude of BP with every 10mm Hg reduction in SBP reducing risk of cardiovascular disease by 20% and stroke in particular by 27%. (Ettehad et al 2016 *[31]*).

Overall, lower blood pressure is likely to be associated with better outcomes in patients with stroke.

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Higher target of blood pressure (130-149 mm Hg) | Lower target of blood pressure (less than 130 mmHg) | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Death** 9 Critical | Hazard Ratio 1.03 (CI 95% 0.79 - 1.35) Based on data from 3,020 patients in 1 studies. (Randomized controlled) Follow up Mean follow-up of 3.7 years | | | **Low** Due to serious imprecision, Due to serious risk of bias [1] | Blood pressure target of less than 130 mm hg may have little or no difference on death in patients with recent lacunar stroke |
| **Recurrent stroke** 8 Critical | Hazard Ratio 0.81 (CI 95% 0.64 - 1.03) Based on data from 3,020 patients in 1 studies. (Randomized | | | **Low** Due to serious imprecision, Due to serious risk of bias [2] | Blood pressure target of less than 130 mm hg may decrease recurrent stroke in patients with recent lacunar stroke |

| | | | | |
|---|---|---|---|---|
| | controlled)<br>Follow up Mean follow-up of 3.7 years. | | | |
| **Recurrent ischaemic stroke**<br>8 Critical | Hazard Ratio 0.84 (CI 95% 0.66 - 1.09)<br>Based on data from 3,020 patients in 1 studies. (Randomized controlled)<br>Follow up Mean follow-up of 3.7 years | | **Low**<br>Due to serious imprecision, Due to serious risk of bias [3] | Blood pressure target of less than 130 mm hg may decrease recurrent ischaemic stroke in patients with recent lacunar stroke |
| **Recurrent intracerebral haemorrhage**<br>8 Critical | Hazard Ratio 0.61 (CI 95% 0.31 - 1.22)<br>Based on data from 3,020 patients in 1 studies. (Randomized controlled)<br>Follow up Mean follow-up of 3.7 years | | **Low**<br>Due to serious imprecision, Due to serious risk of bias [4] | Blood pressure target of less than 130 mm hg may decrease recurrent haemorrhagic stroke in patients with recent lacunar stroke |
| **Adverse events** [5]<br>7 Critical | Hazard Ratio 1.53 (CI 95% 0.8 - 2.93)<br>Based on data from 3,020 patients in 1 studies. (Randomized controlled)<br>Follow up Mean follow-up of 3.7 years | | **Moderate**<br>Due to serious imprecision [6] | Blood pressure target of less than 130 mm hg may have little or no difference on adverse events in patients with recent lacunar stroke |

1. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious.** Subgroup analyses within the study showed no heterogeneity between subgroups. **Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Only data from one study, confidence intervals (for hazard ratio) cross 1, Wide confidence intervals, Only data from one study. **Publication bias: No serious.**
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Single study but similar results to prior studies and large numbers. **Publication bias: No serious.**
3. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Wide confidence intervals, Only data from one study. Similar results to prior studies and large numbers. **Publication bias: No serious.**
5. Serious adverse events related to hypotension
6. **Inconsistency: No serious. Indirectness: No serious.** Comparable and directly transferable to our target population but a single study. **Imprecision: Serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**

## Clinical Question/ PICO

**Population:** Adults with previous stroke or TIA
**Intervention:** Blood pressure reduction medication
**Comparator:** Control/placebo


### Summary

Blood pressure (BP) lowering has consistently been reported to reduce recurrent stroke in patients with/without previous stroke/TIA. Specific to secondary stroke prevention a systematic review (10 RCTs) found that therapy to lower BP, even when initial BP was within normal range, reduced recurrent stroke (OR 0.71, 95% CI 0.59–0.86) and cardiovascular events (OR 0.69, 95% CI 0.57–0.85) in patients with a previous stroke or TIA. (Lakhan and Sapko 2009 *[26]*). It, however, did not lower all-cause mortality (OR 0.95, 95% CI 0.83–1.07).

In terms of specific medication effective in reducing recurrent stroke, the most direct evidence of benefit is for the use of an ACE inhibitor (alone or in combination with a diuretic) based on the PROGRESS trial. However, most antihypertensive agents have been found to be effective with the exception being beta blockers (Rashid et al 2003 *[28]*). A recent meta-analysis of 39,329 patients with previous stroke supported the use of diuretic-based treatment, especially when combined with ACE inhibitor (Wang et al 2016 *[32]*). Another meta-analysis of 251,853 patients showed that all classes of blood pressure lowering medication reduce stroke (except beta blockers), including primary and secondary, with the most effective reported to be calcium channel blockers (Mukete et al 2015 *[33]*).


| **Outcome**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Control/placebo | <br>Blood pressure lowering | **Certainty of the Evidence**<br>(Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Death (all-cause)**<br>End of follow-up<br><br>9 Critical | Odds Ratio 0.95 (CI 95% 0.83 - 1.07)<br>Based on data from 30,866 patients in 7 studies. [1] (Randomized controlled)<br>Follow up 1 to 4 years | 83<br>per 1000 | 79<br>per 1000<br><br>Difference: 4 fewer per 1000<br>( CI 95% 13 fewer - 5 more ) | **High**<br>[2] | Blood pressure lowering medications have little or no difference on all-cause death |
| **Recurrent stroke** [3]<br>End of follow-up<br><br>8 Critical | Odds Ratio 0.71 (CI 95% 0.59 - 0.86)<br>Based on data from 37,737 patients in 10 studies. [4] (Randomized controlled)<br>Follow up 1 to 5 years | 106<br>per 1000 | 78<br>per 1000<br><br>Difference: 28 fewer per 1000<br>( CI 95% 41 fewer - 13 fewer ) | **Moderate**<br>Due to serious inconsistency (heterogeneity) and possible publication bias [5] | Blood pressure lowering medications probably decrease recurrent stroke |

1. Systematic review [26] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Risk of bias not really reported in systematic review but mostly placebo controlled. One smaller trial was open-label but rest were placebo controlled. . **Inconsistency: No serious.** Low statistical heterogeneity: I^2 29%. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. Includes both fatal and non-fatal stroke, and includes ischaemic stroke and intracerebral haemorrhage
4. Systematic review [26] . **Baseline/comparator:** Control arm of reference used for intervention.
5. **Risk of bias: No serious.** Risk of bias not really reported in systematic review but mostly placebo controlled. One smaller trial was open-label but rest were placebo controlled. . **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 78%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** Asymmetrical funnel plot: funnel plot analysis showed one trial with a strong reduction in stroke (OR = 0.4) fell outside the 95% CI. Excluding this study from meta-analysis led to a less pronounced but still significant overall effect (OR 0.77, 95% CI 0.66-0.90, P = 0.0009).

## Clinical Question/ PICO

**Population:** Adults
**Intervention:** Blood pressure lowering therapy
**Comparator:** Placebo or alternative blood pressure lowering therapy


### Summary

The large meta-analysis by Ettehad et al 2016 *[31]* synthesised results from 123 studies involving 613, 815 participants in which blood pressure (BP) lowering therapy was compared to placebo or other BP lowering therapy in adults with a range of comorbidities and baseline BP. A meta-regression analysis was conducted to examine proportional risk reductions relatived to the magnitude of BP reductions achieved. The results found significant risk reductions associated with every 10mmHg reduction in systolic BP for a range of outcomes including all-cause mortality and stroke events. The results were consistent for participants with differing baseline BP and comorbidities.

Mukete et al 2015 *[33]* synthesised 17 studies involving 251,853 participants and compared different classes of BP lowering drugs to all other classes. This included angiotensin-converting-enzyme-inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers, thiazide diuretics and beta blockers. Calcium channel blockers were most effective and reducing risk of stroke and beta blo ckers increased risk of stroke. There were insufficient data reported in this paper to calculate absolute effect estimates.


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Blood pressure lowering therapy | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **All cause mortality for 10mmHg reduction in systolic BP**<br>9 Critical | Relative risk 0.8 (CI 95% 0.77 - 0.83)<br>Based on data from 265,576 patients in 55 studies. (Randomized controlled)<br>Follow up minimum of 1000 patient-years follow-up | 110 per 1000 | 88 per 1000<br>Difference: **22 fewer** per 1000 ( CI 95% 25 fewer - 19 fewer ) | **High** | Blood pressure lowering therapy achieving 10mmHg reduction in systolic BP reduces all cause mortality |
| **Stroke event**<br>9 Critical | Relative risk 0.73 (CI 95% 0.68 - 0.77)<br>Based on data from 265,322 patients in 54 studies. (Randomized controlled)<br>Follow up minimum of 1000 patient-years follow-up | 42 per 1000 | 31 per 1000<br>Difference: **11 fewer** per 1000 ( CI 95% 13 fewer - 10 fewer ) | **High** | Blood pressure lowering therapy achieving 10mmHg in systolic BP reduces stroke events |
| **Stroke event - ACEI drugs**<br>9 Critical | Relative risk 1.01 (CI 95% 0.81 - 1.27)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | | CI 95% | **Moderate**<br>Due to serious inconsistency [1] | ACEI drugs probably have similar effects to other drug classes in preventing stroke events |
| **Stroke event -** | Relative risk 0.83 | | | **Moderate** | ARB drugs probably |

| | | | | |
|---|---|---|---|---|
| **ARB drugs**<br>9 Critical | (CI 95% 0.59 - 1.18)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | Due to serious inconsistency [2] | have similar effects to other drug classes in preventing stroke events |
| **Stroke events - beta blockers**<br>9 Critical | Relative risk 1.42<br>(CI 95% 1.26 - 1.61)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | **High** | Beta blockers increase the risk of stroke |
| **Stroke event - calcium channel blockers**<br>9 Critical | Relative risk 0.83<br>(CI 95% 0.79 - 0.89)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | **High** | Calcium channel blockers decrease the risk of stroke |
| **Stroke event - thiazide diuretics**<br>9 Critical | Relative risk 0.9<br>(CI 95% 0.75 - 1.08)<br>Based on data from 251,853 patients in 17 studies. (Randomized controlled)<br>Follow up min median 6 month follow-up | CI 95% | **Moderate**<br>Due to serious inconsistency [3] | Thiazide diuretics probably have similar effects to other drug classes in preventing stroke events |

1. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2 = 94%. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
2. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2=51%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2=79%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

## Antiplatelet therapy

Antiplatelet agents are medications that reduce the formation of blood clots by preventing platelets in the blood circulation from clumping and sticking together. This reduces the risk of stroke due to blood clots. Antithrombotics (which include antiplatelet agents) are given to 97% of patients with acute ischaemic stroke by discharge (Stroke Foundation 2015 *[197]*) but adherence declines after discharge with 21% of patients with stroke in Australia not taking any antiplatelet therapy according to primary care data (Reid et al 2008 *[58]*).

Commencement of secondary prevention medication prior to hospital discharge is important for improving rates of adherence long-term after stroke (Thrift et al 2014 *[35]*).

Several therapeutic options area available including aspirin, clopidogrel and combination of low dose aspirin and modified release dipryridamole.

Strong Recommendation

Long-term antiplatelet therapy (low-dose aspirin, clopidogrel or combined low-dose aspirin and modified release dipyridamole) should be prescribed to all patients with ischaemic stroke or TIA who are not prescribed anticoagulation therapy, taking into consideration patient co-morbidities. (Rothwell et al 2016 *[44]*; Niu et al 2016 *[45]*; Sandercock et al 2014 *[46]*)

### Practical Info

Aspirin generally commences with initial loading dose of 300mg followed by daily low dose of 100-150mg.
Clopidogrel (Iscover, Plavix) is a daily dose of 75mg and can also be commenced with a loading dose of 300mg if rapid onset is required.
Aspirin plus dipyridamole sustained release (Asasantin SR) contains 200 mg of dipyridamole in a sustained-release form and 25 mg of aspirin in a standard (immediate) release form.
Aspirin may be provided as a suppository in patients with dysphagia.

### Key Info

**Benefits and harms** — Substantial net benefits of the recommended alternative

Aspirin, aspirin-dipyridamole and clopidogrel all reduce recurrent ischaemic events (Rothwell et al 2016 *[44]*; Niu et al 2016 *[45]*; Sandercock et al 2014 *[46]*; Kwok et al 2015 *[47]*; Malloy et al 2013 *[48]*). The absolute benefit outweighs the risk of bleeding complications in the majority of patients. The absolute difference between antiplatelets is small.

**Certainty of the Evidence** — High

The quality of evidence is high.

**Preference and values** — No substantial variability expected

A very small number of patients (<1%) are intolerant to aspirin. No variation in preferences is expected as risk of stroke would outweigh small risk of bleeding.

**Resources and other considerations** — No important issues with the recommended alternative

<u>Resources considerations</u>
Aspirin, dipyridamole, clopidogrel and combinations of these agents have been compared to one another and to placebo in several economic evaluations, and in two reviews (Malinina et al 2007 *[59]*; Jones et al 2004 *[60]*). The settings of these economic evaluations were the UK, USA and France and may not be completely applicable to an Australian setting. Since these evaluations have been conducted, the prices of the antiplatelet medications have been reduced in Australia after expiry of patents for these medications.

Aspirin has been found to be more effective and cost saving (Heeg et al 2007 *[61]*) and cost effective at an additional cost of US$1,725 per QALY gained (cost reference year not reported) (Matchar et al 2005 *[62]*) when compared to placebo. A combination of aspirin and dipyridamole was found to be cost-effective at an additional cost of US$1,769 per QALY gained compared to placebo (cost reference year not reported) (Matchar et al 2005 *[62]*) . There is conflicting evidence about the cost-

effectiveness of clopidogrel compared to placebo, with one economic evaluation finding clopidogrel to be cost effective at an additional cost of US$31,200 per QALY gained (cost reference year 2002) (Schleinitz et al 2004 *[63]*); and another finding it not cost-effective (given a willingness to pay of US$50,000 per QALY gained) at an additional cost of US$57,714 per QALY gained (cost reference year not reported) (Matchar et al 2005 *[62]*). Both studies were performed prior to the availability of cheaper generic clopidogrel post-patent expiry.

A combination of aspirin and dipyridamole appears to have the most consistent economic evidence. It has been found to be cost-effective (Chambers et al 1999 *[67]*; Marissal et al 2004 *[66]* ; Heeg et al 2007 *[61]*; Malinina et al 2007 *[59]*; Shah et al 2000 *[65]*); and more effective and cost saving (Sarasin et al 2000 *[64]*) when compared to aspirin alone. Compared to clopidogrel, there is evidence that aspirin and dipyridamole was cost-effective or more effective and cost saving (Heeg et al 2007 *[61]*; Malinina et al 2007 *[59]*) but again these analyses preceded generic clopidogrel .

Prior to the availability of generic formulations, clopidogrel was found to be less effective and more costly than all other antiplatelet agents (Matchar et al 2005 *[62]*) . There is evidence that clopidogrel was not cost-effective (given a willingness to pay of US$50,000 per QALY gained) when compared to aspirin at an additional cost of US$161,316 per stroke prevented (cost reference year 1999) (Shah et al 2000 *[65]*). However, there is also some evidence that it is cost-effective at an additional cost of US$26,580 per QALY gained (cost reference year 1998) (Sarasin et al 2000 *[64]*); and cost-effective for high-risk patients (Heeg et al 2007 *[61]* ).

**Implementation considerations**
Data are collected against a clinical indicator on early antiplatelet therapy and long term (secondary) prevention in the National Stroke Audit. Antiplatelet therapy is included in the Acute Stroke Clinical Care Standard as a bundle approach with blood pressure lowering and cholesterol lowering medication.

## Rationale

Antiplatelet therapy remains a cornerstone of preventative medicine for those with ischaemic stroke or TIA unless the patient has known atrial fibrillation where anticoagulation therapy should be provided. Long term therapy has been shown to have clear benefits in reducing the risk of further strokes but does have a small increase risk of haemorrhage (Sandercock et al 2014 *[46]*; Niu et al 2016 *[45]*). Aspirin remains the most readily available, cheapest and most widely used antiplatelet agent. Clopidogrel or extended-release dipyridamole plus low-dose aspirin are equally effective and both have been shown to be more effective than aspirin alone in reducing further stroke events.

Initiation of therapy should occur early after stroke onset (once brain scan has excluded intracerebral haemorrhage) taking into consideration issues such as dysphagia. Use of antiplatelet agents increases the chance of complications in those receiving intravenous thrombolysis and as such initiation should be delayed for 24 hours until repeat brain imaging has excluded significant haemorrhagic transformation.

Commencement of therapy prior to discharge from hospital (for those admitted) improves long-term adherence.

## Clinical Question/ PICO

**Population:** Adults with stroke
**Intervention:** Aspirin only
**Comparator:** Placebo


### Summary

Niu et al (2016) *[45]* conducted a network meta-analysis assessing the efficacy of various antiplatelet agents, comparing agents both directly and to placebo. The network analysis included 36 studies with 82,144 patients in total, although not all of these would have included placebo or aspirin only treatment arms. The mean follow-up duration was 26.9 months. Aspirin interventions were broken up into 4 subgroups: very low doses of 30-50mg daily, low doses of 75-162mg daily, median doses of 283-330mg daily, and high doses of 500-1500mg. All dosages of aspirin reduced recurrent stroke, although this reduction was non-significant for very low and median dosages. All dosages also reduced serious vascular events, although this was non-significant for very low dosages. All dosages significantly increased bleeding. No significant differences were found between different dosages of aspirin.

Note that because this review used network meta-analysis, patient data could contribute to the analysis even if it did not come from trials directly comparing aspirin to placebo. This means that larger numbers of patients and trials contributed to the effect estimate than would have been possible in direct comparisons. The authors also conducted a traditional meta-analysis based on direct comparisons. The effect estimates found were similar but did not always attain statistical significance.

Rothwell et al (2016) *[44]* conducted a systematic review of all randomised trials comparing aspirin to control over the short term. In time-to-event analysis, significant reductions for all strokes were seen both over the 0-6 week period and the 0-12 week period. Significant reductions were also seen in both periods when looking at ischaemic strokes only.

In an earlier Cochrane review, Sandercock et al (2014) *[46]* included 4 randomised trials comparing aspirin to control. Two of these trials contributed 98% of the data. One of the larger trials (CAST 1997) was double-blinded with a placebo group but the other (IST 1997) was open-label, although considered to be essentially blinded as outcomes were assessed by a blinded interviewer at 6 months when most patients did not remember their treatment allocation. Aspirin was associated with a small but significant reduction in odds of death or dependency (OR 0.95, 95% CI 0.91 to 0.99) and recurrent stroke (OR 0.77, 95% CI 0.69 to 0.87). As a conventional meta-analysis, this review included fewer patients and studies than the review by Niu et al (2016), but provides evidence based on direct comparisons between aspirin and control.

Kwok et al (2015) *[47]* conducted a systematic review of antiplatelet therapy for secondary prevention following lacunar stroke, including 17 trials with 42,234 participants. Antiplatelets reduced the risk of any recurrent stroke overall compared to placebo (RR 0.77, 95% CI 0.62 to 0.97), although the only aspirin specific data came from a single trial using either aspirin or dipyridamole.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Placebo | <br>Aspirin only | **Certainty of the Evidence**<br>(Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Recurrent stroke - long term - low dose (75 - 162mg daily)**<br>End of follow-up | Odds Ratio 0.78 (CI 95% 0.63 - 0.99) Based on data from 13,327 patients in 33 studies. [1] (Randomized controlled) Follow up Mean follow-up of 27 months | | | **High** | Low dose aspirin decreases recurrent stroke in the long term |
| **Recurrent stroke - short term - any dose**<br>12 weeks | Hazard Ratio 0.47 (CI 95% 0.37 - 0.61) Based on data from 9,635 patients in 12 studies. [2] (Randomized controlled) Follow up 12 weeks | | | **High**<br>[3] | Aspirin decreases recurrent stroke in the short term |
| **Bleeding - long term - low dose (75 - 162mg daily)**<br>End of follow-up | Odds Ratio 2.33 (CI 95% 1.73 - 3.3) Based on data from 13,327 patients in 30 studies. [4] (Randomized controlled) Follow up Mean follow-up of 27 months | | | **High** | Low dose aspirin increases bleeding in the long term |

| | | | | |
|---|---|---|---|---|
| **Serious vascular events - long term - low dose (75 - 162mg daily)**<br>End of follow-up | Odds Ratio 0.83 (CI 95% 0.71 - 0.96)<br>Based on data from 13,327 patients in 36 studies. [5] (Randomized controlled)<br>Follow up Mean follow-up of 27 months | | **High** | Low dose aspirin decreases serious vascular events in the long term |
| **Death or dependence**<br>End of follow-up<br>9 Critical | Odds Ratio 0.95 (CI 95% 0.91 - 0.99)<br>Based on data from 41,291 patients in 4 studies. (Randomized controlled)<br>Follow up 3 to 6 months | 462 per 1000 — 449 per 1000<br>Difference: **13 fewer** per 1000<br>( CI 95% 23 fewer - 2 fewer ) | **High** | Aspirin decreases death or dependence |
| **Death**<br>End of follow-up<br>9 Critical | Odds Ratio 0.92 (CI 95% 0.87 - 0.98)<br>Based on data from 41,291 patients in 4 studies. (Randomized controlled)<br>Follow up 3 to 6 months | 129 per 1000 — 120 per 1000<br>Difference: **9 fewer** per 1000<br>( CI 95% 15 fewer - 2 fewer ) | **High** | Aspirin decreases death |
| **Symptomatic intracranial haemorrhage**<br>During treatment<br>8 Critical | Odds Ratio 1.22 (CI 95% 1 - 1.5)<br>Based on data from 40,850 patients in 3 studies. (Randomized controlled)<br>Follow up 5 days to 3 months of treatment | 8 per 1000 — 10 per 1000<br>Difference: **2 more** per 1000<br>( CI 95% 0 fewer - 4 more ) | **High** | Aspirin slightly increases symptomatic intracranial haemorrhage |
| **6 week risk of recurrent ischaemic stroke** | Hazard Ratio 0.42 (CI 95% 0.32 - 0.55)<br>Based on data from 15,778 patients in 12 studies. (Randomized controlled) | 24 per 1000 — 10 per 1000<br>Difference: **14 fewer** per 1000<br>( CI 95% 16 fewer - 11 fewer ) | **High** | Aspirin reduces 6 week risk of recurrent stroke |
| **6 week risk of fatal or disabling ischaemic stroke** | Hazard Ratio 0.29 (CI 95% 0.2 - 0.42)<br>Based on data from 15,778 patients in 12 studies. (Randomized controlled) | 15 per 1000 — 4 per 1000<br>Difference: **11 fewer** per 1000<br>( CI 95% 12 fewer - 9 fewer ) | **High** | Aspirin reduces 6 week risk of recurrent fatal or disabling stroke |

1. Systematic review [45] . **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [44] . **Baseline/comparator:** Control arm of reference used for intervention.
3. **Inconsistency: No serious. Indirectness: No serious.** Differences between the intervention/comparator of interest and those studied: many trials conducted before 2000 - standard treatment has changed, Differences between the population of interest

and those studied - many patients began treatment after the very early high risk period. **Imprecision: No serious. Publication bias: No serious.**

4. Systematic review [45] . **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [45] . **Baseline/comparator:** Control arm of reference used for intervention.

## Clinical Question/ PICO

**Population:** Adults with stroke
**Intervention:** Aspirin plus dipyridamole
**Comparator:** Placebo

### Summary

Niu et al (2016) *[45]* conducted a network meta-analysis assessing the efficacy of various anti-platelet agents, comparing agents both directly and to placebo. The network analysis included 36 studies in total, although not all of these would have included placebo or aspirin plus dipyridamole treatment arms. The mean follow-up duration was 26.9 months. Aspirin plus dipyridamole regimens were divided into two subgroups, one with 50mg aspirin + 400mg dipyridamole daily and the other with 990-1300mg aspirin + 150-300mg dipyridamole daily. Both regimens significantly reduced recurrent stroke and serious vascular events and significantly increased bleeding events.

Note that because this review used network meta-analysis, patient data could contribute to the analysis even if it did not come from trials directly comparing aspirin + dipyridamole to placebo. This means that larger numbers of patients and trials contributed to the effect estimate than would have been possible in direct comparisons. The authors also conducted a traditional meta-analysis based on direct comparisons. The effect estimates found were similar but did not always attain statistical significance.

Malloy et al (2013) *[48]* also conducted a network meta-analysis of antiplatelet treatments for secondary prevention of stroke, including 24 articles with > 88,000 patients total. They found a significant reduction in recurrent stroke when comparing aspirin and dipyridamole to placebo (RR 0.63, 95% CI 0.52 to 0.79). However, they did not examine the effects of aspirin by dosage, and Niu et al noted that they also did not include two studies of cilostazol, suggesting this review was less comprehensive.

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Placebo | Aspirin plus dipyridamole | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Recurrent stroke - long term - low dose (A 50mg + D 400mg daily)** End of follow-up | Odds Ratio 0.69 (CI 95% 0.56 - 0.89) Based on data from 20,328 patients in 33 studies. [1] (Randomized controlled) Follow up Mean follow-up of 27 months | | | **High** | Low dose aspirin plus dipyridamole decreases recurrent stroke in the long term |
| **Bleeding - long term - low dose (A 50mg + D 400mg daily)** End of follow-up | Odds Ratio 1.95 (CI 95% 1.43 - 2.78) Based on data from 20,328 patients in 30 studies. [2] (Randomized controlled) | | | **High** | Low dose aspirin plus dipyridamole increases bleeding in the long term |

| | | | | |
|---|---|---|---|---|
| | Follow up Mean follow-up of 27 months | | | |
| **Serious vascular events - long term - low dose (A 50mg + D 400mg daily)** End of follow-up | Odds Ratio 0.72 (CI 95% 0.63 - 0.83) Based on data from 20,328 patients in 36 studies. (Randomized controlled) Follow up Mean follow-up of 27 months | | **High** | Low dose aspirin plus dipyridamole decreases serious vascular events in the long term |

1. Systematic review [45] . **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [45] . **Baseline/comparator:** Control arm of reference used for intervention.

## Clinical Question/ PICO

**Population:** Adults with stroke
**Intervention:** Clopidogrel
**Comparator:** Placebo

### Summary

Niu et al (2016) *[45]* conducted a network meta-analysis assessing the efficacy of various anti-platelet agents, comparing agents both directly to each other and to placebo. The network analysis included 36 studies in total, although not all of these would have included placebo or clopidogrel treatment arms. None of the included trials directly compared clopidogrel to placebo, so comparisons were only possible through network meta-analysis techniques. The mean follow-up duration was 26.9 months, hence the moderate grading of evidence in the table.

However, clopidogrel has been shown to be superior to aspirin in the CAPRIE trial (CAPRIE steering committee 1996 *[68]*). The primary composite endpoint of stroke, myocardial infarction or vascular death occurred in 5.3% clopidogrel versus 5.8% aspirin-treated patients (p=0.04). Severe bleeding occurred in 1.4% clopidogrel versus 1.6% aspirin-treated patients (p=NS). Gastrointestinal bleeding was lower with clopidogrel (2.0 vs 2.7% p<0.05) and intracranial bleeding occurred in 0.35% clopidogrel and 0.49% aspirin-treated patients (p=NS). In the sub-group with stroke or TIA as the qualifying event, stroke was the first event in 5.2% versus 5.7% with aspirin (p=0.28).

Clopidogrel was also shown to have very similar efficacy to aspirin-dipyridamole for secondary stroke prevention in the PROFESS trial (Sacco et al 2008 *[69]*). Recurrent stroke occurred in 9.0% of aspirin-dipyridamole and 8.8% of clopidogrel-treated patients (p=0.56). Major bleeding occurred in 4.1% aspirin-dipyridamole versus 3.6% clopidogrel-treated patients (HR 1.15, 95%CI 1.00-1.32) and intracranial haemorrhage was also less common with clopidogrel (HR 1.42; 95%CI 1.11-1.83).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Placebo Clopidogrel | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|
| **Recurrent stroke** End of follow-up | Odds Ratio 0.68 (CI 95% 0.53 - 0.92) Based on data from | | **Moderate** Due to serious indirectness: the | Clopidogrel probably decreases recurrent stroke |

| | | | | |
|---|---|---|---|---|
| | 24,607 patients in 33 studies. [1] (Randomized controlled)<br>Follow up Mean follow-up of 27 months | | reported estimate is based on a network meta-analysis. No trial directly compared clopidogrel with placebo [2] | |
| **Bleeding**<br>End of follow-up | Odds Ratio 1.79 (CI 95% 1.23 - 2.78)<br>Based on data from 24,607 patients in 30 studies. [3] (Randomized controlled)<br>Follow up Mean follow-up of 27 months | | **Moderate**<br>Due to serious indirectness: the reported estimate is based on a network meta-analysis. No trial directly compared clopidogrel with placebo [4] | Clopidogrel probably increases bleeding compared to placebo |
| **Serious vascular events**<br>End of follow-up | Odds Ratio 0.74 (CI 95% 0.65 - 0.86)<br>Based on data from 24,607 patients in 36 studies. [5] (Randomized controlled)<br>Follow up Mean follow-up of 27 months | | **Moderate**<br>Due to serious indirectness: the reported estimate is based on a network meta-analysis. No trial directly compared clopidogrel with placebo [6] | Clopidogrel probably decreases serious vascular events compared to placebo |

1. Systematic review [45] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: Serious.** Direct comparisons not available. **Imprecision: No serious. Publication bias: No serious.**
3. Systematic review [45] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: Serious.** Direct comparisons not available. **Imprecision: No serious. Publication bias: No serious.**
5. Systematic review [45] . **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: No serious. Indirectness: Serious.** Direct comparisons not available: no study directly compared clopidogrel to placebo. **Imprecision: No serious. Publication bias: No serious.**

Strong Recommendation

All ischaemic stroke and TIA patients should have antiplatelet therapy commenced as soon as possible once brain imaging has excluded haemorrhage unless thrombolysis has been administered, in which case antiplatelet therapy can commence after 24-hour brain imaging has excluded major haemorrhagic transformation. (see Antithrombotic therapy in Acute medical and surgical management)

### Practical Info

Aspirin generally commences with initial loading dose of 300mg followed by daily low dose of 100-150mg.

Aspirin can be provided as a suppository in patients with dysphagia.

## Rationale

Initiation of therapy should occur early after stroke onset (once brain scan has excluded intracerebral haemorrhage) taking into consideration any issues such safe swallowing. Use of antiplatelet agents increases the chance of complications in those receiving intravenous thrombolysis and as such initiation should be delayed for 24 hours after a subsequent brain imaging has occurred.

Strong Recommendation

Aspirin plus clopidogrel should be commenced within 24 hours and used in the short term (first three weeks) in patients with minor ischaemic stroke or high-risk TIA to prevent stroke recurrence. (Hao et al. 2018 *[126]*)

## Practical Info

Importantly, trials commenced treatment within 12 or 24 hours of symptom onset and the risk of recurrent stroke is highest in the first few days so treatment should commence within 24 hours. Patients who received thrombolysis and those with an indication for anticoagulation (e.g. AF) were excluded from the trials.

Treatment should commence with a loading dose of 300mg aspirin and 300-600mg clopidogrel followed by 100-150mg aspirin and 75mg clopidogrel daily for a total of 21 days and a single antiplatelet agent thereafter. POINT used a 600mg loading dose whereas CHANCE and FASTER used 300mg, the difference being faster onset and greater degree of antiplatelet effect when 600mg is used (Montalescot et al 2006 *[127]*)

It is worth considering proton pump inhibitor use (e.g. pantoprazole to avoid potential CYP2C19 interactions) to protect against erosive gastritis in these patients.

## Key Info

**Benefits and harms**

Substantial net benefits of the recommended alternative

This recommendation applies to patients with minor stroke and at high risk of TIA who have not received intravenous thrombolysis.
Aspirin plus clopidogrel reduces non-fatal recurrent stroke in the first 90 days by approximately 1.9%.There were trends towards reduced risk of moderate or severe functional disability and of poor quality of life (Hao et al *[126]*).

Aspirin plus clopidogrel results in small (0.2%) increase in moderate to major extracranial bleeding events and a small increase in the risk of minor extracranial bleeding events by approximately 0.7% (Hao et al *[126]*). In the POINT trial, most of the benefit in reduced recurrent ischemic stroke occurred in the first 3 weeks (1.9%) and excess major bleeding in that period was 0.3%. There was no advantage of ongoing use of aspirin plus clopidogrel to 90 days with no reduction in stroke and accumulation of major bleeding events. *[121][125]*

**Certainty of the Evidence**

Moderate

The quality of evidence across outcomes is moderate to high. Some outcomes were rated down from high to moderate for imprecision.

**Preference and values**

No substantial variability expected

Patients are likely to prefer to receive this treatment due to significant benefits (avoid another stroke) over much smaller risk of harm (extracranial bleed).

**Resources and other considerations**

No important issues with the recommended alternative

<u>Resources considerations</u>
In an economic evaluation of patients with acute TIA or minor stroke with a high risk of recurrence, it was found that clopidogrel plus aspirin, compared to aspirin alone, was cost-effective at an additional cost of US$5,200 per QALY gained (cost reference year 2011), and was cost-saving when the cost of the generic clopidogrel drug was used (Pan et al. 2014 *[120]*). This economic evaluation was based on a study conducted in a Chinese setting and clopidogrel was provided beyond the first three weeks and up to 90 days post-event in this study. No equivalent evaluations have been conducted for an Australian setting.

Clopidogrel has come off patent in Australia, which will reduce treatment costs. As a result, it is anticipated that this will improve the cost-effectiveness of this medication.

**Implementation considerations**
There is a clinical indicator collected on early antiplatelet therapy and long term (secondary) prevention in the National Stroke Audit. Antiplatelet therapy is included in the Acute Stroke Clinical Care Standard as a bundle approach with blood pressure lowering and cholesterol lowering medication.

## Rationale

This recommendation applies to patients with minor stroke and at high risk of TIA who have not received intravenous thrombolysis. Evidence from a systematic review and meta-analysis of three trials (involving over 10,000 patients) found that the combination of aspirin and clopidogrel, commenced with a loading dose within 24 hours, significantly improved patient outcomes. The benefit in reducing recurrent stroke is predominantly within the first 21 days. However, the risk of major bleeding increases over time and there is probably no net benefit to continuing clopidogrel plus aspirin beyond 21 days. The benefits of early dual therapy appear to apply to all stroke sub types and therefore should be used.

## Clinical Question/ PICO

**Population:** Adults with stroke
**Intervention:** Aspirin plus clopidogrel
**Comparator:** Aspirin or clopidogrel alone

### Summary

Zhang et al (2014) *[51]* conducted a systematic review comparing combination aspirin plus clopidogrel to aspirin or clopidogrel alone. Interventions were divided into two subgroups: short-term treatments lasting less than 3 months and long-term treatments lasting more than 1 year.

The short-term RCTs showed significant reductions in recurrent stroke, and the combined outcome of recurrent stroke, MI and vascular events. Major bleeding events showed a non-significant increase, with low numbers of events overall.

For long-term treatment, the reductions in recurrent stroke and the composite outcome were not significant, while the increase in major bleeding events was significant.

**Note:** the published version of Zhang et al (2014) contained multiple errors in the reporting of results. Correct results were reported in the errata and the estimates reported here come from these correct results.

Gouya et al (2014) *[50]* also compared aspirin and clopidogrel to aspirin in a systematic review, largely including the same trials. They did not differentiate between short and long-term outcomes in their overall meta-analysis, finding a significant overall reduction in recurrent stroke (RR 0.76, 95% CI 0.68 to 0.86).

In the network meta-analysis by Niu et al (2016) *[45]*, comparisons between aspirin + clopidogrel and aspirin or clopidogrel alone generally showed non-significant differences in the odds of recurrent stroke. Since this was a network meta-analysis, larger numbers of patients and trials could contribute to these comparisons as they did not have to come from trials that directly compared the treatments. Restricting the analysis to the direct comparisons only showed similar results to the earlier reviews, although this review analysed aspirin by dosage. In direct comparisons, combination aspirin and clopidogrel significantly reduced recurrent stroke compared to 75-162mg doses of aspirin daily (OR 0.77, 95% CI 0.60 to 0.99), although this comparison was non-significant in the full network analysis.

For lacunar stroke, Côté et al (2014) *[52]* conducted a post hoc analysis of patient data from 838 patients in the SPS3 trial. Combined aspirin and clopidogrel treatment was compared to aspirin alone. The risk of recurrent stroke following the dual antiplatelet therapy was not significantly different compared to aspirin alone (HR 0.91, 95% CI 0.61 to 1.37).

| **Outcome**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Aspirin or | <br>Aspirin plus | **Certainty of the Evidence** | **Plain text summary** |
|---|---|---|---|---|---|

| | | | (Quality of evidence) | |
|---|---|---|---|---|
| **Secondary stroke - short term treatment** [1]<br>less than 3 months<br>7 Critical | Relative risk 0.69 (CI 95% 0.59 - 0.81)<br>Based on data from 5,789 patients in 5 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | **114** per 1000 — **79** per 1000<br>Difference: **35 fewer** per 1000<br>( CI 95% 22 fewer - 47 fewer ) | **High** [2] | Short term treatment with aspirin plus clopidogrel decreases secondary stroke |
| **Secondary stroke - long term treatment** [3]<br>more than one year<br>7 Critical | Relative risk 0.92 (CI 95% 0.83 - 1.03)<br>Based on data from 14,939 patients in 3 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | **82** per 1000 — **75** per 1000<br>Difference: **7 fewer** per 1000<br>( CI 95% 2 more - 14 fewer ) | **Moderate**<br>Due to serious imprecision [4] | Long term treatment with aspirin plus clopidogrel may decrease secondary stroke slightly |
| **Major bleeding - short term treatment** [5]<br>less than 3 months<br>7 Critical | Relative risk 2.17 (CI 95% 0.18 - 25.71)<br>Based on data from 5,789 patients in 5 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | **3** per 1000 — **7** per 1000<br>Difference: **4 more** per 1000<br>( CI 95% 74 more - 2 fewer ) | **Low**<br>Due to serious inconsistency, Due to serious imprecision [6] | Short term treatment with aspirin plus clopidogrel may increase major bleeding |
| **Major bleeding - long term treatment** [7]<br>more than one year<br>7 Critical | Relative risk 1.9 (CI 95% 1.46 - 2.48)<br>Based on data from 14,939 patients in 3 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | **25** per 1000 — **48** per 1000<br>Difference: **23 more** per 1000<br>( CI 95% 37 more - 12 more ) | **High** [8] | Long term treatment with aspirin plus clopidogrel increases major bleeding |
| **Secondary stroke, MI or vascular death - short term treatment** [9]<br>less than 3 months<br>8 Critical | Relative risk 0.7 (CI 95% 0.6 - 0.82)<br>Based on data from 5,789 patients in 5 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | **116** per 1000 — **81** per 1000<br>Difference: **35 fewer** per 1000<br>( CI 95% 21 fewer - 46 fewer ) | **High** [10] | Short term treatment with aspirin plus clopidogrel decreases secondary stroke, MI or vascular death |
| **Secondary stroke, MI or vascular death - long term** | Relative risk 0.92 (CI 95% 0.84 - 1.01)<br>Based on data from 14,939 patients in 3 | **117** per 1000 — **108** per 1000 | **Moderate**<br>Due to serious imprecision [12] | Long term treatment with aspirin plus clopidogrel may decrease secondary |

| | | | |
|---|---|---|---|
| **treatment** [11] more than one year<br><br>8 Critical | studies. (Randomized controlled) Follow up 7 days to 3.4 years | Difference: **9 fewer** per 1000 ( CI 95% 1 more - 19 fewer ) | stroke, MI or vascular death slightly |

1. Short term treatment meant combination therapy was delivered for between 7 days and 3 months
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** The authors report that funnel plots were not symmetrical but provided no further details, The search in the Systematic review was not comprehensive: only published studies included.
3. Long term treatment occurred for 1 year or more
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.** The authors report that funnel plots were not symmetrical but provided no further details, The search in the Systematic review was not comprehensive: only published studies included.
5. Short term treatment meant combination therapy was delivered for between 7 days and 3 months
6. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2 = 65%., The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: Serious.** Low numbers of events: there were 0 major bleeding events in either the intervention or control group in many trials, Wide confidence intervals. **Publication bias: No serious.** The authors report that funnel plots were not symmetrical but provided no further details, The search in the Systematic review was not comprehensive: only published studies included.
7. Long term treatment occurred for 1 year or more
8. **Inconsistency: No serious.** The magnitude of statistical heterogeneity was high, with I^2: 57%, but excluding an outlying trial did not change conclusions.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** The authors report that funnel plots were not symmetrical but provided no further details, The search in the Systematic review was not comprehensive: only published studies included.
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11. Long term treatment occurred for 1 year or more
12. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.** The authors report that funnel plots were not symmetrical but provided no further details, The search in the Systematic review was not comprehensive: only published studies included.

Strong Recommendation Against

The combination of aspirin plus clopidogrel should not be used for the long-term secondary prevention of cerebrovascular disease in people who do not have acute coronary disease or recent coronary stent. (Zhang et al 2015 *[51]*)

## Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

The combination of aspirin plus clopidogrel did not show superiority compared to aspirin or clopidogrel alone - there was little difference in benefits but a significantly increased risk of major bleeding (23 per 1000 patients treated) (Zhang et al 2015 *[51]*).

**Certainty of the Evidence** — High

Three large well conducted randomised controlled trials

**Preference and values**

No substantial variability expected

No variation expected

**Resources and other considerations**

No important issues with the recommended alternative

Resources considerations
No literature to understand or describe the potential economic implications of this recommendation was identified.

Implementation considerations
There is a clinical indicator collected on early antiplatelet therapy and long term (secondary) prevention in the National Stroke Audit.

## Rationale

A meta-analysis of several large trials has found little benefit of long-term use of combined aspirin plus clopidogrel versus aspirin or clopidogrel alone but there is an increased risk of harm (Zhang et al 2015 *[51]*). This combination should only be considered with other clear indications such as acute coronary disease or coronary stent.

## Clinical Question/ PICO

**Population:** Adults with stroke
**Intervention:** Aspirin plus clopidogrel
**Comparator:** Aspirin or clopidogrel alone

### Summary

Zhang et al (2014) *[51]* conducted a systematic review comparing combination aspirin plus clopidogrel to aspirin or clopidogrel alone. Interventions were divided into two subgroups: short-term treatments lasting less than 3 months and long-term treatments lasting more than 1 year.

The short-term RCTs showed significant reductions in recurrent stroke, and the combined outcome of recurrent stroke, MI and vascular events. Major bleeding events showed a non-significant increase, with low numbers of events overall.

For long-term treatment, the reductions in recurrent stroke and the composite outcome were not significant, while the increase in major bleeding events was significant.

**Note:** the published version of Zhang et al (2014) contained multiple errors in the reporting of results. Correct results were reported in the errata and the estimates reported here come from these correct results.

Gouya et al (2014) *[50]* also compared aspirin and clopidogrel to aspirin in a systematic review, largely including the same trials. They did not differentiate between short and long-term outcomes in their overall meta-analysis, finding a significant overall reduction in recurrent stroke (RR 0.76, 95% CI 0.68 to 0.86).

In the network meta-analysis by Niu et al (2016) *[45]*, comparisons between aspirin + clopidogrel and aspirin or clopidogrel alone generally showed non-significant differences in the odds of recurrent stroke. Since this was a network meta-analysis, larger numbers of patients and trials could contribute to these comparisons as they did not have to come from trials that directly compared the treatments. Restricting the analysis to the direct comparisons only showed similar results to the earlier reviews, although this review analysed aspirin by dosage. In direct comparisons, combination aspirin and clopidogrel significantly reduced recurrent stroke compared to 75-162mg doses of aspirin daily (OR 0.77, 95% CI 0.60 to 0.99), although this comparison was non-significant in the full network analysis.

For lacunar stroke, Côté et al (2014) *[52]* conducted a post hoc analysis of patient data from 838 patients in the SPS3 trial.

Combined aspirin and clopidogrel treatment was compared to aspirin alone. The risk of recurrent stroke following the dual antiplatelet therapy was not significantly different compared to aspirin alone (HR 0.91, 95% CI 0.61 to 1.37).

| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Aspirin or clopidogrel alone | <br>Aspirin plus clopidogrel | Certainty of the Evidence<br>(Quality of evidence) | Plain text summary |
|---|---|---|---|---|---|
| **Secondary stroke - short term treatment** [1]<br>less than 3 months<br>7 Critical | Relative risk 0.69<br>(CI 95% 0.59 - 0.81)<br>Based on data from 5,789 patients in 5 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | 114<br>per 1000 | 79<br>per 1000<br>Difference: **35 fewer** per 1000<br>( CI 95% 22 fewer - 47 fewer ) | **High**<br>[2] | Short term treatment with aspirin plus clopidogrel decreases secondary stroke |
| **Secondary stroke - long term treatment** [3]<br>more than one year<br>7 Critical | Relative risk 0.92<br>(CI 95% 0.83 - 1.03)<br>Based on data from 14,939 patients in 3 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | 82<br>per 1000 | 75<br>per 1000<br>Difference: **7 fewer** per 1000<br>( CI 95% 2 more - 14 fewer ) | **Moderate**<br>Due to serious imprecision [4] | Long term treatment with aspirin plus clopidogrel may decrease secondary stroke slightly |
| **Major bleeding - short term treatment** [5]<br>less than 3 months<br>7 Critical | Relative risk 2.17<br>(CI 95% 0.18 - 25.71)<br>Based on data from 5,789 patients in 5 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | 3<br>per 1000 | 7<br>per 1000<br>Difference: **4 more** per 1000<br>( CI 95% 74 more - 2 fewer ) | **Low**<br>Due to serious inconsistency, Due to serious imprecision [6] | Short term treatment with aspirin plus clopidogrel may increase major bleeding |
| **Major bleeding - long term treatment** [7]<br>more than one year<br>7 Critical | Relative risk 1.9<br>(CI 95% 1.46 - 2.48)<br>Based on data from 14,939 patients in 3 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | 25<br>per 1000 | 48<br>per 1000<br>Difference: **23 more** per 1000<br>( CI 95% 37 more - 12 more ) | **High**<br>[8] | Long term treatment with aspirin plus clopidogrel increases major bleeding |
| **Secondary stroke, MI or vascular death - short term treatment** [9]<br>less than 3 months | Relative risk 0.7<br>(CI 95% 0.6 - 0.82)<br>Based on data from 5,789 patients in 5 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | 116<br>per 1000 | 81<br>per 1000<br>Difference: **35 fewer** per 1000<br>( CI 95% 21 fewer - 46 fewer ) | **High**<br>[10] | Short term treatment with aspirin plus clopidogrel decreases secondary stroke, MI or vascular death |

| | | | | | |
|---|---|---|---|---|---|
| 8 Critical<br><br>**Secondary stroke, MI or vascular death - long term treatment** [11]<br>more than one year<br><br>8 Critical | Relative risk 0.92<br>(CI 95% 0.84 - 1.01)<br>Based on data from 14,939 patients in 3 studies. (Randomized controlled)<br>Follow up 7 days to 3.4 years | 117<br>per 1000<br><br>108<br>per 1000<br><br>Difference: **9 fewer** per 1000<br>( CI 95% 1 more - 19 fewer ) | **Moderate**<br>Due to serious imprecision [12] | Long term treatment with aspirin plus clopidogrel may decrease secondary stroke, MI or vascular death slightly |

1. Short term treatment meant combination therapy was delivered for between 7 days and 3 months
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** The authors report that funnel plots were not symmetrical but provided no further details, The search in the Systematic review was not comprehensive: only published studies included.
3. Long term treatment occurred for 1 year or more
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11. Long term treatment occurred for 1 year or more
12. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.** The authors report that funnel plots were not symmetrical but provided no further details, The search in the Systematic review was not comprehensive: only published studies included.

Strong Recommendation Against

Antiplatelet agents should not be used for stroke prevention in patients with atrial fibrillation. (Connolly et al 2011 *[54]*)

## Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

Antiplatelet agents have been shown to be inferior in preventing stroke compared to the direct acting oral anticoagulants (21 more stroke and systemic embolism per 1000 patients treated) with similar safety profile (no difference in major bleeding events) (Connolly et al 2011 *[54]*).

**Certainty of the Evidence** — High

High-quality evidence from a large randomised controlled trial with low risk of bias.

**Preference and values** — No substantial variability expected

Due to the increased risk of bleeding and uncertain benefits in preventing stroke, patients are unlikely to want to receive antiplatelet agents.

**Resources and other considerations** — No important issues with the recommended alternative

Resources considerations
No literature to understand or describe the potential economic implications of this recommendation was identified.

Implementation considerations
Antiplatelet use along with AF is collected as part of the National Stroke Audit.

## Rationale

Patients with atrial fibrillation and previous stroke and transient ischaemic attack are at high risk of recurrent stroke. Compared to anticoagulants, antiplatelet agents are ineffective in reducing recurrent stroke. Moreover, apixaban has been shown to significantly reduce the risk of recurrent stroke without increasing major bleeding versus aspirin. Therefore, in patients with atrial fibrillation, antiplatelet agents should not be used for secondary prevention of stroke. If the patient's risk of major bleeding is genuinely deemed to be too high to prescribe apixaban then this is also likely to apply to aspirin. Combined aspirin and clopidogrel was trialled as an alternative to anticoagulation prior to DOAC availability. This combination was less effective than warfarin and still caused significant bleeding.

## Clinical Question/ PICO

**Population:** Adults with AF and unsuitable for vitamin K antagonist therapy
**Intervention:** Factor Xa inhibitor
**Comparator:** Aspirin

### Summary

The AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study was designed to determine the efficacy and safety of apixaban, at a dose of 5 mg twice daily, as compared with aspirin, at a dose of 81 to 324 mg daily, for the treatment of patients with atrial fibrillation for whom vitamin K antagonist therapy was considered unsuitable (Connolly et al 2011 *[54]*). Most of the reasons for warfarin ineligibility related to adherence, INR control or patient preference rather than bleeding risk. Conducted in 36 countries with 5599 patients, this trial showed reduction in stroke and systemic embolism (21 fewer per 1000) very similar rates of major bleeding and intracranial haemorrhage. There was also a non-significant trend in reduction of the outcome death per year. In a predefined subgroup analysis of patients with previous stroke and transient ischaemic attack (TIA) (Diener et al 2012 *[55]*), the benefit of apixaban appeared even greater (HR 0.29, 95%CI 0.15 - 0.60), with cumulative hazard at one year of 2.39 in apixaban group and 9.16 in aspirin group. This also highlights that patients with AF and previous stroke and TIA are at high risk of recurrent stroke.

The National Clinical Guideline Centre in UK has summarised the evidence for using anticoagulation and antiplatelets for

patients with atrial fibrillation (AF) (NICE 2014 *[56]*). They concluded that anticoagulation was more effective in reducing ischaemic stroke (HR 0.31, 95% CI 0.22 - 0.45) but increased risk of intracerebral haemorrhage (HR 3.44, 95%CI 1.12 - 12.50). On the other hand, single agent antiplatelet by itself did not significantly reduce recurrent stroke (HR 0.78, 95% CI 0.55 - 1.09), and dual-antiplatelet therapy also increased the risk of intracerebral haemorrhage (HR 2.10, 95%CI 0.53 - 9.59). This evidence was largely based on comparisons with vitamin K antagonist therapy (i.e. warfarin). Direct acting oral anticoagulants (DOACs) have been shown to have a favourable risk-benefit profile compared to warfarin, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding (Ruff et al 2014 *[70]*).

| **Outcome**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Aspirin | <br>Factor Xa inhibitor | **Certainty of the Evidence**<br>(Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **All-case death**<br>1 year<br><br>9 Critical | Hazard Ratio 0.79<br>(CI 95% 0.62 - 1.02)<br>Based on data from 5,599 patients in 1 studies. (Randomized controlled)<br>Follow up mean 1.1 year | 44<br>per 1000 | 35<br>per 1000<br><br>Difference: **9 fewer** per 1000<br>( CI 95% 1 more - 17 fewer ) | **Moderate**<br>Due to serious imprecision [1] | Factor Xa inhibitors probably decrease all-case death |
| **Stroke and systemic embolism**<br>1 year<br><br>8 Critical | Relative risk 0.45<br>(CI 95% 0.32 - 0.62)<br>Based on data from 5,599 patients in 1 studies. (Randomized controlled)<br>Follow up mean 1.1 year | 37<br>per 1000 | 16<br>per 1000<br><br>Difference: **21 fewer** per 1000<br>( CI 95% 14 fewer - 25 fewer ) | **High**<br>[2] | Factor Xa inhibitors decrease stroke and systemic embolism |
| **Major bleeding** [3]<br>1 year<br><br>8 Critical | Hazard Ratio 1.13<br>(CI 95% 0.74 - 1.75)<br>Based on data from 5,599 patients in 1 studies. (Randomized controlled)<br>Follow up mean 1.1 year | 12<br>per 1000 | 14<br>per 1000<br><br>Difference: **2 more** per 1000<br>( CI 95% 9 more - 3 fewer ) | **High**<br>[4] | Factor Xa inhibitors have little or no difference on major bleeding |

1. **Inconsistency: No serious. Indirectness: No serious.** Primary analysis was not for patients with previous stroke, but subgroup analysis of that population still showed significant benefits. **Imprecision: Serious.** Only one study but it's multi-center in a number of countries; confidence interval just cross null value, and the study was terminated early so the confidence interval could have been narrower. **Publication bias: No serious.**
2. **Inconsistency: No serious. Indirectness: No serious.** Primary analysis was not for patients with previous stroke, but subgroup analysis of that population still showed significant benefits. **Imprecision: No serious.** Only one study but it's multi-center in a number of countries. **Publication bias: No serious.**
3. The primary safety outcome major bleeding was defined as clinically overt bleeding accompanied by one or more of the following: a decrease in the haemoglobin level of 2 gper deciliter or more over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding.
4. **Inconsistency: No serious. Indirectness: No serious.** Primary analysis was not for patients with previous stroke, but subgroup analysis of that population still showed significant benefits. **Imprecision: No serious.** Only one study but it's multi-center in a number of countries. **Publication bias: No serious.**

## Anticoagulant therapy

Anticoagulation is used for long-term secondary prevention following cardioembolic stroke, particularly due to atrial fibrillation (AF). Twenty-nine percent of patients with stroke were admitted with AF in the last National Stroke Audit of Acute Services (Stroke Foundation 2015 *[197]*) and a further 5% were identified during the stroke admission. Only 62% of patients with AF were discharged on oral anticoagulation following ischaemic stroke (Stroke Foundation 2015 *[197]*). Until recently, treatment was usually warfarin which required monitoring of INR levels. Direct oral anticoagulants (DOACs), which inhibit thrombin and factor Xa, are now available and do not require INR monitoring. DOACs include dabigatran, rivaroxaban, apixaban and edoxaban.

Uncertainty remains about the ideal time to commence therapy and no clear data are available to inform this decision. Trials generally enrolled patients after one or two weeks to reduce the risk of haemorrhage (only 12% of patients in the ESPRIT trial were enrolled within one week).

Medication adherence and the need for careful monitoring is a major issue. Anticoagulant therapy is consistently found to be under-used in primary practice.

Strong Recommendation

- For patients with ischaemic stroke or TIA, with atrial fibrillation (both paroxysmal and permanent), oral anticoagulation is recommended for long-term secondary prevention. (Saxena et al 2004 *[85]*; Saxena 2004 *[86]*; Ruff et al 2014 *[70]*)
- Direct oral anticoagulants (DOACs) should be initiated in preference to warfarin for patients with non-valvular atrial fibrillation and adequate renal function. (Ruff et al 2014 *[70]*)
- For patients with valvular atrial fibrillation or inadequate renal function, warfarin (target INR 2.5, range 2.0-3.0) should be used. Patients with mechanical heart valves or other indications for anticoagulation should be prescribed warfarin. (Tawfik et al 2016 *[99]*)

### Practical Info

Valvular AF is defined as mechanical prosthetic valve or moderate-severe mitral stenosis (Di Biase et al 2016 *[100]*, Kirchhof et al 2016 *[101]*).

When considering DOAC use, Creatinine Clearance should be calculated using the Cockcroft-Gault formula (eGFR is insufficiently accurate), with reference to the product information for each specific agent regarding the CrCl ranges for dosage adjustment.

Bleeding risk factors should be actively monitored and treated including intensive management of blood pressure, avoidance of concurrent antiplatelet therapy and minimising alcohol intake. In addition, patients should be provided with education regarding these bleeding risk factors, and the role they can take in minimising them.

Idarucizumab has been shown to successfully reverse the anticoagulant effect of dabigatran (Pollack et al 2016 *[98]*). Idarucizumab is TGA approved and available in Australia. Andexanet alfa has been shown to reverse the inhibition of factor Xa in healthy volunteers (Connolly et al 2016 *[97]*). This is not currently available in Australia.

If warfarin is used, information should be provided to patients about the potential impact of certain foods and other medications. Implications of ongoing INR testing is also required, including things to consider such as pathology centre location, collection times and any assistance the patient may need. (Some labs provide a mobile blood collection / venipuncture service at the patient's place of residence).

### Key Info

**Benefits and harms**

Substantial net benefits of the recommended alternative

Warfarin substantially reduces the risk of stroke for patients with atrial fibrillation versus antiplatelet or no antithrombotic therapy (Tawfik et al 2016 *[99]*). Compared to Warfarin, DOACs further reduce the risk of stroke with less bleeding. In a meta-analysis of 71684 patients in four phase 3 RCTs, DOACs reduced all-cause mortality (RR 0.90, 95%CI 0.85 -0.95), intracranial haemorrhage (RR 0.48, 95%CI 0.39 - 0.59) and stroke or systematic embolic events (RR 0.81, 95%CI 0.73 - 0.91) versus warfarin in patients with AF (Ruff et al 2014 *[70]*). DOACs also slightly decreased the risk of recurrent stroke or systematic embolic events (8 per 1000 patients) and major bleeding (7 per 100 patients) versus warfarin in patients with previous stroke (Ruff et al 2014 *[70]*). The relative risk of major gastrointestinal bleeding versus warfarin appears to vary between DOACs, being higher than warfarin with rivaroxaban and 150mg BD dabigatran and similar to warfarin with 110mg BD dabigatran and

apixaban. Antiplatelet agents are not effective for stroke prevention in patients with atrial fibrillation and in the AVERROES trial the safety profile of apixaban was equivalent to aspirin with superior efficacy (Diener et al 2012 *[74]*).

**Certainty of the Evidence** High

Component randomised trials were of high quality. The validity of meta-analysis of the different DOACs could be questioned.

**Preference and values** No substantial variability expected

In general for patients initiating anticoagulation, the efficacy and convenience of DOACs make them the preferred option, provided the atrial fibrillation is non-valvular and kidney function is adequate. Patients with long-term stable warfarin use may elect to continue warfarin although the risk of intracerebral haemorrhage remains higher on warfarin.

**Resources and other considerations** No important issues with the recommended alternative

Resources considerations

For patients with atrial fibrillation, there is evidence from the Australian secondary prevention setting that warfarin is a cost-effective alternative to aspirin at $480 per DALY avoided (cost reference year 1997) (Mihalopoulos et al 2005 *[94]*). In overseas settings, warfarin has been found to more cost-effective when provided to patients at greater cardiovascular risk (Holloway et al 1999 *[87]*) or at an optimal dosage (Sorensen et al 2009 *[88]*).

Several economic evaluations of DOACs (Apixaban, Dabigatran and Rivaroxaban) have also been conducted. The settings of the evaluations were Asia, Europe and North America and the majority involved the utilisation of clinical trial data in decision analytic modelling. Two evaluations were specific to secondary stroke prevention (Kamel et al 2012 *[89]*; Kamel et al 2012 *[90]*). In 2010 costs, Dabigatran would be cost-effective at $US25,000 more per QALY gained compared to warfarin and Apixaban would be cost-effective at $US11,400 more per QALY gained compared to warfarin.

In 16 economic evaluations comparing DOACs to warfarin using clinical trial data, DOACs were cost-effective. There was also some evidence in four of these evaluations that DOACs could be cost saving compared to warfarin (Amin et al 2014 *[76]*; Chang et al 2013 *[77]*; Lee et al 2012 *[78]*; Zheng et al 2014 *[79]*). Two studies provided some evidence that DOACs were not cost-effective compared to warfarin (Canestaro et al 2013 *[80]*; Freeman et al 2011 *[81]*). These findings may be explained by a greater disparity in costs between anticoagulation with DOACs and anticoagulation with warfarin used in these latter studies.

There was evidence that treatment with DOACs was more favourable in settings where the anticoagulation with warfarin was not optimal (Chang et al 2014 *[82]*; Davidson et al 2013 *[83]*; You 2014 *[84]*). In general, a decrease in the cost-price of DOACs would be required to make them equivalent to warfarin in terms of cost-effectiveness. In one observational study, it was found that drug price constituted 13.6% of the total cost of anticoagulation with warfarin, but 94% of the total cost of anticoagulation with Dabigatran (Ali et al 2012 *[91]*).

Overall, there is evidence that anticoagulants are an economically acceptable treatment for the prevention of recurrent stroke in patients with stroke and atrial fibrillation.

Implementation considerations

There is a clinical indicator collected on anticoagulation therapy in the National Stroke Audit. Anticoagulation therapy is included in the Acute Stroke Clinical Care Standard for people with AF.

## Rationale

The early studies of warfarin versus no antithrombotic, single antiplatelet or dual antiplatelets clearly demonstrated a substantial reduction in ischaemic stroke with warfarin. Each of the DOACS has high quality randomised trial evidence of non-inferiority and in some cases superiority for stroke prevention compared to warfarin. There was a consistent reduction in intracranial haemorrhage with all the DOACs versus warfarin which is the adverse effect most likely to cause disability and death. DOACs had variable effects on gastrointestinal bleeding versus warfarin. Although during these trials of DOACs versus warfarin there was no DOAC reversal agent available, outcomes after major bleeding, particularly intracerebral bleeding were similar, despite the capacity to reverse warfarin. More recently, idarucizumab has become available for immediate reversal of dabigatran (Pollack et al 2016 *[98]*) and andexenet alfa may become available for Xa inhibitors (Connolly et al 2016 *[97]*). The availability of these reversal agents for major bleeding or emergency surgery may further strengthen the recommendation for DOACs over warfarin.

## Clinical Question/ PICO

**Population:** Adults with stroke with non-valvular atrial fibrillation
**Intervention:** DOACs
**Comparator:** Warfarin

### Summary

Ruff et al (2014) *[70]* conducted a meta-analysis of recent phase 3 trials of direct oral anticoagulants (DOACs) for patients with atrial fibrillation, including 71,683 patients from 4 trials. The DOACs assessed included dabigatran, rivaroxaban, apixaban and edoxaban, and all were compared to warfarin. Meta-analysis showed significant reductions in stroke or systemic embolic events (RR 0.81, 95% CI 0.73 to 0.91) and all-cause mortality (RR 0.90, 95% CI 0.85 to 0.95) in DOAC groups. Reductions in stroke were mainly driven by a significant reduction in intracerebral haemorrhage (RR 0.49, 95% CI 0.38 to 0.64). Overall DOACs were associated with a non-significant reduction in major bleeding, although they significantly increased gastrointestinal bleeding.

Providência et al (2014) *[71]* conducted a similar meta-analysis of phase 3 trials of DOACs. They included the same 4 trials as the Ruff et al. analysis, but did not restrict inclusion to recent trials so also included 3 smaller earlier trials, including 80,290 total patients from 7 trials. DOACs were again associated with significant reductions in recurrent stroke, major bleeding and total mortality. Subgroup analyses compared the two different classes of DOACs used in the trials, direct thrombin inhibitors (DTI) and direct factor Xa inhibitors (FXaI). FXaI treatments showed significant benefits in some comparisons where DTI showed no benefit, although statistical comparisons between the two treatments showed no significant differences.

These trials all included a mixture of patients with and without prior stroke/TIA. Subsequent analyses of the secondary prevention subgroups in each trial demonstrated very similar effects, albeit with reduced power due to lower numbers of patients.

The validity of meta-analyzing results from 4 different DOACs may be questioned given differences in dosing. However, the reduction in intracerebral haemorrhage was a consistent finding in each of the individual trials.

In the RELY trial, Dabigatran 150mg BD significantly reduced ischaemic stroke as well as intracerebral haemorrhage compared to warfarin and had similar rates of major bleeding (although gastrointestinal bleeding was increased). Dabigatran 110mg BD was non-inferior to warfarin for reducing stroke and had less major bleeding compared to warfarin (although gastrointestinal bleeding was similar).

In the ARISTOTLE trial, apixaban 5mg BD (with dose reduction for patients with at least 2 of age>80, weight<60kg or creatinine>133micromol/L) was superior to warfarin in reducing stroke (due to reduction in intracerebral haemorrhage and similar rates of ischaemic stroke). Major bleeding was reduced compared to warfarin, although the rate of gastrointestinal haemorrhage was similar.

In the ROCKET-AF trial rivaroxaban 20mg daily (or 15mg for patients with creatinine clearance 30-49mL/min) was non-inferior to warfarin for stroke prevention and had similar rates of major bleeding although gastrointestinal haemorrhage was higher.

Rasmussen et al (2012) *[73]* conducted an indirect comparison analysis in order to compare the efficacy of the DOACs used in 3 of the recent phase 3 trials. The analysis compared apixaban, dabigatran and rivaroxaban for patients with prior stroke or TIA. Comparing apixaban to dabigatran 150mg twice daily, the only significant difference was a reduction of myocardial infarction with apixaban. Apixaban and dabigatran 150mg twice daily showed no significant differences when compared rivaroxaban. However, dabigatran 110mg twice daily compared to rivaroxaban was associated with less intracerebral haemorrhage, vascular death, major bleeding and intracranial bleeding. Indirect comparison analysis provides only limited evidence for potential differences between these treatments, and evidence from direct comparison trials is required to properly investigate these differences.

The AVERROES trial by Connolly et al (2011) [64] was not included in the other reviews. This trial randomised 5599 patients who had been deemed ineligible for warfarin to either apixaban or aspirin. Most of the reasons for warfarin ineligibility related to adherence, INR control or patient preference rather than bleeding risk. Compared to aspirin, apixaban significantly reduced stroke or systemic embolism in the subgroup of patients with previous stroke or TIA (n=764) (HR 0.29, 95% CI 0.15 to 0.60) (Diener et al 2012 *[74]*) and 6.4 strokes or systemic embolic events would be prevented per 100

patients treated for 1 year on apixaban versus aspirin (number needed to treat for 1 year = 16). The incidence of major bleeding did not differ between aspirin and apixaban (HR 1.28 (0.58–2.82) p=0.73). Intracranial bleeding also did not differ (HR 0.25 (0.03–2.25) p=0.25). This was consistent with the overall AVERROES trial results which had greater precision due to the larger sample size: stroke/systemic embolism 1.6%p.a. apixaban vs 3.7%p.a. aspirin, HR 0.45 (0.32-0.62), p<0.001; major bleeding 1.4%/year apixaban vs 1.2%p.a. aspirin, HR 1.13 (0.74-1.75), p=0.57; intracranial bleeding 0.4%p.a. apixaban vs 0.4%p.a. aspirin, HR 0.85 (0.38–1.90), p=0.69. Note that the number needed to treat to prevent stroke was lower in those with prior stroke due to the higher absolute risk in these patients.

Subsequent meta-analysis (e.g. Ntaois et al 2017; Sterne et al 2017; Liu et al 2020) have all included the same studies as the Ruff et al 2014 paper (with the exception of a subgroup publication specifically in those with existing stroke from the ENGAGE AF-TIMI 48 trial, Rost et al 2016). Liu et al (2020)*[102]* included an additional analysis of observational studies (n=10) published between 2009-2019. Reassuringly NOACs compared to warfarin reduced the risk of stroke or systemic emobolism (RR 0.79, 95% CI 0.72-0.88) and major bleeding (RR 0.70, 95% CI 0.57, 0.86). This analysis also showed dabigatran and rivaroxaban reduced risk of stroke or systemic emobolism, whereas dabigatran and apixaban decreased risk of major bleeding.

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Warfarin | DOACs | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Stroke or systemic embolic events** [1] 2 years<br>8 Critical | Relative risk 0.86 (CI 95% 0.76 - 0.98) Based on data from 17,298 patients in 4 studies. (Randomized controlled) Follow up <2 years | 57 per 1000 | 49 per 1000<br>Difference: 8 fewer per 1000 ( CI 95% 1 fewer - 14 fewer ) | **High** [2] | DOACs decrease stroke or systemic embolic events |
| **Major bleeding** [3]<br>7 Critical | Relative risk 0.89 (CI 95% 0.77 - 1.02) Based on data from 17,298 patients in 4 studies. (Randomized controlled) Follow up <2 years | 64 per 1000 | 57 per 1000<br>Difference: 7 fewer per 1000 ( CI 95% 1 more - 15 fewer ) | **Moderate** Due to serious inconsistency [4] | DOACs probably has little or no difference on major bleeding |

1. All ischemic strokes and Systemic embolic events
2. **Inconsistency: No serious.** The magnitude of statistical heterogeneity was high, with I^2: 47%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** Mostly commercially funded studies.
3. Major bleeding including intracranial hemorrhage and gastrointestinal bleeding
4. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 83%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** Mostly commercially funded studies.

## Clinical Question/ PICO

**Population:** Adults with stroke
**Intervention:** Vitamin K antagonists
**Comparator:** Antiplatelets

**Summary**

In a Cochrane review, Saxena and Koudstaal (2004) *[85]* compared anticoagulants to antiplatelet therapy for secondary prevention in people with nonrheumatic atrial fibrillation who had a transient ischaemic attack or minor ischaemic stroke. Two randomised trials were included with a total of 1371 participants. Both used warfarin for anticoagulation with INR 2.5 to 4.0 or INR 2.0 to 3.5 respectively, while for antiplatelet therapy one trial used aspirin and the other indobufen. Meta-analysis showed that anticoagulants significantly reduced all vascular events (odds ratio 0.67, 95% CI 0.50 to 0.91) and recurrent stroke (odds ratio 0.49, 95% CI 0.33 to 0.72). Anticoagulants significantly increased major extracranial bleeding (odds ratio 5.16, 95% CI 2.08 to 12.83) but the absolute increase in risk was small. Differences in intracranial bleeding were not statistically significant. Both trials were open label, meaning there was some risk of bias, but used blinded assessors, so the quality of the evidence is moderate to high.

Another Cochrane review by Saxena and Koudstaal (2004) *[86]* compared anticoagulants (warfarin) to no treatment controls or placebo for patients with nonrheumatic atrial fibrillation and a previous TIA or minor ischaemic stroke. Two trials involving 485 participants were included, with follow-up of 1.7 and 2.3 years respectively. Anticoagulants significantly reduced recurrent stroke and all vascular events, but significantly increased major extracranial haemorrhage. No intracranial bleeds were reported. One trial was open-label but assessors were blinded and the outcomes assessed were unlikely to be influenced by lack of blinding. The review authors judged that anticoagulants appeared to be beneficial for secondary prevention and without serious adverse events.

| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>Antiplatelets | <br>Vitamin K antagonists | Certainty of the Evidence<br>(Quality of evidence) | Plain text summary |
|---|---|---|---|---|---|
| **Recurrent stroke**<br>End of follow-up<br>8 Critical | Odds Ratio 0.49<br>(CI 95% 0.33 - 0.72)<br>Based on data from 1,371 patients in 2 studies. [1] (Randomized controlled)<br>Follow up 1 - 2+ years | 108<br>per 1000 | 56<br>per 1000<br>Difference: 52 fewer per 1000<br>( CI 95% 70 fewer - 28 fewer ) | **Moderate**<br>Due to serious inconsistency (statistical heterogeneity) [2] | Vitamin K antagonists probably decrease recurrent stroke |
| **All vascular events**<br>End of follow-up<br>7 Critical | Odds Ratio 0.67<br>(CI 95% 0.5 - 0.91)<br>Based on data from 1,371 patients in 2 studies. [3] (Randomized controlled)<br>Follow up 1 to 2+ years | 172<br>per 1000 | 122<br>per 1000<br>Difference: 50 fewer per 1000<br>( CI 95% 78 fewer - 13 fewer ) | **High**<br>[4] | Vitamin K antagonists decrease all vascular events |
| **Any intracranial bleed**<br>End of follow-up<br>7 Critical | Odds Ratio 1.99<br>(CI 95% 0.4 - 9.88)<br>Based on data from 1,371 patients in 2 studies. [5] (Randomized controlled)<br>Follow up 1 to 2+ years | 3<br>per 1000 | 6<br>per 1000<br>Difference: 3 more per 1000<br>( CI 95% 2 fewer - 26 more ) | **Low**<br>Due to very serious imprecision [6] | Vitamin K antagonists may increase intracranial bleeding |
| **Major extracranial bleed**<br>End of follow-up<br>7 Critical | Odds Ratio 5.16<br>(CI 95% 2.08 - 12.83)<br>Based on data from 1,371 patients in 2 studies. [7] (Randomized controlled)<br>Follow up 1 to 2+ years | 3<br>per 1000 | 15<br>per 1000<br>Difference: 12 more per 1000<br>( CI 95% 3 more - 34 more ) | **Moderate**<br>Due to serious imprecision (few events) [8] | Vitamin K antagonists probably increase major extracranial bleeding |

1. Systematic review [85] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Both included trials were open label. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 73%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. Systematic review [85] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: No serious.** Both included trials were open label. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
5. Systematic review [85] . **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: No serious.** Both included studies were open label. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals, few events. **Publication bias: No serious.**
7. Systematic review [85] . **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Few events. **Publication bias: No serious.**

Practice Statement

**Consensus-based recommendation**
For patients with ischaemic stroke, the decision to begin anticoagulant therapy can be delayed for up to two weeks but should be made prior to discharge.

## Practical Info

Timing of commencement of anticoagulation after stroke is complex and based on the perceived risk balance between haemorrhagic transformation of the infarct and recurrent embolic stroke. In the absence of evidence, it is recommended that anticoagulation be commenced urgently after minor stroke / TIA, at 5-7 days after moderate stroke and at 10-14 days after severe stroke. But it is important to commence therapy prior to discharge, as that has been demonstrated to improve long term adherence.

Recommendation Strength Not Set

**Practice points**

- Concurrent antiplatelet therapy should not be used for patients who are anticoagulated for atrial fibrillation unless there is clear indication (e.g. recent coronary stent). Addition of antiplatelet for stable coronary artery disease in the absence of stents should not be used.
- For patients with TIA, anticoagulant therapy should begin once CT or MRI has excluded intracranial haemorrhage as the cause of the current event.
- For patients with ischaemic stroke due to atrial fibrillation and a genuine contraindication to long-term anticoagulation, percutaneous left atrial appendage occlusion may be a reasonable treatment to reduce recurrent stroke risk.

## Key Info

**Resources and other considerations**

**Implementation considerations**
There is a clinical indicator collected on anticoagulation therapy in the National Stroke Audit. Anticoagulation therapy is included in the Acute Stroke Clinical Care Standard for people with AF.

## Rationale

There is unequivocally increased risk of bleeding complications in patients taking concurrent antiplatelets with both warfarin and DOACs. Previous trials have demonstrated that warfarin is actually more effective than aspirin for prevention of future coronary events and stroke but this is not standard practice due to the increased bleeding risk (Hurlen et al 2002 *[92]*; van Es et al 2002 *[93]*) . Nonetheless this indicates that addition of an antiplatelet to anticoagulation for stable ischaemic heart disease is not necessary. There was no significant additional benefit of combined warfarin and aspirin over warfarin in these trials. Although direct evidence for DOACs is lacking, consensus was that addition of an antiplatelet to anticoagulant is not required for patients with atrial fibrillation and concurrent stable ischaemic heart disease. If a stent is required the minimum duration of concurrent antiplatelet should be used.

## Cholesterol lowering therapy

The most recent National Stroke Audit showed that around 80% of eligible patients with ischaemic stroke were on lipid-lowering therapy on discharge from hospital (Stroke Foundation 2016 *[198]*). Records from a large Australian GP registry indicate that in the community this rate fell to 65 % (Reid et al 2008 *[58]*). Commencement of secondary prevention medications prior to hospital discharge is the most important for improving rates of adherence long-term after stroke (Thrift et al 2014 *[35]*).

Lifestyle change strategies involving dietary modification have been shown to lower cholesterol levels in those with cardiovascular risks and should be used as an alternative or in addition to pharmacotherapy (see Adherence to pharmacotherapy).

Statins are the main class of cholesterol-lowering medication.

Strong Recommendation

All patients with ischaemic stroke or TIA with possible atherosclerotic contribution and reasonable life expectancy should be prescribed a high-potency statin, regardless of baseline lipid levels. (Manktelow et al 2009 *[107]*; Tramacer et al 2019 *[118]*)

### Practical Info

Indication is primarily for those with stroke due to atherosclerotic disease. Patients with atrial fibrillation and other cardiac complications were excluded from the SPARCL trial but may still have atherosclerotic disease. Examples of "high potency statin" include atorvastatin 80mg and rosuvastatin 40mg.

### Key Info

**Benefits and harms**

Substantial net benefits of the recommended alternative

Statins provide significant benefit for secondary stroke prevention without significant toxicity (e.g. liver toxicity or myopathy) although these side effects can occur occasionally. The rate of intracerebral haemorrhage when statins are used for secondary ischaemic stroke prevention is slightly increased (20 fewer ischaemic stroke and 8 more intracerebral haemorrhage per 1000 patients treated) (Manktelow et al 2009 *[107]*).

**Certainty of the Evidence**

High

The evidence for benefit with statins is consistent and is likely related to low-density lipoprotein (LDL) cholesterol reduction (Manktelow et al 2009 *[107]*). The evidence mainly comes from a large trial (N = 4731) of high methodological quality SPARCL, in which 98% of patients had ischaemic stroke or TIA (Amarenco et al 2006 *[108]*).

**Preference and values**

No substantial variability expected

Most patients will prefer to use statins for secondary stroke prevention. However, occasional patients may value side effect prevention over stroke prevention.

**Resources and other considerations**

No important issues with the recommended alternative

<u>Resources considerations</u>
There is some evidence that cholesterol-lowering therapy with statins is cost-effective or cost-saving. Simvastatin has been found to be cost-effective at an additional cost of £2,500 per life year gained (cost reference year 2001) (Heart Protection Study Collaborative 2006 *[105]*). Atorvastatin has also been found to be cost-effective at an additional cost of US$13,916 per QALY gained (cost reference year 2005) (Kongnakorn et al 2009 *[106]*). Historically, the price of statins in Australia has been considerably higher than in comparable countries such as New Zealand (Simeons et al 2011 *[110]*; Cobiac et al 2012 *[111]*). However, the price of statins in Australia is expected to fall with the expiry of patent protections on statins (Clarke and Fitzgerald 2010 *[109]*), which will improve the cost-effectiveness estimates for Australia.

<u>Implementation considerations</u>
There is a clinical indicator collected on cholesterol-lowering therapy in the National Stroke Audit. Cholesterol-lowering therapy is included in the Acute Stroke Clinical Care Standard as a bundle approach with blood pressure lowering and antithrombotic medication.

## Rationale

Statins provide significant prevention of secondary ischaemic stroke with few side effects and are strongly recommended for this indication.

## Clinical Question/ PICO

**Population:** Patients with previous stroke or TIA
**Intervention:** Statins
**Comparator:** Control

## Summary

Manktelow and Potter et al (2009) *[107]* conducted a Cochrane review of interventions for managing serum lipids in patients with a history of stroke or TIA. Five randomised controlled trials that investigated statins were included (using pravastatin, simvastatin or atorvastatin). Risk of bias in the trials was not reported in detail but all trials investigating statins had adequate allocation concealment and were considered high-quality evidence. Statins had a marginal effect on overall stroke recurrence (OR 0.88, 95% CI 0.77 to 1.00), but analysing ischaemic stroke and intracerebral haemorrhage separately showed a significant decrease in secondary ischaemic stroke (OR 0.78, 95% CI 0.67 to 0.92) and a significant increase in secondary intracerebral haemorrhage (OR 1.72, 95% CI 1.20 to 2.46). There was no significant difference in all-cause mortality in the one trial that reported this outcome.

An updated review (Tramacere et al 2019 *[118]*) included nine trials (N=10,741 patients). Similar results were reported with main benefit a reduction in subsequent ischaemic strokes (OR 0.81, 95% CI 0.70-0.93) with greater benefits for high dose statins based on high quality evidence. No difference was found for mortality or harms (rhabdomyolysis, myalgia or rise in creatine kinase) based on lower quality evidence. Risk of hemorrhage was significantly higher (OR 1.54 95% CI 1.10-2.15) which was influenced by the largest trial (SPARCL). No difference between various statin's was found.

Other reviews have reported slight increase in risk of ICH with statins although absolute numbers are small and outweighed by ischaemic stroke reduction (Teoh et al 2019 *[115]*).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Statins | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Secondary intracerebral haemorrhage** End of follow-up<br>8 Critical | Odds Ratio 1.72 (CI 95% 1.2 - 2.46) Based on data from 8,011 patients in 2 studies. [1] (Randomized controlled) Follow up Around 5 years | 11 per 1000 | 19 per 1000<br>Difference: 8 more per 1000 ( CI 95% 2 more - 16 more ) | **High** [2] | Statins increase secondary intracerebral haemorrhage (although the absolute risk and absolute risk increase were low) |
| **Death** [3] End of follow-up<br>9 Critical | Odds Ratio 1.03 (CI 95% 0.84 - 1.25) Based on data from 4,731 patients in 1 studies. [4] (Randomized controlled) Follow up Median of approximately 5 years | 89 per 1000 | 91 per 1000<br>Difference: 2 more per 1000 ( CI 95% 13 fewer - 20 more ) | **Moderate** Due to indirectness and imprecision: only one study that excluded patients with cardio-embolic stroke [5] | Statins probably have little or no difference on all-cause mortality |
| **Secondary stroke - all** [6] End of follow-up | Odds Ratio 0.88 (CI 95% 0.77 - 1) Based on data from | 121 per 1000 | 108 per 1000 | **Moderate** Due to serious imprecision: | Statins probably decrease all secondary strokes (ischaemic and |

| | | | | |
|---|---|---|---|---|
| 8 Critical | 9,224 patients in 5 studies. [7] (Randomized controlled) Follow up 90 days to 6 years | Difference: **13 fewer** per 1000 ( CI 95% 25 fewer - 0 fewer ) | confidence interval includes null effect [8] | haemorrhagic) slightly |
| **Secondary ischaemic stroke** End of follow-up 8 Critical | Odds Ratio 0.78 (CI 95% 0.67 - 0.92) Based on data from 8,011 patients in 2 studies. [9] (Randomized controlled) Follow up Around 5 years | **99** per 1000 **79** per 1000 Difference: **20 fewer** per 1000 ( CI 95% 30 fewer - 7 fewer ) | **High** 10 | Statins slightly decrease secondary ischaemic stroke |

1. Systematic review [107] with included studies: SPARCL, HPS. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Adequate allocation concealment in both trials. **Inconsistency: No serious.** Low statistical heterogeneity: I^2 = 0%. **Indirectness: No serious.** SPARCL, the larger of the 2 studies, excluded patients with presumed cardio-embolic stroke. **Imprecision: No serious. Publication bias: No serious.**
3. All cause mortality including sudden deaths
4. Systematic review [107] with included studies: SPARCL. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Inconsistency: No serious.** Can't be assessed due to single study, but large number of patients. **Indirectness: Serious.** Differences between the population of interest and those studied: SPARCL study excluded patients with presumed cardio-embolic stroke. **Imprecision: No serious.** Only data from one study. **Publication bias: No serious.**
6. All ischaemic or haemorrhagic strokes
7. Systematic review [107] with included studies: CARE, HPS, LIPID, FASTER, SPARCL. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: No serious.** Adequate allocation concealment in all studies. **Inconsistency: No serious.** Low to moderate heterogeneity: I^2 = 26%. **Indirectness: No serious.** Little data available for patients with previous cerebral haemorrhage. **Imprecision: Serious.** Wide confidence intervals: don't quite exclude a null effect. **Publication bias: No serious.**
9. Systematic review [107] with included studies: SPARCL, HPS. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: No serious.** Adequate allocation concealment in both trials. **Inconsistency: No serious.** Low statistical heterogeneity: I^2 = 0%. **Indirectness: No serious.** SPARCL, the larger of the 2 studies, excluded patients with presumed cardio-embolic stroke. **Imprecision: No serious. Publication bias: No serious.**

Strong Recommendation

DRAFT FOR PUBLIC CONSULTATION SEPTEMBER 2020

In patients with ischaemic stroke, cholesterol lowering therapy should target LDL cholesterol < 1.8 mmol/L for secondary prevention of atherosclerotic cardiovascular disease. (Amarenco et al 2020 *[112]*)

## Practical Info

Indication is primarily for those with stroke due to atherosclerotic disease. Examples of "high potency statin" include atorvastatin 80mg and rosuvastatin 40mg. If thresholds are not met with statin therapy and lifestyle changes alone the addition of ezetimibe (10mg daily) (Amarenco et al 2020 *[112]*; Zhan et al 2018 *[114]*) should be considered. If targets are still not achieved a PCSK-9 inhibitor (e.g. for evolocumab 140 mg every 2 weeks) (Giugliano et al 2020 *[113]*) can be added.

If higher statin doses are not tolerated, lower doses of statin combined with ezetimibe may achieve similar LDL lowering with better

tolerability.

## Key Info

**Benefits and harms** — Substantial net benefits of the recommended alternative

Treating to lower LDL-C targets (<1.8 mmol/L) reduced subsequent CVD events (MI or ischaemic stroke) by about 20% without significantly increasing new onset diabetes or ICH (although numbers were small).

**Certainty of the Evidence** — Moderate

One direct trial specifically investigating lower targets versus higher targets (Amarenco et al 2020 *[112]*) was rated as moderate evidence overall. However, there is strong evidence of the relationship of reduced LDL-C levels and reduced stroke risk (Baigent et al 2010 *[119]*).

**Preference and values** — No substantial variability expected

Most patients and their families will prefer to reduce the risk of further strokes compared to the small risk of side effects with lower LDL levels.

**Resources and other considerations** — No important issues with the recommended alternative

Resources considerations

Cholesterol-lowering therapy with statins generally is cost-effective or cost-saving. One third of patients in the Treat To Target trial required the addition of ezetimibe to meet targets and this needs to be considered. There is evidence from one simulation modelling study by Davies et al 2017 *[123]* that ezetimibe-statin combination is cost effective compared to statin treatment. Data from patients with prior coronary heart disease (CHD) and/or stroke (n=548) were obtained from US linked claims and electronic medical records with model inputs related to direct medical costs (reference year 2013 US dollars) and utility weight obtained from recent clinical trials, meta-analyses, and cost effectiveness analyses. Over a lifetime, treatment with ezetimibe-statin combination therapy was estimated to cost an additional $US9,149 per QALY gained compared to statin treatment alone. Ezetimibe-statin combination therapy was potentially more cost effective compared to statin treatment alone for patients at greater risk, costing an additional $US 839 per QALY gained for patients with LDL cholesterol levels ≥2.6 mmol/L and $US560 per QALY gained for patients with diabetes mellitus and LDL cholesterol levels ≥1.8 mmol/L. A 90% reduction in the price of ezetimibe after 1 year was accounted for in this economic analysis (based on an impending patent expiration) (Davies et al 2017 *[123]*).

Other studies assessing the cost effectiveness of evolocumab plus statin therapy compared to statin treatment alone have been less favourable and dependent on the cost of evolocumab. Arrieta et al 2017 *[122]* used a simulation model based on a cohort (n=1000) from the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial. Data on outcomes and cost to the health system (reference year 2016 US dollars) were obtained from published literature. Over a lifetime, evolocumab plus statin therapy was estimated to cost an additional $US337,729 per QALY gained compared to statin treatment alone, despite a 43% drop in the price of the drug after 12 years of patent protection taken into account. Evolocumab plus statin therapy was estimated to cost an additional $US100,000 per QALY gained compared to statin treatment alone with a 62% drop in the price of evolocumab overall. There were similar findings from another USA based economic simulation model in patients with LDL cholesterol levels ≥1.8 mmol/L in which evolocumab and standard therapy (moderate- to high-intensity statin with or without ezetimibe) was compared to standard therapy alone (Fonarow et al 2017 *[120]*). Both direct and indirect costs associated with cardiovascular events were included in this analysis (reference year 2017 US dollars). At a yearly cost of $US14,523, evolocumab in addition to standard therapy was estimated to cost an additional $US268,637 per QALY gained compared to standard therapy alone. However, at a yearly cost of $US5,850, evolocumab in addition to standard therapy was estimated to cost an additional $US56,655 to $US7,667 per QALY gained compared to standard therapy alone (Fonarow et al 2019 *[121]*).

Implementation considerations

There is a clinical indicator collected on cholesterol-lowering therapy in the National Stroke Audit. Cholesterol-lowering therapy is included in the Acute Stroke Clinical Care Standard as a bundle approach with blood pressure lowering and antithrombotic medication.

## Rationale

Only 42% of people with stroke in the community were reported to have their cholesterol levels treated to target (LDL-C <1.8 mmol/L) (Carrington et al 2020*[124]*). The Treat Stroke to Target trial (Amarenco et al 2020) *[112]* found reduced combined CVD events (primarily MI and ischaemic strokes) in patients with ischaemic stroke or TIA due to atherosclerotic disease treated to a low

(<1.8 mmol/L) LDL target compared to a higher (2.3-2.8 mmol/L) target (HR 0.78, 95% CI 0.61-0.98). ICH or new diabetes was not statistically increased with more aggressive treatment but were numerically higher in the lower target group. Importantly 34% of patients in the lower target group were taking ezetimibe plus a statin compared to 6% in the higher target group indicating that additional ezetimibe may be needed to reach lower targets. A PCSK9 inhibitor in addition to a statin has also been shown to reduce stroke risk in a prespecified subgroup analysis of the FOURIER trial (Giugliano et al 2020 *[113]*) and may also need to be considered in order to reach LDL target <1.8 mmol/L.

## Clinical Question/ PICO

**Population:** Patients with previous stroke or TIA
**Intervention:** more intense LDL-C lowering target (<1.8 mmol/L)
**Comparator:** less intense LDL-C lowering target (2.3-2.8 mmol/L)

### Summary

Amerenco et al (2020) *[112]* included 2860 patients with ischaemic stroke or TIA in France and South Korea and compared treatment to a low (<1.8 mmol/L) LDL level to higher (2.3-2.8 mmol/L) target. The trial was terminated early due to funding restraints after 277 of planned 385 events occurred. Patient selection included those with atherosclerotic disease that included stenosis of an extracranial or intracranial cerebral artery, ipsilateral or contralateral to the region of imputed brain ischemia; atherosclerotic plaques of the aortic arch measuring at least 4 mm in thickness; or a known history of coronary artery disease. The primary endpoint (composite CVD events including stroke, MI revascularisation or death from CV causes) was reduced in the lower target group (HR 0.78, 95% CI 0.61-0.98). There was a reduction in fatal or non-fatal strokes in the lower target group but relatively small numbers meant this was not significant. ICH (HR 1.38, 95% CI 0.68-2.82) or new diabetes (HR 1.27, 95% CI 0.95-1.70) was not statistically increased with more aggressive treatment but were numerically higher in the lower target group. Importantly 34% of patients in the lower target group were taking ezetimide plus a statin compared to 6% in the higher target group. There was a slightly higher risk on the composite outcome for those with TIA (HR 2.06 95% CI 1.03-4.12) compared to ischaemic stroke (HR 0.67, 95% CI 0.52-0.87) however, numbers were relatively low for TIA (24/205 v 12/200). Overall the certainty of evidence was rated moderate due to single trial and relatively few patient outcomes.

Giugliano et al (2020)*[113]* reported a prespecified stroke subgroup of the FOURIER trial which compared PCSK9 inhibitor (evolocumab) in those on a statin with LDL levels >1.8 mmol/L. 5337 (19%) of the 27564 patients had a prior ischaemic stroke on randomisation with a median LDL-C level of 2.4 mmol/L. Those in the intervention arm reduced LDL-C from 4 weeks to a median of 0.8 mmol/L. There were significantly fewer CVD events (composite CVD death, MI, stroke, hospital admission for angina or coronary revascularization) in the intervention group after mean of 2.2 years (HR 0.85, 95% 0.72-1.00) mainly driven by lower MI and revascularization. Subsequent ischaemic strokes or TIAs were less but results were non-significant (HR 0.89, 95% CI 0.68-1.17). There was no increase reported in heamorrhagic stroke (14 in each arm; HR 99, 95% CI 0.47-2.07).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** less intense LDL-C lowering | more intense LDL-C lowering (<1.8 mmol/L) | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Recurrent ischaemic stroke or TIA** median 3.5 years<br>8 Critical | Hazard Ratio 0.81 (CI 95% 0.68 - 1.11) Based on data from 2,860 patients in 1 studies. [1] (Randomized controlled) Follow up median 3.5 year | **97.2** per 1000 | **79** per 1000<br>Difference: **18 fewer** per 1000 ( CI 95% 30 fewer - 10 more ) | **Moderate** Due to serious imprecision [2] | More intense LDL-C lowering (<1.8 mmol/l) may improve risk of recurrent ischaemic stroke or TIA |
| **Major cardiovascular event** [3] | Hazard Ratio 0.78 (CI 95% 0.61 - 0.98) Based on data from | **109** per 1000 | **86** per 1000 | **Moderate** Due to serious imprecision [5] | More intense LDL-C lowering (<1.8 mmol/l) probably improves major |

| | | | |
|---|---|---|---|
| 3.5 years<br><br>8 Critical | 2,860 patients in 1 studies. [4] (Randomized controlled)<br>Follow up 3.5 years | Difference: **23 fewer** per 1000<br>( CI 95% 41 fewer - 2 fewer ) | cardiovascular event |

1. Primary study. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [112],
2. **Risk of bias: No serious.** Trials stopping earlier than scheduled and open label design (physicians knew what medication / target was provided). . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
3. includes non-fatal stroke, non-fatal MI, urgent coronary revascularisation, urgent carotid revascularisation, cardiovascular mortality
4. Primary study. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [112],
5. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**

Weak Recommendation Against

Statins should not be used routinely for intracerebral haemorrhage. (Manktelow et al 2009 *[107]*; Amarenco et al 2006 *[108]*)

## Practical Info

There is some limited evidence that statins may be harmful for patients with a history of haemorrhagic stroke. If there is a strong prior indication for statin use that would outweigh this risk then it may be reasonable to continue them. There may also be other cardiovascular disease indications for the use of statins, which should be considered.

## Key Info

**Benefits and harms** — Substantial net benefits of the recommended alternative

There is no clear benefit in this situation and there are concerns about an increase in the rate of recurrent intracerebral haemorrhage (Manktelow et al 2009 *[107]*).

**Certainty of the Evidence** — Very Low

There is very little evidence assessing the impact of statin use in patients presenting with intracerebral haemorrhage. The largest trial to date is SPARCL but only 2% of the participants had an intracerebral haemorrhage (Amarenco et al 2006 *[108]*).

**Preference and values** — No substantial variability expected

Most patients would prefer not to initiate statin usage in the absence of clear evidence for benefit in secondary prevention.

**Resources and other considerations** — No important issues with the recommended alternative

Resources considerations

Economic evidence shows that cholesterol-lowering therapy with statins is cost-effective or cost-saving: simvastatin costs <£2500 per life year gained and atorvastatin costs $13916/QALY gained (Heart Protection Study Collaborative 2006 *[105]*; Kongnakorn et al 2009 *[106]*). The price of statins in Australia is expected to fall with the expiry of patent protections on statins (Clarke and Fitzgerald 2010 *[109]*), which will favourably affect cost-effectiveness estimates for Australia.

**Implementation considerations**
There is a clinical indicator collected on cholesterol-lowering therapy in the National Stroke Audit. Cholesterol-lowering therapy is included in the Acute Stroke Clinical Care Standard as a bundle approach with blood pressure lowering and antithrombotic medication.

## Rationale

There is no clear evidence that statins provide any benefit to patients presenting with haemorrhagic stroke and there are concerns about cost and side effects.

## Clinical Question/ PICO

**Population:** Patients with previous stroke or TIA
**Intervention:** Statins
**Comparator:** Control

## Summary

Manktelow and Potter et al (2009) *[107]* conducted a Cochrane review of interventions for managing serum lipids in patients with a history of stroke or TIA. Five randomised controlled trials that investigated statins were included (using pravastatin, simvastatin or atorvastatin). Risk of bias in the trials was not reported in detail but all trials investigating statins had adequate allocation concealment and were considered high-quality evidence. Statins had a marginal effect on overall stroke recurrence (OR 0.88, 95% CI 0.77 to 1.00), but analysing ischaemic stroke and intracerebral haemorrhage separately showed a significant decrease in secondary ischaemic stroke (OR 0.78, 95% CI 0.67 to 0.92) and a significant increase in secondary intracerebral haemorrhage (OR 1.72, 95% CI 1.20 to 2.46). There was no significant difference in all-cause mortality in the one trial that reported this outcome.

An updated review (Tramacere et al 2019 *[118]*) included nine trials (N=10,741 patients). Similar results were reported with main benefit a reduction in subsequent ischaemic strokes (OR 0.81, 95% CI 0.70-0.93) with greater benefits for high dose statins based on high quality evidence. No difference was found for mortality or harms (rhabdomyolysis, myalgia or rise in creatine kinase) based on lower quality evidence. Risk of hemorrhage was significantly higher (OR 1.54 95% CI 1.10-2.15) which was influenced by the largest trial (SPARCL). No difference between various statin's was found.

Other reviews have reported slight increase in risk of ICH with statins although absolute numbers are small and outweighed by ischaemic stroke reduction (Teoh et al 2019 *[115]*).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Statins | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Secondary intracerebral haemorrhage** End of follow-up<br>8 Critical | Odds Ratio 1.72 (CI 95% 1.2 - 2.46) Based on data from 8,011 patients in 2 studies. [1] (Randomized controlled) Follow up Around 5 years | **11** per 1000 | **19** per 1000<br>Difference: **8 more** per 1000 ( CI 95% 2 more - 16 more ) | **High** [2] | Statins increase secondary intracerebral haemorrhage (although the absolute risk and absolute risk increase were low) |
| **Death** [3] End of follow-up<br>9 Critical | Odds Ratio 1.03 (CI 95% 0.84 - 1.25) Based on data from 4,731 patients in 1 studies. [4] (Randomized | **89** per 1000 | **91** per 1000<br>Difference: **2 more** per 1000 | **Moderate** Due to indirectness and imprecision: only one study that | Statins probably have little or no difference on all-cause mortality |

| | | | | |
|---|---|---|---|---|
| | controlled)<br>Follow up Median of approximately 5 years | ( CI 95% 13 fewer - 20 more ) | excluded patients with cardio-embolic stroke [5] | |
| **Secondary stroke - all** [6]<br>End of follow-up<br><br>8 Critical | Odds Ratio 0.88 (CI 95% 0.77 - 1)<br>Based on data from 9,224 patients in 5 studies. [7] (Randomized controlled)<br>Follow up 90 days to 6 years | **121**<br>per 1000<br>**108**<br>per 1000<br>Difference: **13 fewer** per 1000<br>( CI 95% 25 fewer - 0 fewer ) | **Moderate**<br>Due to serious imprecision: confidence interval includes null effect [8] | Statins probably decrease all secondary strokes (ischaemic and haemorrhagic) slightly |
| **Secondary ischaemic stroke**<br>End of follow-up<br><br>8 Critical | Odds Ratio 0.78 (CI 95% 0.67 - 0.92)<br>Based on data from 8,011 patients in 2 studies. [9] (Randomized controlled)<br>Follow up Around 5 years | **99**<br>per 1000<br>**79**<br>per 1000<br>Difference: **20 fewer** per 1000<br>( CI 95% 30 fewer - 7 fewer ) | **High**<br>10 | Statins slightly decrease secondary ischaemic stroke |

1. Systematic review [107] with included studies: SPARCL, HPS. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** Adequate allocation concealment in both trials. **Inconsistency: No serious.** Low statistical heterogeneity: I^2 = 0%. **Indirectness: No serious.** SPARCL, the larger of the 2 studies, excluded patients with presumed cardio-embolic stroke. **Imprecision: No serious. Publication bias: No serious.**
3. All cause mortality including sudden deaths
4. Systematic review [107] with included studies: SPARCL. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Inconsistency: No serious.** Can't be assessed due to single study, but large number of patients. **Indirectness: Serious.** Differences between the population of interest and those studied: SPARCL study excluded patients with presumed cardio-embolic stroke. **Imprecision: No serious.** Only data from one study. **Publication bias: No serious.**
6. All ischaemic or haemorrhagic strokes
7. Systematic review [107] with included studies: CARE, HPS, LIPID, FASTER, SPARCL. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: No serious.** Adequate allocation concealment in all studies. **Inconsistency: No serious.** Low to moderate heterogeneity: I^2 = 26%. **Indirectness: No serious.** Little data available for patients with previous cerebral haemorrhage. **Imprecision: Serious.** Wide confidence intervals: don't quite exclude a null effect. **Publication bias: No serious.**
9. Systematic review [107] with included studies: SPARCL, HPS. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of bias: No serious.** Adequate allocation concealment in both trials. **Inconsistency: No serious.** Low statistical heterogeneity: I^2 = 0%. **Indirectness: No serious.** SPARCL, the larger of the 2 studies, excluded patients with presumed cardio-embolic stroke. **Imprecision: No serious. Publication bias: No serious.**

Weak Recommendation Against

Fibrates should not be used routinely for the secondary prevention of stroke. (Zhou et al 2013 *[104]*; Wang et al 2015 *[103]*)

## Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

The available data did not show a significant benefit of fibrate therapy for secondary stroke prevention. Indeed, the point estimate for the relative risk of stroke was 1.28 indicating that an increase in stroke was possible (95% CI 0.86 - 1.90) (Zhou et al 2013 *[104]*). Other cholesterol lowering agents should be used in preference.

**Certainty of the Evidence** — Moderate

The overall quality of evidence is moderate, based on a meta-analysis of 627 patients from 10 studies with various methodological quality (Zhou et al 2013 *[104]*).

**Preference and values** — No substantial variability expected

The use of fibrates is unlikely to vary due to clear evidence of lack of benefit at this stage.

**Resources and other considerations** — Factor not considered

## Rationale

The effect of fibrates on the rate of secondary stroke in patients with a prior history of stroke is not clear. The best estimate is drawn from a subgroup analysis of 627 patients with prior stroke, within a meta-analysis of 10 studies totalling over 20000 patients (Zhou et al 2013 *[104]*). This suggests a nonsignificant trend towards a higher rate of secondary stroke when patients with prior stroke are treated with fibrates (but may lower rate of fatal stroke). Despite the ready availability of fibrates and their benefit in other clinical situations, fibrates appear ineffective for secondary stroke prevention.

## Clinical Question/ PICO

**Population:** Patients with previous stroke
**Intervention:** Fibrates
**Comparator:** Control

### Summary

A systematic review and meta-analysis by Zhou et al (2013) *[104]* analysed the effects of fibrates in patients who had previous stroke. Overall, 10 trials were included, with 37,791 total patients. Pooled data from 627 patients with previous stroke showed an increase in recurrent stroke and a decrease in recurrent fatal stroke, however these effects were not significant.

A Cochrane review by Wang et al (2015) *[103]* aimed to assess the efficacy and safety of fibrates for the prevention of serious vascular events in people with previous cardiovascular disease (including coronary heart disease and stroke). In an analysis of three studies (N=7189) without clofibrate (discontinued in 2002 due to serious side-effects), they found little benefit from fibrate therapy in the prevention of secondary stroke (RR 0.94 (0.78 to 1.14)).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Fibrates | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Secondary stroke** | Relative risk 1.28 (CI 95% 0.86 - 1.9) Based on data from 627 | 144 per 1000 | 184 per 1000 | **Moderate** Due to serious risk of bias [2] | Fibrate therapy probably has little or no effect on secondary stroke. |

| | | | | | |
|---|---|---|---|---|---|
| 9 Critical | patients in 10 studies. [1] (Randomized controlled) Follow up variable (30-104 months) | Difference: 40 more per 1000 ( CI 95% 20 fewer - 130 more ) | | | |
| **Secondary fatal stroke** 8 Critical | Relative risk 0.59 (CI 95% 0.23 - 1.47) Based on data from 627 patients in 10 studies. (Randomized controlled) Follow up variable (30-104 months) | 38 per 1000 | 22 per 1000 Difference: 16 fewer per 1000 ( CI 95% 29 fewer - 18 more ) | **Moderate** Due to serious risk of bias [3] | Fibrate therapy probably has little or no effect on secondary fatal stroke. |
| **Stroke (IS; ICH; fatal & non-fatal)** 9 Critical | Relative risk 0.94 (CI 95% 0.78 - 1.14) Based on data from 7,189 patients in 3 studies. (Randomized controlled) | 56 per 1000 | 53 per 1000 Difference: 3 fewer per 1000 ( CI 95% 12 fewer - 8 more ) | **Low** Due to serious inconsistency, Due to serious risk of bias [4] | Fibrate therapy may have little or no effect on non-fatal and fatal IS & ICH |

1. Systematic review [103] . In the Cochrane review by Wang et al. (2015) of fibrates for secondary prevention of cardiovascular disease and stroke, analysis 1.10 suggests a nonsignificant effect on the rate of stroke (ischaemic and haemorrhagic, fatal or nonfatal); RR 1.03; 95% CI 0.91,1.16, although the patient group was predominantly patients seen after cardiovascular events rather than stroke.. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** Some included studies have high risk of bias. **Inconsistency: No serious.** The direction of the effect is not consistent between the included studies. **Indirectness: No serious. Imprecision: No serious.** Wide confidence intervals. **Publication bias: No serious.**
3. **Risk of bias: Serious.** Some included studies have high risk of bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
4. **Risk of bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2 =44%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

## Carotid surgery

Narrowing of the carotid arteries is commonly associated with stroke and TIA. There is well-established evidence for the use of carotid endarterectomy (CEA) as the management of choice for symptomatic carotid stenosis.

Implementation of best practice for carotid surgery requires:

- availability of well-trained sonographers with validated reproducible carotid imaging in an appropriate vascular or imaging centre,
- availability of skilled specialists with clinical and interventional experience,
- appropriate referral processes to facilitate rapid assessment and intervention, and
- appropriate skilled staff and processes to undertake routine audits.

Strong Recommendation

- Carotid endarterectomy is recommended for patients with recent (<3 months) non-disabling carotid artery territory ischaemic stroke or TIA with ipsilateral carotid stenosis measured at 70-99% (NASCET criteria) if it can be performed by a specialist team with audited practice and a low rate (<6%) of perioperative stroke and death.
- Carotid endarterectomy can be considered in selected patients with recent (<3 months) non-disabling ischaemic stroke or TIA patients with symptomatic carotid stenosis of 50–69% (NASCET criteria) if it can be performed by a specialist team with audited practice and a very low rate (<3%) of perioperative stroke and death.
- Carotid endarterectomy should be performed as soon as possible (ideally within two weeks) after the ischaemic stroke or TIA.
- All patients with carotid stenosis should be treated with intensive vascular secondary prevention therapy.

(Bangalore et al 2011 *[137]*, Rerkasem & Rothwell 2011 *[152]*)

### Practical Info

Symptomatic is defined as symptoms within the last 3 months. Beyond 3 months the risk of stroke is similar to asymptomatic patients.

Intensive medical treatment with dual antiplatelet and high potency statin may reduce pre-operative recurrent stroke and TIA in patients awaiting endarterectomy and does not appear to cause excessive perioperative bleeding (Batchelder et al 2015 *[151]*; Shahidi et al 2016 *[150]*).

NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria
The diameter of the arterial lumen at the tightest region of stenosis is compared with the region of the distal internal carotid artery that is free of disease and has non-tapering walls. The formula used to calculate the degree of stenosis is: Percentage stenosis = [1 - (minimum diameter/distal diameter)] ×100.

### Key Info

**Benefits and harms** — Substantial net benefits of the recommended alternative

For patients with recently symptomatic 70-99% carotid stenosis, the benefit of carotid endarterectomy in reducing recurrent stroke clearly outweighs the risk of perioperative stroke and death, provided the patient has sufficient life expectancy to accrue benefit (Rerkasem & Rothwell 2011 *[152]*). The reduced magnitude of benefit in 50-70% stenosis makes this a more finely balanced decision, and improvements in medical therapy since the randomised trials were performed may also have reduced the additional benefit of surgery. Carotid stenting has consistently demonstrated a higher risk of perioperative stroke than carotid endarterectomy (Bangalore et al 2011 *[137]*).

**Certainty of the Evidence** — High

Multiple high quality randomised trials had consistent results

**Preference and values** — Substantial variability is expected or uncertain

In recently symptomatic 70-99% carotid stenosis, most patients and physicians will choose carotid endarterectomy unless there

is limited life expectancy or significant perioperative risk. Preferences will vary in the milder stenosis group.

**Resources and other considerations**

No important issues with the recommended alternative

Resources considerations

Economic evaluations of carotid endarterectomy (CEA) compared to standard medical treatment have been conducted in North American and UK settings. It was found that CEA was cost-effective in certain sub-groups of patients and in settings with low peri-operative morbidity and mortality (Benade et al 2002 *[149]*; Henriksson et al 2008 *[143]*). In the most recently conducted economic evaluation in this area, it was found that early CEA compared to medical therapy was cost-effective at an additional cost of £7,584 per QALY gained compared to deferral of treatment, but not cost-effective (given a willingness to pay of £30,000 per QALY gained) in men aged over 75 years at an additional cost of £71,699 per QALY gained compared to deferral (cost reference year 2010) (Thapar et al 2013 *[131]*).

## Rationale

Randomised controlled trials have reported that patients with a recent (<6months) non-disabling stroke or TIA in the territory of a 70-99% carotid stenosis (NASCET criteria) receive substantial benefit from carotid endarterectomy compared to best medical management alone (NASCET/ ECST) with absolute risk reduction (ARR) 16.0% (Rerkasem & Rothwell 2011 *[152]*). In subsequent analyses, the benefit was restricted to patients treated within 3 months of symptoms and greatest when patients were treated within 2 weeks (Rerkasem & Rothwell 2011 *[152]*). The trials also reported a lesser degree of benefit of carotid endarterectomy in patients with a recently symptomatic 50-69% stenosis (NASCET criteria), ARR 4.6%. Once occluded, the risk of subsequent stroke is substantially lower and endarterectomy is generally not feasible. Trials did not demonstrate benefits of carotid endarterectomy in patients with <50% stenosis (Rerkasem & Rothwell 2011 *[152]*). It should be noted that medical management has changed since these trials were conducted. It is likely that the stroke risk with medical management alone has reduced.

## Clinical Question/ PICO

**Population:** Adults with recently symptomatic carotid stenosis
**Intervention:** Carotid artery stenting
**Comparator:** Carotid endarterectomy

## Summary

The most recent systematic review and meta-analysis by Bangalore et al (2011) *[137]* reported that carotid stenting was associated with increased perioperative stroke compared with carotid endarterectomy. Carotid stenting is associated with reduced incidence of perioperative myocardial infarction compared with carotid endarterectomy but the clinical significance of these cardiac events is less clear since many were diagnosed on the basis of cardiac enzyme elevation and there was no improvement in survival over intermediate follow-up (Bangalore 2011 *[137]*).

Furthermore, outcomes of carotid stenting in administrative datasets analysed by Paraskevas et al (2016) *[127]* suggest that in routine practice carotid stenting is associated with a higher stroke rate than carotid endarterectomy. A recent small randomised trial involving 150 patients reported that new cerebral infarcts on MRI were present in 49% of carotid stenting patients compared to 25% of carotid endarterectomy patients (Kuliha et al 2015 *[128]*).

Long-term follow-up of ICSS (median 4.2 years, up to 10 years) found that the 5 year risk of procedural stroke or death or ipsilateral stroke during follow-up was 11.8% with stenting versus 7.2% with endarterectomy (absolute risk difference 4.6% 95%CI 1.6-7.6%) (Bonati et al 2015 *[129]*). This was related to the periprocedural period with the risk of ipsilateral stroke beyond 30 days similar between treatments (4.7% vs 3.4% at 5 years HR 1.29 95%CI 0.74-2.24 p=0.36). There was also no difference in the primary outcome of fatal or disabling stroke throughout the entire period of follow-up (6.4% vs 6.5%) and the distribution of modified Rankin scale scores was not different (p=0.49). The incidence of severe restenosis or occlusion were also similar at 5 years (10.8% vs 8.6%, absolute risk difference 2.2% 95%CI -1.1 to 5.4%). Long term follow-up of the CREST trial (median 7.4 years, up to 10 years), in whom approximately 50% of 2,502 patients had symptomatic carotid stenosis has also been reported. Overall the risk of stroke or periprocedural death at 10 years was 11% with stenting versus 7.9% with endarterectomy (HR 1.37 95%CI 1.01-1.86, p=0.04). The subgroup with symptomatic stenosis had a 10-year risk of stroke or periprocedural death of 12.8% with stenting versus 7.8% with endarterectomy (HR 1.44 95%CI 0.98-2.13,

p=0.07). Again, the excess risk occurred in the periprocedural period (Brott et al 2016 *[125]*). Restenosis (>70% or requiring revascularization) occurred in 12.2% with stenting versus 9.7% with endarterectomy (HR 1.24; 95%CI 0.91-1.70).

Randomised controlled trials have also eported that patients with a recent (<6months) non-disabling stroke or TIA in the territory of a 70-99% carotid stenosis (NASCET criteria) receive substantial benefit from carotid endarterectomy compared to best medical management alone (NASCET/ ECST) with absolute risk reduction (ARR) 16.0%. In subsequent analyses, the benefit was restricted to patients treated within 3 months of symptoms and greatest when patients were treated within 2 weeks (Rerkasem & Rothwell 2011 *[152]*). The trials also reported a lesser degree of benefit of carotid endarterectomy in patients with a recently symptomatic 50-69% stenosis (NASCET criteria), ARR 4.6%. Once occluded, the risk of subsequent stroke is substantially lower and endarterectomy is generally not feasible. Trials did not demonstrate benefits of carotid endarterectomy in patients with <50% stenosis (Rerkasem & Rothwell 2011 *[152]*).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Carotid endarterectomy | Carotid artery stenting | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Periprocedural stroke** | Odds Ratio 1.66 (CI 95% 1.31 - 2.09) Based on data from 5,588 patients in 10 studies. (Randomized controlled) | 41 per 1000 | 66 per 1000 Difference: 25 more per 1000 ( CI 95% 41 more - 12 more ) | **Moderate** Due to serious indirectness [1] | Carotid artery stenting probably increases periprocedural stroke |
| **Death or stroke - Long term** | Odds Ratio 1.29 (CI 95% 1.08 - 1.54) Based on data from 4,463 patients in 9 studies. (Randomized controlled) Follow up varied | 135 per 1000 | 168 per 1000 Difference: 33 more per 1000 ( CI 95% 59 more - 9 more ) | **Moderate** Due to serious indirectness [2] | Carotid artery stenting probably increases death or stroke - long term |
| **Stroke - long term** | Odds Ratio 1.47 (CI 95% 1.22 - 1.78) Based on data from 5,784 patients in 10 studies. (Randomized controlled) Follow up varied | 70 per 1000 | 100 per 1000 Difference: 30 more per 1000 ( CI 95% 48 more - 14 more ) | **Moderate** Due to serious indirectness [3] | Carotid artery stenting probably increases stroke - long term |
| **Periprocedural death or stroke** | Odds Ratio 1.66 (CI 95% 1.34 - 2.07) Based on data from 5,807 patients in 11 studies. (Randomized controlled) Follow up perioperative | 46 per 1000 | 74 per 1000 Difference: 28 more per 1000 ( CI 95% 45 more - 15 more ) | **Moderate** Due to serious indirectness [4] | Carotid artery stenting probably increases periprocedural death or stroke |

1. **Inconsistency: No serious. Indirectness: Serious.** It remains unclear whether stenting outcomes in trials can be repeated in routine practice. **Imprecision: No serious. Publication bias: No serious.**
2. **Inconsistency: No serious. Indirectness: Serious.** It remains unclear whether stenting outcomes in trials can be repeated in routine practice. **Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: Serious.** It remains unclear whether stenting outcomes in trials can be repeated in routine practice. **Imprecision: No serious. Publication bias: No serious.**

4. **Inconsistency: No serious. Indirectness: Serious.** It remains unclear whether stenting outcomes in trials can be repeated in routine practice. **Imprecision: No serious. Publication bias: No serious.**

## Clinical Question/ PICO

**Population:** Adults with symptomatic carotid stenosis
**Intervention:** Endarterectomy
**Comparator:** no endarterectomy

### Summary

Three RCTs relevant to current practice have been published up to date: Veterans Affairs Trial (VACSP), European Carotid Surgery Trial (ECST), and North American Symptomatic Carotid Endarterectomy Trial (NASCET). They reported conflicting results but that was considered due to differences in the measurement methods of degree of stenosis on the pre-randomisation catheter angiogram. To appropriately pool these data, Rerkasem et al (2011) *[152]* reviewed all original angiograms, applied same measurement method (NASCET criteria), and conducted a patient-level meta-analysis. It was shown that endarterectomy was highly beneficial for 70-99% symptomatic stenosis and of marginal benefit to 50-69% stenosis. It had no significant effects in other stenosis groups. Subgroup analysis showed that the benefit is greatest when patients received surgery within two weeks of stroke or TIA (risk difference 0.17, 95%CI 0.11 - 0.24).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** no endarterectomy | Endarterectomy | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Any stroke or operative death - Near occlusion** | Relative risk 0.95 (CI 95% 0.59 - 1.53) Based on data from 271 patients in 2 studies. [1] (Randomized controlled) | 219 per 1000 | 208 per 1000 Difference: **11 fewer** per 1000 ( CI 95% 90 fewer - 116 more ) | **High** | surgery has little or no difference on any stroke or operative death in patients near occlusion |
| **Any stroke or operative death - 70% to 99%** | Relative risk 0.53 (CI 95% 0.42 - 0.67) Based on data from 1,095 patients in 3 studies. [2] (Randomized controlled) | 292 per 1000 | 155 per 1000 Difference: **137 fewer** per 1000 ( CI 95% 169 fewer - 96 fewer ) | **Moderate** Due to serious inconsistency [3] | surgery probably decreases any stroke or operative death in patients with 70% to 99% stenosis |
| **Any stroke or operative death - 50% to 69%** | Relative risk 0.77 (CI 95% 0.63 - 0.94) Based on data from 1,549 patients in 3 studies. [4] (Randomized controlled) | 232 per 1000 | 179 per 1000 Difference: **53 fewer** per 1000 ( CI 95% 86 fewer - 14 fewer ) | **High** | surgery decreases any stroke or operative death in patients with 50% to 69% stenosis |
| **Any stroke or operative death - 30% to 49%** | Relative risk 0.97 (CI 95% 0.79 - 1.19) Based on data from 1,429 patients in 2 | 211 per 1000 | 205 per 1000 | **High** | surgery has little or no difference on any stroke or operative death in patients with 30% to |

| | | | | |
|---|---|---|---|---|
| | studies. [5] (Randomized controlled) | Difference: **6 fewer** per 1000 ( CI 95% 44 fewer - 40 more ) | | 49% stenosis |
| **Any stroke or operative death - < 30%** | Relative risk 1.25 (CI 95% 0.99 - 1.56) Based on data from 1,746 patients in 2 studies. [6] (Randomized controlled) | **138** per 1000 **173** per 1000 Difference: **35 more** per 1000 ( CI 95% 1 fewer - 77 more ) | **High** | surgery has little or no difference on any stroke or operative death in patients with < 30% stenosis |

1. Systematic review [152] with included studies: ECST, NASCET. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [152] with included studies: VACSP, ECST, NASCET. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:68%.. **Indirectness: No serious. Imprecision: No serious.**
4. Systematic review [152] with included studies: NASCET, VACSP, ECST. **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [152] with included studies: ECST, NASCET. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [152] with included studies: NASCET, ECST. **Baseline/comparator:** Control arm of reference used for intervention.

Weak Recommendation

- Carotid endarterectomy should be performed in preference to carotid stenting due to a lower perioperative stroke risk. However, in selected patients with unfavourable anatomy, symptomatic re-stenosis after endarterectomy or previous radiotherapy, stenting may be reasonable.
- In patients aged <70 years old, carotid stenting with an experienced proceduralist may be reasonable.

(Bangalore et al 2011 *[137]*)

## Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

Multiple randomised trials have compared carotid stenting to carotid endarterectomy. The perioperative stroke rate is consistently higher with carotid stenting than carotid endarterectomy. Beyond the peri-procedural period outcomes including ipsilateral ischaemic stroke are similar (Bonati et al 2015 *[129]*). Stenting was associated with fewer periprocedural myocardial infarctions but, in contrast to stroke, these were unlikely to lead to disability.

**Certainty of the Evidence** — High

Findings from multiple randomised trials were consistent.

**Preference and values** — Substantial variability is expected or uncertain

Peri-operative myocardial infarction is unlikely to be considered of equal consequence to stroke by patients and therefore carotid endarterectomy is generally preferred to carotid stenting.

*Areas of major debate*
Some clinicians believe that the chances of potential benefits of stenting are so low that stenting should not be used, while others argue that selected patients can still benefit from stenting, for example, those are not suitable for endarterectomy, or those younger than 70 years old in whom the long-term benefits may offset the short-term risks.

**Resources and other considerations**

No important issues with the recommended alternative

Resources considerations
In three economic evaluations conducted in North American settings, it has been found that carotid endarterectomy was more effective and cost saving when compared to carotid arterial stenting (Vilain et al 2012 *[135]*; Almekhlati et al 2014 *[144]*; Young et al 2014 *[145]*). However, carotid arterial stenting was cost-effective for patients with high surgical risk (Almekhlati et al 2014 *[144]*).Over a lifetime, carotid arterial stenting was cost-effective at an additional cost of US$6,555 per QALY gained compared to carotid endarterectomy in patients with high risk of stroke recurrence (cost reference year 2002) (Mahoney et al, 2011 *[139]*). Carotid arterial stenting was not cost-effective (given a willingness to pay of $50,000 per QALY gained) at an additional cost of US$67,891 per QALY gained compared to carotid endarterectomy over a 1 year time horizon (cost reference year 2006) (Maud et al, 2010 *[140]*).

## Rationale

A number of trials have compared carotid stenting to carotid endarterectomy. Meta-analyses of these trials indicate that the perioperative stroke rate is significantly higher with carotid stenting than carotid endarterectomy (Bangalore et al 2011 *[137]*; Bonati et al 2015 *[129]*), Although some trials found a lower rate of perioperative myocardial infarction following carotid stenting than after carotid endarterectomy, the consequences of stroke and myocardial infarction for the patient are unlikely to be considered equivalent. Based on the consistent increased perioperative stroke rate following carotid stenting this procedure cannot be routinely recommended at this time. There are individuals in whom anatomy or post-radiation changes would make carotid endarterectomy technically challenging, in which case stenting may be considered. Subanalyses of the randomised trials have indicated that there is a strong relationship between perioperative stroke risk and increasing age. These studies suggest that carotid stenting may be equivalent to carotid endarterectomy in patients aged <70 (Bonati et al 2015 *[129]*, Brott et al 2016 *[125]*).

## Clinical Question/ PICO

**Population:** Adults with recently symptomatic carotid stenosis
**Intervention:** Carotid artery stenting
**Comparator:** Carotid endarterectomy

### Summary

The most recent systematic review and meta-analysis by Bangalore et al (2011) *[137]* reported that carotid stenting was associated with increased perioperative stroke compared with carotid endarterectomy. Carotid stenting is associated with reduced incidence of perioperative myocardial infarction compared with carotid endarterectomy but the clinical significance of these cardiac events is less clear since many were diagnosed on the basis of cardiac enzyme elevation and there was no improvement in survival over intermediate follow-up (Bangalore 2011 *[137]*).

Furthermore, outcomes of carotid stenting in administrative datasets analysed by Paraskevas et al (2016) *[127]* suggest that in routine practice carotid stenting is associated with a higher stroke rate than carotid endarterectomy. A recent small randomised trial involving 150 patients reported that new cerebral infarcts on MRI were present in 49% of carotid stenting patients compared to 25% of carotid endarterectomy patients (Kuliha et al 2015 *[128]*).

Long-term follow-up of ICSS (median 4.2 years, up to 10 years) found that the 5 year risk of procedural stroke or death or ipsilateral stroke during follow-up was 11.8% with stenting versus 7.2% with endarterectomy (absolute risk difference 4.6% 95%CI 1.6-7.6%) (Bonati et al 2015 *[129]*). This was related to the periprocedural period with the risk of ipsilateral stroke beyond 30 days similar between treatments (4.7% vs 3.4% at 5 years HR 1.29 95%CI 0.74-2.24 p=0.36). There was also no difference in the primary outcome of fatal or disabling stroke throughout the entire period of follow-up (6.4% vs 6.5%) and

the distribution of modified Rankin scale scores was not different (p=0.49). The incidence of severe restenosis or occlusion were also similar at 5 years (10.8% vs 8.6%, absolute risk difference 2.2% 95%CI -1.1 to 5.4%). Long term follow-up of the CREST trial (median 7.4 years, up to 10 years), in whom approximately 50% of 2,502 patients had symptomatic carotid stenosis has also been reported. Overall the risk of stroke or periprocedural death at 10 years was 11% with stenting versus 7.9% with endarterectomy (HR 1.37 95%CI 1.01-1.86, p=0.04). The subgroup with symptomatic stenosis had a 10-year risk of stroke or periprocedural death of 12.8% with stenting versus 7.8% with endarterectomy (HR 1.44 95%CI 0.98-2.13, p=0.07). Again, the excess risk occurred in the periprocedural period (Brott et al 2016 *[125]*). Restenosis (>70% or requiring revascularization) occurred in 12.2% with stenting versus 9.7% with endarterectomy (HR 1.24; 95%CI 0.91-1.70).

Randomised controlled trials have also eported that patients with a recent (<6months) non-disabling stroke or TIA in the territory of a 70-99% carotid stenosis (NASCET criteria) receive substantial benefit from carotid endarterectomy compared to best medical management alone (NASCET/ ECST) with absolute risk reduction (ARR) 16.0%. In subsequent analyses, the benefit was restricted to patients treated within 3 months of symptoms and greatest when patients were treated within 2 weeks (Rerkasem & Rothwell 2011 *[152]*). The trials also reported a lesser degree of benefit of carotid endarterectomy in patients with a recently symptomatic 50-69% stenosis (NASCET criteria), ARR 4.6%. Once occluded, the risk of subsequent stroke is substantially lower and endarterectomy is generally not feasible. Trials did not demonstrate benefits of carotid endarterectomy in patients with <50% stenosis (Rerkasem & Rothwell 2011 *[152]*).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Carotid endarterectomy | Carotid artery stenting | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Periprocedural stroke** | Odds Ratio 1.66 (CI 95% 1.31 - 2.09) Based on data from 5,588 patients in 10 studies. (Randomized controlled) | 41 per 1000 | 66 per 1000 Difference: 25 more per 1000 ( CI 95% 41 more - 12 more ) | **Moderate** Due to serious indirectness [1] | Carotid artery stenting probably increases periprocedural stroke |
| **Death or stroke - Long term** | Odds Ratio 1.29 (CI 95% 1.08 - 1.54) Based on data from 4,463 patients in 9 studies. (Randomized controlled) Follow up varied | 135 per 1000 | 168 per 1000 Difference: 33 more per 1000 ( CI 95% 59 more - 9 more ) | **Moderate** Due to serious indirectness [2] | Carotid artery stenting probably increases death or stroke - long term |
| **Stroke - long term** | Odds Ratio 1.47 (CI 95% 1.22 - 1.78) Based on data from 5,784 patients in 10 studies. (Randomized controlled) Follow up varied | 70 per 1000 | 100 per 1000 Difference: 30 more per 1000 ( CI 95% 48 more - 14 more ) | **Moderate** Due to serious indirectness [3] | Carotid artery stenting probably increases stroke - long term |
| **Periprocedural death or stroke** | Odds Ratio 1.66 (CI 95% 1.34 - 2.07) Based on data from 5,807 patients in 11 studies. (Randomized controlled) Follow up perioperative | 46 per 1000 | 74 per 1000 Difference: 28 more per 1000 ( CI 95% 45 more - 15 more ) | **Moderate** Due to serious indirectness [4] | Carotid artery stenting probably increases periprocedural death or stroke |

1. **Inconsistency: No serious. Indirectness: Serious.** It remains unclear whether stenting outcomes in trials can be repeated in

routine practice. **Imprecision: No serious. Publication bias: No serious.**
2. **Inconsistency: No serious. Indirectness: Serious.** It remains unclear whether stenting outcomes in trials can be repeated in routine practice. **Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: Serious.** It remains unclear whether stenting outcomes in trials can be repeated in routine practice. **Imprecision: No serious. Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: Serious.** It remains unclear whether stenting outcomes in trials can be repeated in routine practice. **Imprecision: No serious. Publication bias: No serious.**

## Clinical Question/ PICO

**Population:** Adults with asymptomatic carotid stenosis
**Intervention:** Carotid artery stenting
**Comparator:** Carotid endarterectomy

### Summary

The most recent meta-analysis of carotid stenting in asymptomatic patients reports a non-significant increase in periprocedural strokes with the stenting compared to the endarterectomy (Bangalore et al 2011 *[137]*). A more recent large trial involving 1453 asymptomatic patients reported a 2.9% perioperative stroke or death rate in the stenting group compared to 1.7% in the endarterectomy group, a non-significant difference with p=0.33 (Rosenfield et al 2016 *[126]*). Long-term outcomes were not significantly different for composite end-points. The data is in keeping with findings discussed above for symptomatic carotid stenosis that perioperative stroke appears to be higher following carotid stenting but that long-term risk of stroke is similar after either procedure (when the perioperative risk is ignored). Given the low risk of stroke now reported with medical treatment of asymptomatic carotid stenosis (<1%/year) it would appear inappropriate to be considering carotid stenting of asymptomatic carotid stenoses (Spence et al 2016 *[148]*).

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Carotid endarterectomy | Carotid artery stenting | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Periprocedural death or stroke** | Odds Ratio 1.7 (CI 95% 0.87 - 3.33) Based on data from 1,503 patients in 3 studies. (Randomized controlled) Follow up perioperative | 17 per 1000 | 29 per 1000 Difference: **12 more** per 1000 ( CI 95% 37 more - 2 fewer ) | **Moderate** Due to serious indirectness. [1] | Carotid artery stenting probably increases periprocedural death or stroke |
| **Periprocedural stroke** | Odds Ratio 1.75 (CI 95% 0.88 - 3.49) Based on data from 1,503 patients in 3 studies. (Randomized controlled) | 16 per 1000 | 28 per 1000 Difference: **12 more** per 1000 ( CI 95% 38 more - 2 fewer ) | **Moderate** Due to serious indirectness [2] | Carotid artery stenting probably increases periprocedural stroke |
| **Death or stroke - Long term** | Odds Ratio 0.83 (CI 95% 0.46 - 1.49) Based on data from 322 patients in 2 studies. (Randomized controlled) Follow up varied | 198 per 1000 | 170 per 1000 Difference: **28 fewer** per 1000 ( CI 95% 71 more - 96 fewer ) | **Very Low** Due to serious inconsistency, Due to serious indirectness, Due to serious | We are uncertain whether carotid artery stenting increases or decreases death or stroke - long term |

| | | | | | |
|---|---|---|---|---|---|
| | | | | imprecision [3] | |
| **Stroke - long term** | Odds Ratio 1.53 (CI 95% 0.91 - 2.58) Based on data from 1,503 patients in 3 studies. (Randomized controlled) | **70** per 1000 | **103** per 1000<br>Difference: **33 more** per 1000 ( CI 95% 93 more - 6 fewer ) | **Moderate** Due to serious indirectness [4] | Carotid artery stenting probably increases stroke - long term |

1. **Inconsistency: No serious. Indirectness: Serious.** Findings in population samples suggest trial results may not be representative. **Imprecision: No serious. Publication bias: No serious.**
2. **Inconsistency: No serious. Indirectness: Serious.** Findings in population samples suggest trial results may not be representative. **Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: Serious.** Variation between SAPPHIRE AND OTHER TRIALS. **Indirectness: Serious.** It is unclear whether outcomes of carotid stenting in trials can be replicated in routine practice. **Imprecision: Serious.** small sample sizes. **Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: Serious.** Findings in population samples suggest trial results may not be representative. **Imprecision: No serious. Publication bias: No serious.**

Weak Recommendation Against

In patients with asymptomatic carotid stenosis, carotid endarterectomy or stenting should not be performed. (Rosenfield et al 2016 *[126]*; Raman et al 2013 *[133]*; Bangalore et al 2011 *[137]*)

## Key Info

**Benefits and harms**

Small net benefit, or little difference between alternatives

Earlier RCTs have reported that patients with an asymptomatic 60-99% carotid stenosis received some benefit (approximate absolute stroke risk reduction 4.6% at 10 years) from carotid endarterectomy compared to best medical management alone (Raman et al 2013 *[133]*). The benefit, however, comes with an increased risk of periprocedural stroke and was limited to patients aged <75 years and those surviving >3 years. There is concern that medical therapy has improved since these trials and recent series reporting the outcome of medical therapy alone suggest annual stroke rates associated with asymptomatic carotid stenosis are <1%/ year (Abbott et al 2009 *[146]*).

A number of trials have compared carotid stenting and endarterectomy in patients with asymptomatic carotid stenosis. A meta-analysis of carotid stenting in asymptomatic patients reported a non-significant increase in stroke with stenting compared to endarterectomy (Bangalore et al 2011 *[137]*). A more recent large trial involving 1453 asymptomatic patients reported a 2.9% perioperative stroke or death rate in the stenting group compared to 1.7% in the endarterectomy group, p = 0.33 (Rosenfield et al 2016 *[126]*). Given the low risk of stroke now reported with medical treatment of asymptomatic carotid stenosis (<1%/year) the routine use of carotid stenting or endarterectomy for asymptomatic carotid stenosis is not recommended. Further trials are ongoing in this group of patients.

**Certainty of the Evidence**

Moderate

Results from RCTs were consistent but these are now probably out of date - medical therapy appears to have improved.

**Preference and values** — Substantial variability is expected or uncertain

Internationally there is marked variation in the treatment of asymptomatic carotid stenosis with physicians variably favouring medical treatment alone, carotid endarterectomy or carotid stenting. Results of contemporary administrative dataset registries, which may underestimate peri-operative stroke rates, suggest that stroke rates after carotid stenting would lead to harm or no benefit for patients with asymptomatic carotid stenosis in many cases (Paraskevas et al 2016 *[127]*).

**Resources and other considerations** — Factor not considered

## Rationale

Although the available randomised trials indicated a small benefit of endarterectomy for asymptomatic stenosis, consensus opinion is that medical therapy has improved since these trials were conducted. As a result, the current annual risk of stroke in patients taking intensive medical therapy is likely to be less than the up-front periprocedural risk of stroke. There is some evidence supporting selection of patients with asymptomatic carotid stenosis at higher risk, such as those with evidence of silent cerebral infarcts, multiple transcranial detected micro-emboli or concerning plaque morphology on imaging (e.g. echolucent plaque). However, no randomised trial has proven the benefit of this selective approach and the practical application of reliable ways to identify unstable plaque at centres throughout the world has proved difficult. A number of current trials are underway in patients with asymptomatic carotid stenosis. However, currently routine intervention for asymptomatic carotid stenosis is not recommended.

## Clinical Question/ PICO

**Population:** Adults with asymptomatic carotid stenosis
**Intervention:** Carotid artery stenting
**Comparator:** Carotid endarterectomy


## Summary

The most recent meta-analysis of carotid stenting in asymptomatic patients reports a non-significant increase in periprocedural strokes with the stenting compared to the endarterectomy (Bangalore et al 2011 *[137]*). A more recent large trial involving 1453 asymptomatic patients reported a 2.9% perioperative stroke or death rate in the stenting group compared to 1.7% in the endarterectomy group, a non-significant difference with p=0.33 (Rosenfield et al 2016 *[126]*). Long-term outcomes were not significantly different for composite end-points. The data is in keeping with findings discussed above for symptomatic carotid stenosis that perioperative stroke appears to be higher following carotid stenting but that long-term risk of stroke is similar after either procedure (when the perioperative risk is ignored). Given the low risk of stroke now reported with medical treatment of asymptomatic carotid stenosis (<1%/year) it would appear inappropriate to be considering carotid stenting of asymptomatic carotid stenoses (Spence et al 2016 *[148]*).


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Carotid endarterectomy | Carotid artery stenting | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Periprocedural death or stroke** | Odds Ratio 1.7 (CI 95% 0.87 - 3.33) Based on data from 1,503 patients in 3 studies. (Randomized controlled) Follow up perioperative | 17 per 1000 | 29 per 1000 | **Moderate** Due to serious indirectness. [1] | Carotid artery stenting probably increases periprocedural death or stroke |
| | | Difference: **12 more** per 1000 ( CI 95% 37 more - 2 fewer ) | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Periprocedural stroke** | Odds Ratio 1.75 (CI 95% 0.88 - 3.49) Based on data from 1,503 patients in 3 studies. (Randomized controlled) | 16 per 1000 | 28 per 1000 | **Moderate** Due to serious indirectness [2] | Carotid artery stenting probably increases periprocedural stroke |
| | | Difference: **12 more** per 1000 ( CI 95% 38 more - 2 fewer ) | | | |
| **Death or stroke - Long term** | Odds Ratio 0.83 (CI 95% 0.46 - 1.49) Based on data from 322 patients in 2 studies. (Randomized controlled) Follow up varied | 198 per 1000 | 170 per 1000 | **Very Low** Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision [3] | We are uncertain whether carotid artery stenting increases or decreases death or stroke - long term |
| | | Difference: **28 fewer** per 1000 ( CI 95% 71 more - 96 fewer ) | | | |
| **Stroke - long term** | Odds Ratio 1.53 (CI 95% 0.91 - 2.58) Based on data from 1,503 patients in 3 studies. (Randomized controlled) | 70 per 1000 | 103 per 1000 | **Moderate** Due to serious indirectness [4] | Carotid artery stenting probably increases stroke - long term |
| | | Difference: **33 more** per 1000 ( CI 95% 93 more - 6 fewer ) | | | |

1. **Inconsistency: No serious. Indirectness: Serious.** Findings in population samples suggest trial results may not be representative. **Imprecision: No serious. Publication bias: No serious.**
2. **Inconsistency: No serious. Indirectness: Serious.** Findings in population samples suggest trial results may not be representative. **Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: Serious.** Variation between SAPPHIRE AND OTHER TRIALS. **Indirectness: Serious.** It is unclear whether outcomes of carotid stenting in trials can be replicated in routine practice. **Imprecision: Serious.** small sample sizes. **Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: Serious.** Findings in population samples suggest trial results may not be representative. **Imprecision: No serious. Publication bias: No serious.**

## Clinical Question/ PICO

**Population:** Adults with asymptomatic carotid stenosis
**Intervention:** Carotid endarterectomy
**Comparator:** Medical therapy alone

### Summary

A systematic review and meta-analysis of older trials by Raman et al (2013) *[133]* demonstrated clearly that carotid endarterectomy reduces the long-term incidence of ipsilateral stroke compared to medical treatment alone at the time of the trials. The benefit was however relatively small and this advantage did come at an increased risk of short-term stroke (i.e. periprocedural), thus patients need to be fit enough to expect long-term survival to benefit *[133]*. There is concern that medical therapy has improved since these trials and recent series reporting the outcome of medical therapy alone suggest annual stroke rates associated with asymptomatic carotid stenosis are <1%/ year (Abbott 2009 *[146]*). Whether these analyses are representative of all asymptomatic carotid stenoses is unclear and on-going trials will hopefully clarify whether medical treatment alone is appropriate for asymptomatic carotid stenosis.

In the interim the most appropriate treatment of asymptomatic carotid stenosis is controversial. However, the population benefit of carotid surgery for patients with asymptomatic carotid stenosis would appear to be low, since observational studies suggest that 1000 carotid endarterectomies have to be performed to prevent 40-50 strokes (Naylor 2012 *[147]*).

The selective use of carotid endarterectomy is favoured by some, yet optimal ways of determining the higher risk asymptomatic carotid stenosis (which might be selected out for endarterectomy) are not agreed. A number of techniques being used include high-resolution ultrasound or other imaging of the carotid stenosis, transcranial Doppler to identify micro-emboli and brain imaging to find silent cerebral infarcts. However, no trial has demonstrated that a particular sub-group benefit more from endarterectomy.

Overall current evidence would appear to support a medical treatment alone approach to asymptomatic carotid stenosis unless the treating physician feels the patients have a higher risk of stroke and can expect long-term survival.

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Medical therapy alone | Carotid endarterectomy | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Stroke** [1] | Relative risk 0.72 (CI 95% 0.58 - 0.9) Based on data from 5,223 patients in 3 studies. (Randomized controlled) Follow up VARIED | 69 per 1000 | 50 per 1000 Difference: **19 fewer** per 1000 ( CI 95% 29 fewer - 7 fewer ) | **Low** Due to very serious indirectness [2] | Carotid endarterectomy may reduce the risk for stroke |

1. Ispilateral stroke, including any stroke within 30 days
2. **Inconsistency: No serious. Indirectness: Very Serious.** There is concern that patients recruited to these trials were not on modern best medical treatment as treatment has advanced since 2000 when recruited ended for these trials.. **Imprecision: No serious. Publication bias: No serious.**

Strong Recommendation Against

In patients with symptomatic carotid occlusion, extracranial/ intracranial bypass is not recommended. (Powers et al 2011 *[138]*; Fluri et al 2010 *[141]*)

## Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

Three randomised trials reported no benefit of extracranial/ intracranial bypass for symptomatic carotid occlusion (Powers et al 2011 *[138]*; Fluri et al 2010 *[141]*). The perioperative stroke rate associated with extracranial/ intracranial bypass is substantial - 14.3% in the most recent trial (Powers et al 2011 *[138]*). Given these findings extracranial/ intracranial bypass appears to have more harm than benefit.

**Certainty of the Evidence** — High

Findings from three randomised trials were consistent.

**Preference and values** — No substantial variability expected

There is no reason to prefer intervention given the demonstrated risks and lack of benefit.

**Resources and other considerations** Factor not considered

## Rationale

Consistent findings from multiple trials show harm and no benefit from extracranial to intracranial bypass in patients with carotid occlusion.

## Clinical Question/ PICO

**Population:** Adults with symptomatic carotid occlusion
**Intervention:** Extracranial-intracranial arterial bypass surgery
**Comparator:** Medical therapy alone


## Summary

A systematic review of RCTs published before 2010 by Fluri et al (2010) *[141]* did not find extracranial/intracranial bypass to be either better or worse than medical care alone, however not all patients included had haemodynamic compromise. A more recent trial by Powers et al (2011) *[138]* did select patients with haemodynamic cerebral ischaemia but still reported no benefit in terms of reducing stroke and death and a perioperative stroke rate of 14.3% within the intervention group. Overall, extracranial/intracranial bypass was not effective in reducing stroke or death in adults with symptomatic carotid occlusion.


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Medical therapy alone | Extracranial-intracranial arterial bypass surgery | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| Death | Odds Ratio 0.81 (CI 95% 0.62 - 1.05) Based on data from 1,691 patients in 2 studies. (Randomized controlled) Follow up 56 and 25 months | 181 per 1000 | 152 per 1000 Difference: 29 fewer per 1000 ( CI 95% 7 more - 60 fewer ) | Low Due to serious indirectness, Due to serious imprecision [1] | Extracranial-intracranial arterial bypass surgery may decrease death slightly |
| Death or dependency | Odds Ratio 0.94 (CI 95% 0.74 - 1.21) Based on data from 1,377 patients in 1 studies. (Randomized controlled) | 251 per 1000 | 240 per 1000 Difference: 11 fewer per 1000 ( CI 95% 41 more - 52 fewer ) | Low Due to serious imprecision, Due to serious indirectness [2] | Extracranial-intracranial arterial bypass surgery may have little or no difference on death or dependency |
| Stroke | Odds Ratio 0.99 (CI 95% 0.79 - 1.23) Based on data from 1,691 patients in 2 studies. (Randomized controlled) Follow up 56 and 25 months | 263 per 1000 | 261 per 1000 Difference: 2 fewer per 1000 ( CI 95% 42 more - 43 fewer ) | Low Due to serious indirectness, Due to serious imprecision [3] | Extracranial-intracranial arterial bypass surgery may have little or no difference on stroke |
| Ipsilateral ischaemic | n/a | 20 | 144 | Moderate Due to serious | Extracranial-intracranial arterial bypass surgery |

| | | | | |
|---|---|---|---|---|
| **stroke**<br>30 days<br><br>9 Critical | Based on data from 195 patients in 1 studies.<br>(Randomized controlled)<br>Follow up 2 years | per 1000 per 1000<br>Difference: **124 more** per 1000 | risk of bias, Due to very serious risk of bias, Upgraded due to Large magnitude of effect [4] | probably increases the risk of stroke at 30 days. |

1. **Inconsistency: No serious. Indirectness: Serious.** not all patients included had haemodynamic compromise . **Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
2. **Inconsistency: No serious. Indirectness: Serious.** not all patients included had haemodynamic compromise . **Imprecision: Serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: Serious.** not all patients included had haemodynamic compromise . **Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
4. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious. Upgrade: Large magnitude of effect.** Trial stopped early due to futility.

## Cervical artery dissection

Cervical artery dissection (CAD) accounts for only 2% of all ischaemic strokes (Biller et al 2014 *[157]*). However, it is an important cause of stroke in young and middle-aged patients, accounting for 8% to 25% of stroke in patients <45 years of age (Biller et al 2014 *[157]*). It is unclear what the natural history of CAD is as all patients diagnosed receive treatments such as antithrombotic therapies or thrombolysis. Some studies suggest that patients presenting with stroke or TIA and CAD have a risk of secondary stroke of around 15% (Weimar et al 2010 *[158]*; Beletsky et al 2003 *[159]*), while others report a much lower rate at 3% (Kennedy et al 2012 *[160]*). Embolism from thrombus formation at the dissection site is thought to play the major part in stroke pathogenesis. This is supported by Transcranial Doppler studies showing cerebral microemboli soon after dissection (Srinivasan et al 1996 *[155]*), and by the brain imaging results suggesting an embolic pattern (Benninger et al 2004 *[156]*). The risk of recurrent stroke and the pathogenesis have led to clinicians to advocate for preventive measures.

Strong Recommendation

Patients with acute ischaemic stroke due to cervical arterial dissection should be treated with antithrombotic therapy. There is no clear benefit of anticoagulation over antiplatelet therapy. (CADISS 2015 *[153]*)

### Practical Info

Given that there is no clear benefit in reducing recurrent stroke of anticoagulant over antiplatelet therapy, antiplatelet therapy may be preferred due to resource implications, patient preferences and bleeding risk considerations. Refer to antiplatelet therapy section.

### Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

Antiplatelet and anticoagulant therapy have a similar benefit and risk profile when used in the management of cervical artery dissection up to one year after the stroke (CADISS 2015 *[153]*; Markus et al 2019 *[161]*). Further, the rate of recanalisation is similar between antiplatelets and anticoagulants (Markus et al 2019 *[161]*).

**Certainty of the Evidence** — Moderate

The quality of evidence is moderate. There is a single randomised controlled trial (CADISS 2015 *[153]*). In addition, there are several meta-analyses of observational and largely low-quality studies (Sarikaya et al 2013 *[154]*).

**Preference and values** — No substantial variability expected

Antiplatelets may be preferred given the perception of lower risk and potentially easier adherence due to single daily dose and no need for blood test monitoring.

**Resources and other considerations** — Factor not considered

### Rationale

There is no direct evidence comparing antithrombotic therapies and no therapy. It is likely to be unethical to withhold antithrombotic treatments in clinical trials given the link of physiological mechanism of cervical artery dissection and stroke. There is good evidence to indicate that selection of antithrombotic agent (i.e. antiplatelet or anticoagulant) does not significantly impact on stroke recurrence but antiplatelet may be preferred due to the perception of its safety profile and easier adherence.

## Clinical Question/ PICO

**Population:** Stroke patients with cervical artery dissection
**Intervention:** Anticoagulant
**Comparator:** Antiplatelet


### Summary

CADISS was a randomised controlled trial (RCT) of 250 patients comparing antiplatelet use (n=126) with anticoagulant use (n=124) following cervical artery dissection (CADISS trial investigators 2015 *[153]*). The primary outcome was ipsilateral stroke or death at 3 months. Secondary outcomes included any stroke, death, and major bleeding. While there were numerically more strokes (3/126, 2%) in the antiplatelet group compared with the anticoagulant group (1/124, 1%) this difference was not statistically significant. Major bleeding was rare in the anticoagulant group (1/124, 1%) and there were none in the antiplatelet group (0/126). There were no deaths at three months in either group and there was no difference in outcomes at 12 months (Markus et al 2019*[161]*). There was no difference in residual narrowing between treatments between baseline and 3 months (Markus et al 2019*[161]*).

A prior meta-analysis (Sarikaya et al 2013 *[154]*) suggested that antiplatelets were more effective than anticoagulation in preventing the composite outcome of stroke, intracranial haemorrhage, or death at 3 months (RR 0.32 95%CI 0.12-0.63) although the quality of the studies included, all of which were either observational or quasi-randomised, was much lower than the CADISS RCT and the latter should be viewed as the more definitive evidence to guide treatment decisions.


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Antiplatelet | Anticoagulant | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Stroke or death** 3 months<br>8 Critical | Odds Ratio 0.34 (CI 95% 0.01 - 4.23) Based on data from 250 patients in 1 studies. (Randomized controlled) Follow up 3 months | 24 per 1000 | 8 per 1000<br>Difference: **16 fewer** per 1000 ( CI 95% 70 more - 24 fewer ) | **Moderate** Due to only a single study, small patient number, incomplete blinding, and heterogeneity of patients studied. [1] | This RCT provides moderately high evidence that anticoagulation is not superior to antiplatelets in the prevention of stroke or death following cervical artery dissection. While the events per 1000 was higher in the antiplatelet group the 95% confidence interval crossed 1.0 resulting in a non-significant outcome difference. |
| **Death** 3 months<br>9 Critical | Odds Ratio<br>Based on data from 250 patients in 1 studies. (Randomized controlled) Follow up 3 months | 0 per 1000 | 0 per 1000<br>Difference: **0 fewer** per 1000 CI 95% | **Moderate** Due to only a single study, small patient number, incomplete blinding, and heterogeneity of patients studied. [2] | This RCT provides moderately high evidence that the risk of death after cervical dissection is the same whether antiplatelets or anticoagulants are used for secondary prevention. |
| **Stroke** [3] 3 months | Odds Ratio 0.34 (CI 95% 0.01 - 4.23) Based on data from 250 | 24 | 8 | **Moderate** Due to only a single study, small | This RCT provides evidence that anticoagulants are not |

| | | | | |
|---|---|---|---|---|
| 8 Critical | patients in 1 studies. (Randomized controlled) Follow up 3 months | per 1000 per 1000<br>Difference: 16 fewer per 1000 ( CI 95% 24 fewer - 70 more ) | patient number, incomplete blinding, and heterogeneity of patients studied. [4] | significantly superior to antiplatelets in the secondary prevention of stroke following cervical dissection. |
| Major bleeding<br>8 Critical | Odds Ratio<br>Based on data from 250 patients in 1 studies. (Randomized controlled) Follow up 3 months | 0 per 1000 8 per 1000<br>Difference: 8 more per 1000 CI 95% | Moderate<br>Due to only a single study, small patient number, incomplete blinding, and heterogeneity of patients studied [5] | This RCT found a higher number of major bleeding episodes per 1000 in the anticoagulation compared with the antiplatelet groups following cervical dissection, but this difference did not reach statistical significance. |

1. **Risk of bias: Serious.** Neither patients nor clinicians were blinded although, but investigators assessing endpoints were masked. . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, Low number of patients and heterogeneity of patients (e.g. included both carotid and vertebral dissection) may have resulted an underestimate of a treatment benefit. **Publication bias: No serious.**
2. **Risk of bias: Serious.** Neither patients nor clinicians were blinded although, but investigators assessing endpoints were masked. . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, Low number of patients and heterogeneity of patients (e.g. included both carotid and vertebral dissection) may have resulted an underestimate of a treatment benefit, Low number of patients, Only data from one study. **Publication bias: No serious.**
3. Any stroke ipsi- or contralateral to dissection.
4. **Risk of bias: Serious.** Neither patients nor clinicians were blinded although, but investigators assessing endpoints were masked.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study. **Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, Low number of patients and heterogeneity of patients (e.g. included both carotid and vertebral dissection) may have resulted an underestimate of a treatment benefits. **Publication bias: No serious.**

## Cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis (CVST) is a distinct cerebrovascular disorder that often affects young individuals. It has two mechanisms usually occurring simultaneously: thrombosis of cerebral veins which can cause localised oedema of the brain and venous infarction, and thrombosis of the major sinuses which can cause intracranial hypertension (Stam 2005 *[166]*). CVST is not typical of a 'regular' stroke. Symptoms usually won't appear in a way that can be identiifed with FAST. For many patients with CVST, seizures will be a lead symptom.

No population studies have reported the incidence of CVST and very few stroke registries included cases with CVST (Saposnik et al 2011 *[167]*). The overall risk of recurrence of any thrombotic event after a CVST is around 6.5% (Saposnik et al 2011 *[167]*). Approximately 3% to 15% of patients die in the acute phase of the disorder (Saposnik et al 2011 *[167]*). Regarding the long-term outcome, the biggest prospective study on this medical condition, International Study on Cerebral Vein and Dural Sinus Thrombosis, reported a complete recovery of 79% of the patients at last follow-up (median 16 months). However, there was an 8.3% overall death rate and a 5.1% dependency rate (mRS >2) (Ferro et al 2004 *[165]*).

Strong Recommendation

Patients with cerebral venous sinus thrombosis (CVST) without contraindications to anticoagulation should be treated with either body weight-adjusted subcutaneous low molecular weight heparin or dose-adjusted intravenous heparin, followed by warfarin, regardless of the presence of intracerebral haemorrhage. (Coutinho et al 2011 *[162]*; Misra et al 2012 *[163]*; Afshari et al 2015 *[164]*)

### Practical Info

The diagnosis of CVST can be confirmed using CT venography or MRI venography. Treatment with heparin or enoxaparin should be commenced even when there is haemorrhagic transformation of the venous infarct. There is limited experience with endovascular techniques (intra-sinus thrombolysis or thrombectomy) and the safety profile is poorly characterised.

There is little evidence on which to base the duration of anticoagulation and recommendations tend to be adapted from systemic venous thromboembolism due to similarities in the risk of recurrent thrombosis after initial CVST. For patients with CVST provoked by a transient risk factor, anticoagulation is recommended for 3-6 months. For patients with CVST that is idiopathic or due to a mild thrombophilia (heterozygous Factor V Leiden or prothrombin gene mutation), anticoagulation may be considered for 6-12 months. For patients with CVST due to a severe thrombophilia or combined thrombophilias (homozygous Factor V Leiden or prothrombin gene mutation, protein C, S or antithrombin deficiency and antiphospholipid syndrome), and for patients with recurrent CVST, indefinite anticoagulation is recommended. In patients with CVST in the setting of malignancy, anticoagulation (with low molecular weight heparin) is recommended for at least 3-6 months or until the malignancy resolves. In the setting of pregnancy and puerperal CVST, anticoagulation (with low molecular weight heparin) is recommended for the remainder of the pregnancy and for at least 6 weeks postpartum for a total of 6 months of therapy (Caprio 2012 *[168]*; Einhaupl et al 2010 *[169]*).

### Key Info

**Benefits and harms**

Substantial net benefits of the recommended alternative

Based upon the limited evidence available, anticoagulant treatment for cerebral venous sinus thrombosis appeared to be safe and was associated with a potentially important reduction in the risk of death or dependency (Coutinho et al 2011 *[162]*).

The choice of anticoagulant probably has little or no impact on functional outcome and adverse events but low molecular weight heparin may have some benefit on mortality when compared to unfractionated heparin (Misra et al 2012 *[163]*; Afshari et al 2015 *[164]*).

**Certainty of the Evidence**

Low

Quality of evidence was low due to small sample size and wide confidence intervals.

**Preference and values**

No substantial variability expected

The consequences of untreated cerebral venous sinus thrombosis are life threatening. Although the existing randomised data are from very small trials, the treatment effect appears convincing and anticoagulation is regarded as standard care.

**Resources and other considerations** Factor not considered

## Rationale

A number of small trials found lower death or dependency in patients treated with anticoagulation, and low molecular weight heparin and unfractionated heparin appeared to have similar efficacy.

## Clinical Question/ PICO

**Population:** Adults with venous sinus thrombosis
**Intervention:** Anticoagulation (heparin)
**Comparator:** Control

## Summary

A Cochrane review by Coutinho et al (2011) *[162]* analysed the efficacy and safety of anticoagulation with heparin. It included two small RCTs involving 79 patients with cerebral venous sinus thrombosis (CVST). One trial (20 patients) examined the efficacy of intravenous, adjusted dose unfractionated heparin. The other trial (59 patients) examined high dose, body weight adjusted, subcutaneous, low-molecular weight heparin (nadroparin). Anticoagulation was found to be associated with a non-significant reduced risk of death, and death or dependency. In both trials, no new symptomatic intracerebral haemorrhage (ICH) were diagnosed after initiation of anticoagulation, despite the fact that many patients who received heparin had some degree of ICH on their pre-treatment CT scans. The included RCTs have a low risk of bias, but the small sample size and wide confidence interval limit precision.

Two RCTs have been published after the Cochrane review and compared low molecular weight heparin (LMWH) and unfractionated heparin (UFH). Misra et al (2012) *[163]* found that LMWH resulted in significantly lower hospital mortality in CVST compared to UFH (six patients died and they were all in UFH group), whereas Afshari et al (2015) *[164]* did not find any significant difference between LMWH and UFH in terms of death and disability. Both studies had low risk of bias but their sample sizes were small: N = 52 in Afshari et al (2015) and N = 62 in Misra et al (2012). Moreover, they were conducted in India and Iran, meaning the results may not be applicable in Australia. Considering the inconsistent results and low quality of evidence, one cannot be certain that either LMWH or UFH is superior.

Overall, the limited evidence suggests that anticoagulation with LMWH or UFH may be a safe and beneficial option.

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Anticoagulation (heparin) | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Death from any cause at the end of scheduled trial follow-up** 3 months<br>9 Critical | Relative risk 0.33 (CI 95% 0.08 - 1.28) Based on data from 79 patients in 2 studies. [1] (Randomized controlled) Follow up 3 months | 179 per 1000 | 59 per 1000<br>Difference: **120 fewer** per 1000 ( CI 95% 50 more - 165 fewer ) | **Low** Due to very serious imprecision [2] | anticoagulation (heparin) may decrease death from any cause at the end of scheduled trial follow-up |
| **Death or dependency at the end of the scheduled trial follow-up period** 3 months | Relative risk 0.46 (CI 95% 0.16 - 1.31) Based on data from 79 patients in 2 studies. [3] (Randomized controlled) Follow up 3 months | 231 per 1000 | 106 per 1000<br>Difference: **125 fewer** per 1000 ( CI 95% 72 more - 194 fewer ) | **Low** Due to very serious imprecision [4] | anticoagulation (heparin) may decrease death or dependency at the end of the scheduled trial follow-up period |

| | | | | |
|---|---|---|---|---|
| 9 Critical<br>**Symptomatic intracerebral haemorrhage (new or increased)**<br>3 months<br>8 Critical | n/a<br>Based on data from 79 patients in 2 studies. [5]<br>(Randomized controlled)<br>Follow up 3 months | | **Low**<br>Due to very serious imprecision [6] | The risk of intracerebral haemorrhage in patients with sinus thrombosis who are treated with anticoagulants (heparin) may be low. |
| **Any severe haemorrhage**<br>3 months<br>7 Critical | Relative risk 2.9<br>(CI 95% 0.12 - 68.5)<br>Based on data from 79 patients in 2 studies. [7]<br>(Randomized controlled)<br>Follow up 3 months | **0**<br>per 1000<br>**25**<br>per 1000<br>Difference: **0 fewer** per 1000<br>( CI 95% 0 fewer - 0 fewer ) | **Low**<br>Due to very serious imprecision [8] | anticoagulation (heparin) may increase any severe haemorrhage |

1. Systematic review [162] with included studies: Einhaupl 1991, CVST Group 1999. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients, Wide confidence intervals. **Publication bias: No serious.**
3. Systematic review [162] with included studies: Einhaupl 1991, CVST Group 1999. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals, Low number of patients. **Publication bias: No serious.**
5. Systematic review [162] with included studies: Einhaupl 1991, CVST Group 1999. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Low number of patients; zero cases in both groups. **Publication bias: No serious.**
7. Systematic review [162] with included studies: Einhaupl 1991, CVST Group 1999. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals, Low number of patients (only one case). **Publication bias: No serious.**

## Clinical Question/ PICO

**Population:** Adults with venous sinus thrombosis
**Intervention:** Low molecular weight heparin
**Comparator:** Unfractionated heparin


### Summary

Two randomised controlled trials have compared low molecular weight heparin and unfractionated heparin in patients with cerebral venous sinus thrombosis (CVST). They both had low risk of bias but Afshari et al (2015) *[164]* was powered to detect statistical significance whereas Misra et al (2012) *[163]* was not.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Absolute effect estimates**<br>Unfractionated heparin | <br>Low molecular weight heparin | **Certainty of the Evidence**<br>(Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Death**<br>During hospital stay | n/a<br><br>Based on data from 52 patients in 1 studies. [1]<br>(Randomized controlled) | 56<br>per 1000 | 38<br>per 1000<br><br>Difference: **18 fewer** per 1000<br>CI 95% | **Low**<br>Due to serious indirectness, Due to serious imprecision [2] | One study showed non-significant reduction (P = 0.99) in mortality with LMWH compared to UFH |
| **Functional outcome - Poor or incomplete recovery**<br>30 days to 3 months<br><br>5 Important | Relative risk<br><br>Based on data from 110 patients in 2 studies. [3]<br>Follow up 30 days to 3 months | 100<br>per 1000 | 67<br>per 1000<br><br>CI 95% | **Moderate**<br>Neither study found a significant difference in functional outcome at 1 month and 3 months between LMWH and heparin group. | The choice of anticoagulant probably has little or no difference to the functional outcome. |
| **Adverse events**<br>1 month to 3 months<br><br>6 Important | Relative risk<br><br>Based on data from 66 patients in 1 studies.<br>Follow up 3 months | 125<br>per 1000 | 0<br>per 1000<br><br>Difference: **125 fewer** per 1000<br>( CI 95% 0 fewer - 0 fewer ) | **Low**<br>The Misra et al study did not find significant difference in the side effects between two arms. In the Afshar et al study ththere was no statistically significant difference between UFH and LMWH in the mean NIHSS and mRS scores during the follow up period. Afshar et al found that at end point the NIHSS and mRS decreased significantly in the 2 groups. [4] | The choice of anticoagulant probably has little or no difference to the incidence of adverse events. |

1. Primary study[163], [164]. **Baseline/comparator:** Control arm of reference used for intervention[163], [164].
2. **Inconsistency: No serious. Indirectness: Serious.** Differences between the population of interest and those studied - study was conducted in Iran. **Imprecision: Serious.** Only data from one study, Low number of patients. **Publication bias: No serious.**
3. Systematic reviewwith included studies: [163], [164]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Low number of patients. **Publication bias: No serious.**

Practice Statement

**Consensus-based recommendations**

- In patients with CVST, the optimal duration of oral anticoagulation after the acute phase is unclear and may be taken in consultation with a haematologist.
- In patients with CVST with an underlying thrombophilic disorder, or who have had a recurrent CVST, indefinite anticoagulation should be considered.
- In patients with CVST, there is insufficient evidence to support the use of either systemic or local thrombolysis.
- In patients with CVST and impending cerebral herniation, craniectomy can be used as a life-saving intervention.
- In patients with the clinical features of idiopathic intracranial hypertension, imaging of the cerebral venous system is recommended to exclude CVST.

## Diabetes management

Diabetes and glucose intolerance post stroke have been found to be independent risk factors for subsequent strokes (Vermeer et al 2006 *[170]*) Hyperglycaemia in the first few days after a stroke is very common and levels fluctuate (see Glycaemic therapy). Assessment of glucose tolerance after stroke or TIA would allow identification and subsequent management of patients with undiagnosed diabetes or glucose intolerance and provide additional secondary prevention measures for stroke recurrence.

Evidence for the management of diabetes is primarily based on primary prevention. Important aspects of care include intensive management of BP and cholesterol, careful management of glycaemic status using behavioural modification (e.g. diet and exercise) and pharmacotherapy. National guidelines for the management of diabetes are available and the relevant recommendations should be followed.

Recommendation Strength Not Set

**Practice point**

Patients with glucose intolerance or diabetes should be managed in line with Diabetes Australia Best Practice Guidelines.

## Patent foramen ovale management

Patent foramen ovale (PFO) is found in an increased proportion (~50%) of patients with cryptogenic stroke, especially those aged under 55. PFO has not been found to increase the risk of subsequent stroke or death compared to other patients with cryptogenic stroke. (Katsanos et al 2014 *[174]*) There are subgroups that may be at increased risk, for example, if PFO is present in combination with an atrial septal aneurysm, and the RoPE score (Kent et al 2013 *[173]*) was devised to assist assessment of the likelihood that PFO is relevant to stroke aetiology in a particular individual. Essentially younger patients with a cortical infarct and fewer traditional vascular risk factors (diabetes, hypertension, smoking, previous stroke/TIA) have a greater likelihood that their stroke was due to the PFO.

Strong Recommendation

Patients with ischaemic stroke or TIA and PFO should receive optimal medical therapy including antiplatelet therapy or anticoagulation if indicated. (Romoli et al 2020 *[187]*; Sagris et al 2019 *[186]*)

### Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

Antithrombotic agents appear to reduce recurrent stroke in patients with PFO just as they do in other stroke aetiologies. No significant difference in the risk of recurrent stroke has been reported between antiplatelets and anticoagulants in patients with PFO (Romoli et al 2020*[187]*; Sagris et al 2019*[186]*). Antiplatelets have better safety profile although no significant differences were reported in major bleeding.

**Certainty of the Evidence** — Moderate

Overall quality is moderate due to imprecision and risk of bias.

**Preference and values** — Substantial variability is expected or uncertain

Patients' preferences for anticoagulation therapycan vary substantially (especially for warfarin). There is uncertainty as to the overall preferences of possible benefits of each intervention.

**Resources and other considerations** — Factor not considered

### Rationale

Meta-analysis of five RCTs (two subgroup analysis) report non-significant reduction in ischaemic strokes but with non-significant increase in major bleeding using anticoagulation therapy compared with antiplatelet therapy. While the current data may not discount a potential benefit of anticoagulation therapy especially for some subgroups, significant uncertainty remains and antiplatelet therapy has a better risk profile and should be used unless there is a clear indication for anticoagulation (e.g. atrial fibrillation).

### Clinical Question/ PICO

**Population:** Stroke patients with PFO
**Intervention:** Anticoagulation therapy
**Comparator:** Antiplatelet therapy

### Summary

Two meta-analysis of five RCTs report similar outcomes based on slightly different methods. Romoli et al (2020)*[187]* reported anticoagulation therapy may reduce stroke (OR 0.66, 95% CI 0.41-1.07) but offset by potential increase in major

bleeding (OR 1.64, 95% CI 0.79-3.43). Numbers of events were relatively small in both outcomes and follow up was less than 2 years in 4/5 trials. Subgroup analysis in two trials found patients with high RoPE score (n=531) had reduced stroke recurrence (OR 0.22, 95% CI, 0.06-0.80) but this is based on very small absolute numbers. Similar result was found in patients with atrial septal aneurysm. Further studies are need to confirm any real differences in various subgroups.

Another meta-analysis by Sargris et al (2019)*[186]* reported anticoagulation therapy may reduce stroke recurrence (HR 0.68, 95% CI, 0.32-1.48) but increase major bleeding (HR 1.61, 95% CI, 0.72-3.59). Overall the combined data indicated 52 events occurred with anticoagulation vs 54 for antiplatelet therapy (OR 1.05, 95% CI, 0.65-1.70).
*[173][171]*
Antiplatelet therapy is expected to have a better risk profile overall but there is little overall difference in benefits and harms.

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Antiplatelet therapy | Anticoagulation therapy | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Ischaemic stroke** 1-5 years<br>9 Critical | Odds Ratio 0.66 (CI 95% 0.41 - 1.07) Based on data from 1,515 patients in 4 studies. (Randomized controlled) Follow up mean 2 years | 58 per 1000 | 39 per 1000<br>Difference: **19 fewer** per 1000 ( CI 95% 33 fewer - 4 more ) | **Moderate** Downgraded due to risk of bias and imprecision [1] | Anticoagulation therapy probably has little or no difference on ischaemic stroke |
| **Major bleeding** [2] 0.9-5.3 years<br>9 Critical | Odds Ratio 1.64 (CI 95% 0.79 - 3.43) Based on data from 1,467 patients in 4 studies. (Randomized controlled) Follow up mean 2 years | 16 per 1000 | 26 per 1000<br>Difference: **10 more** per 1000 ( CI 95% 3 fewer - 37 more ) | **Moderate** Due to serious risk of bias, Due to serious imprecision [3] | Anticoagulation therapy probably has little or no difference on major bleeding |

1. **Risk of bias: Serious.** One trial stopped early. One trial had issues with allocation concealment and unblinded outcome. Two trials were prespecified subgroup analysis.. **Inconsistency: No serious.** Point estimates vary widely. **Indirectness: No serious.** most trials followed up for less than 2 years. Three trials used warfarin and two included two different NOACs, Direct comparisons not available, The outcome time frame in studies were insufficient. **Imprecision: Serious.** Wide confidence intervals, Low number of patients, Wide confidence intervals, Low number of patients. **Publication bias: No serious.**
2. Major bleeding was defined differently in each trial but main driver was ICH
3. **Risk of bias: Serious.** One trial stopped early. Two trials had issues with allocation concealment and unblinded outcome. Two trials were prespecified subgroup analysis.. **Inconsistency: No serious. Indirectness: No serious.** Direct comparisons not available, The outcome time frame in studies were insufficient. **Imprecision: Serious.** Wide confidence intervals, Low number of patients. **Publication bias: No serious.**

Strong Recommendation

In patients with ischaemic stroke aged <60 in whom a patent foramen ovale is considered the likely cause of stroke after thorough exclusion of other aetiologies, percutaneous closure of the PFO is recommended (Turc et al 2018 *[175]*, Saver et al 2018 *[177]*).

### Practical Info

Investigation for PFO should be performed in all patients aged <60 who have not had another cause of stroke found on

cerebrovascular imaging (e.g. aortic arch to cerebral vertex CT angiography) and cardiac investigations. In the PFO closure trials a 24h Holter monitor was considered sufficient search for paroxysmal atrial fibrillation. However, longer term monitoring could be considered if there is a high clinical suspicion for atrial fibrillation. Joint decision-making between stroke and cardiology teams is encouraged when considering the appropriateness of PFO closure.

A transthoracic echocardiogram with agitated saline contrast ("bubble study") is sensitive to shunting and the quality of Valsalva manoeuvre may be better than under sedation for transoesophageal echocardiography. Transcranial Doppler ultrasound with agitated saline contrast study is more sensitive but less often performed in Australia and New Zealand. If a shunt is discovered using saline contrast with transthoracic echocardiography or transcranial Doppler ultrasound, a transoesophageal echocardiogram will be required to clarify the anatomy and plan for percutaneous closure. Atrial septal aneurysm (hypermobile inter-atrial septum) in addition to PFO has been associated with higher risk of recurrent stroke in several studies. Evidence is also reasonable for shunt size as a predictor; however, while bubble studies are commonly performed to detect an intracardiac shunt, the number of bubbles that cross to the left atrium varies with technical factors and pulmonary pressure, and is not closely related to the anatomical size of the PFO. In some cases injection of saline contrast into the femoral vein may detect an interatrial shunt that is occult with brachial injection - inferior vena caval flow is preferentially towards the interatrial septum and foramen ovale. Not all shunts detected with agitated saline are intracardiac - intrapulmonary shunts (eg pulmonary AVMs in hereditary haemorrhagic telangiectasia) can also occur and may be a cause of paradoxical embolism.

## Key Info

**Benefits and harms** — Substantial net benefits of the recommended alternative

The individual trials included carefully selected patients aged <60 (mean age 45) with no other apparent cause of stroke. Rates of recurrent stroke were low in both intervention and control groups but the Gore-REDUCE, CLOSE and long-term follow-up of RESPECT showed statistically significant reductions in recurrent ischaemic stroke in the closure versus medical therapy groups. There were no differences in mortality. Serious adverse events occurred in 2.4%. Meta-analysis demonstrated a significant reduction in recurrent stroke (RR 0.36, 95%CI 0.17–0.79, P=0.01) (Turc et al 2018 *[175]*). Rates of recurrent stroke on medical therapy are low (1.3% per annum) and hence many years may be required to accumulate benefit. The estimated number needed to treat to prevent stroke is 67 at 2.5 years and 8 at 20 years, highly meaningful in a younger patient with long life expectancy. There is also evidence that some of the recurrent strokes occurred due to non-PFO related mechanisms that may have also caused the initial stroke despite the extensive investigation that the trial patients underwent to assess eligibility, emphasising the care required in selection of any patient who might be considered for this procedure. The presence of an atrial septal aneurysm (hypermobile inter-atrial septum) or large shunt probably increases the risk of recurrent stroke. There is an increase in atrial fibrillation following closure that is mostly transient and the significance is uncertain.

**Certainty of the Evidence** — High

Overall quality of evidence is high although incomplete patient follow-up of >10% occurred in 3/6 trials.

**Preference and values** — No substantial variability expected

In carefully selected patients in whom other causes of stroke have been excluded and age is <60 years no substantial variability in patient preferences is anticipated. Patients value avoiding stroke over possible complications or adverse events due to PFO closure. The increased risk of atrial fibrillation with PFO closure is noted which may be associated with a risk of stroke. However, the trials demonstrated an overall net reduction in risk of recurrent stroke with PFO closure.

**Resources and other considerations** — No important issues with the recommended alternative

<u>Resource considerations</u>
Using a decision analytic modelling, it was found that PFO closure became cost-effective (cost an additional $50,000 per QALY gained) at 2.6 years after the procedure compared to other medical therapy (Pickett et al 2014 *[?]*). Cost reference year, setting and perspective of the analysis in this study were not reported. Subsequent modelling (for UK and USA health systems) confirms PFO closure is cost-effective over medical therapy alone (Hildick-Smith et al 2019 *[182]*, Tirschwell et al 2018 *[183]*, Leppert et al 2018 *[184]*, Volpi et al 2019 *[185]*).

## Rationale

Endovascular closure of PFO has been a controversial field. With the publication of the GORE-REDUCE(*[180]*), CLOSE(*[178]*) and DEFENSE-PFO (*[181]*) trials, and long term follow-up of the RESPECT(*[179]*) trial, updated meta-analysis of randomised trials found a significant reduction in recurrent stroke with closure. Patients enrolled in the trials were generally aged < 60 (median ~45) with non-lacunar stroke, no significant atherosclerosis and at least a Holter monitor to search for atrial fibrillation *[172]*. When considering closure in an individual patient, the key factors to assess are whether a sufficiently intensive search for alternative

causes of stroke (including occult paroxysmal atrial fibrillation) has been undertaken and whether the patient's expected lifespan is likely to lead to a substantial long-term risk of recurrent PFO-related stroke. Patients should be involved in a thorough discussion of the state of evidence and those with traditional vascular risk factors should have these intensively managed.

## Clinical Question/ PICO

**Population:** Stroke patients with PFO
**Intervention:** Closure
**Comparator:** Medical therapy


### Summary

Endovascular closure of PFO has been a controversial field. With the publication of the GORE-REDUCE(*[180]*), CLOSE(*[178]*) and DEFENSE-PFO (*[181]*) trials, and long term follow-up of the RESPECT(*[179]*) trial, updated meta-analysis of randomised trials found a significant reduction in recurrent stroke with closure of approximately 1% per annum. Patients enrolled in the trials were generally aged < 60 (median ~45) with non-lacunar stroke and exclusion of atrial fibrillation or significant atherosclerosis *[172]*. Procedural complications were reported in 2.4%, mostly without long-term sequelae. Atrial fibrillation was slightly increased with PFO closure vs controls.


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Medical therapy | Closure | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Recurrent ischaemic stroke** End of follow-up 9 Critical | Relative risk 0.36 (CI 95% 0.17 - 0.79) Based on data from 3,560 patients in 6 studies. [1] (Randomized controlled) Follow up median 2 to 6 years of follow-up | 12.7 per 1000 | 4.57 per 1000 Difference: 8.13 fewer per 1000 ( CI 95% 10.54 fewer - 2.67 fewer ) | High [2] | Closure decreases recurrent ischaemic stroke in carefully selected patients |
| **Recurrent ischaemic stroke - double disc occluder only** End of follow-up 9 Critical | Hazard Ratio 0.2 (CI 95% 0.08 - 0.54) Based on data from 2,651 patients in 5 studies. [3] (Randomized controlled) Follow up median 2 to 6 years of follow-up | 55 per 1000 | 11 per 1000 Difference: 44 fewer per 1000 50 fewer - 25 fewer | High [4] | Closure with double disc devices decreases recurrent ischaemic stroke in carefully selected patients |
| **Atrial fibrillation** End of follow-up 8 Critical | Relative risk 4.33 (CI 95% 2.37 - 7.89) Based on data from 3,560 patients in 6 studies. [5] (Randomized controlled) Follow up median 2 to 6 years of follow-up | 10.2 per 1000 | 44 per 1000 Difference: 33.8 more per 1000 ( CI 95% 13.97 more - 70.28 more ) | High [6] | Closure slightly increases atrial fibrillation |

1. Systematic review [172] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: No serious.** loss to follow up occurred in some component studies, participants were not blinded.

**Inconsistency: No serious. Indirectness: No serious.** Differences between the population of interest and those studied: trials

included younger patients (mean age 45 years) and results may not apply to older patients with PFO. **Imprecision: No serious. Publication bias: No serious.**

3. Systematic review [172] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias: No serious.** Loss to follow-up occurred in some trials and was somewhat higher in medical therapy groups, participants were not blinded. **Inconsistency: No serious. Indirectness: No serious.** Differences between the population of interest and those studied: trials included younger patients (mean age 45 years) and results may not apply to older patients with PFO. **Imprecision: No serious. Publication bias: No serious.**
5. Systematic review [172] . **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias: No serious.** Loss to follow-up occurred and was somewhat higher in medical therapy groups. **Inconsistency: No serious. Indirectness: No serious.** Differences between the population of interest and those studied: trials included younger patients (mean age 45 years) and results may not apply to older patients with PFO. **Imprecision: No serious. Publication bias: No serious.**

## Hormone replacement therapy

Hormone replacement therapy (HRT) was previously thought to have a protective effect against CVD events but a meta-analysis found no protective effect of HRT and an overall increase in stroke risk by about 25% driven mainly by primary prevention trials (there was no increase in risk for secondary prevention trials mainly including patients with heart disease) (Boardman et al 2015 *[188]*). The effect of HRT on stroke and TIA risk is present in younger women and increases with age (Nudy et al 2019 *[191]*). HRT significantly increases the risk of VTE and PE (Boardman et al 2015 *[188]*).

Some women may still wish to continue with HRT for control of menopausal symptoms and an enhanced quality of life. In these situations, the decision whether to continue HRT should be discussed with the patient and based on an overall assessment of risk and benefit.

Practice Statement

**Consensus-based recommendation**

In patients with stroke or TIA, continuation or initiation of hormone replacement therapy is not recommended, but will depend on discussion with the patient and an individualised assessment of risk and benefit. (Boardman et al 2015 *[188]*; Yang et al 2013 *[189]*; Marjoribanks et al 2012 *[190]*; Nudy et al 2019 *[191]*)

### Practical Info

Further studies are required to determine whether risks are different if HRT is taken for shorter time periods or during the perimenopause. If there are compelling reasons to use HRT, it is suggested to use the lowest dose for shortest time.

### Key Info

**Benefits and harms** — Small net benefit, or little difference between alternatives

All-cause mortality is not increased (or decreased) with hormone replacement therapy use. In women with established cardiovascular disease (mostly cardiac disease) there is no significant increase risk of ischaemic stroke (Boardman et al 2015 *[188]*). However, systematic reviews of between 10-31 studies (mostly primary prevention) found consistent increase in stroke of approximately 25-50% (Yang et al 2013 *[189]*; Marjoribanks et al 2012 *[190]*; Nudy et al 2019*[191]*).

**Certainty of the Evidence** — High

The studies are meta-analyses of large randomised controlled trials.

**Preference and values** — Substantial variability is expected or uncertain

There is likely to be considerable variation in patient preference for hormone replacement therapy depending on symptoms of menopause.

**Resources and other considerations** — Important issues, or potential issues not investigated

No economic studies were identified. There is currently no audit data collected as part of the National Stroke Audit on HRT.

### Rationale

High-quality evidence shows inconsistent effects of hormone replacement therapy (HRT). The meta-analysis of secondary prevention trials of participants with existing cardiovascular disease did not show an increased risk for stroke (Boardman et al 2015 *[188]*). In primary prevention trials (healthy postmenopausal women), HRT appears to increase stroke risk by approximately 25% and does not appear to have any benefits of overall cardiovascular disease reduction (Yang et al 2013 *[189]*; Marjoribanks et al 2012 *[190]*). Overall, there may be potential risks with the use of HRT.

Benefit of HRT is purely symptomatic for vasomotor symptoms. If there are compelling reasons to use HRT, it is suggested to use the lowest dose for the shortest possible time.

## Clinical Question/ PICO

**Population:** Women with established cardiovascular disease
**Intervention:** Hormone therapy
**Comparator:** Placebo


### Summary

Hormone replacement therapy in post-menopausal women increases the risk of stroke overall (based on primary prevention studies) but not in the subgroup with established cardiovascular disease (mostly cardiac disease), according to a Cochrane review of 5 trials involving 5172 patients (Boardman et al 2015 *[188]*). However systematic reviews of between 10-31 studies (mostly primary prevention) found consistent increase in stroke risk of approximately 25-50% (Yang et al 2013 *[189]*; Marjoribanks et al 2012 *[190]*; Nudy et al 2019 *[191]*).


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Placebo | Hormone therapy | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Secondary stroke if pre-existing CVD**<br>8 Critical | Relative risk 1.09 (CI 95% 0.89 - 1.33)<br>Based on data from 5,172 patients in 5 studies. (Randomized controlled)<br>Follow up Varied - 2 to 4.1 years | 65 per 1000 | 71 per 1000<br>Difference: 6 more per 1000<br>( CI 95% 7 fewer - 21 more ) | **High**<br>1 | hormone therapy has little or no difference on secondary stroke |
| **All-cause death**<br>9 Critical | Relative risk 1.04 (CI 95% 0.87 - 1.24)<br>Based on data from 5,445 patients in 7 studies. (Randomized controlled)<br>Follow up Varied - 0.5 to 4.1 years | 84 per 1000 | 87 per 1000<br>Difference: 3 more per 1000<br>( CI 95% 11 fewer - 20 more ) | **High**<br>2 | hormone therapy has little or no difference on all-cause death |
| **Stroke, TIA and systemic embolism (all populations)**<br>8 Critical | Odds Ratio 1.52 (CI 95% 1.38 - 1.67)<br>Based on data from 36,844 patients in 18 studies. (Randomized controlled)<br>Follow up Average 4.13 years | 41 per 1000 | 61 per 1000<br>Difference: 20 more per 1000<br>( CI 95% 15 more - 26 more ) | **High**<br>3 | hormone therapy appears to increase risk for stroke |

1. **Inconsistency: No serious.** No significant heterogeneity between trials. **Indirectness: No serious.** A smaller subset of the systematic review was studied for secondary prevention but still included a large number of patients. **Imprecision: No serious. Publication bias: No serious.** Funnel plot was included and showed no evidence of asymmetry.
2. **Inconsistency: No serious.** No statistically significant heterogeneity between trials for this outcome. **Indirectness: No serious.** Applicable - a subgroup of secondary prevention was directly looked at in the systematic review. **Imprecision: No serious. Publication bias: No serious.**
3. **Risk of bias: No serious.** Low bias overall, with 15/126 (12%) of domains rated as problems. **Inconsistency: No serious.** Some heterogeneity between trials not being significant (p=0.08, I=34%). **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

## Oral contraception

Stroke in women of child-bearing age is uncommon, with a rate of 28 strokes per 100 000 women aged 15–44 reported in a community-based incidence study. (Thrift et al 2000 *[195]*). Several meta-analyses have reported conflicting findings depending on the oral contraceptive formulations used which included pills with high concentrations of estrogens (>50 ug), newer combination pills and progesterone-only pills (Roach et al 2015 *[192]*, Peragallo et al 2013 *[194]*). If an association between oral contraception and stroke does exist, it is likely to be small in relative and absolute terms given the small number of events in this age group, particularly in women younger than 35 years who do not smoke and are normotensive.

Weak Recommendation

For women of child-bearing age who have had a stroke, non-hormonal methods of contraception should be considered. If systemic hormonal contraception is required, a non-oestrogen containing medication is preferred. (Roach et al 2015 *[192]*; Plu-Bureau 2013 *[193]*; Peragallo et al 2013 *[194]*; Li et al 2019 *[196]*)

### Practical Info

Having a dedicated appointment with a health professional as part of the medicare rebatable rehabilitation journey, specifically outlining options for oral contraception, would be useful. All risk factors for stroke should be considered for women considering different contraceptive measures. Where possible, non-hormonal or local contraceptive measures should be discussed.

### Key Info

**Benefits and harms**

Small net benefit, or little difference between alternatives

Meta-analyses of observational studies show that oral contraception may be associated with increased risk of ischaemic stroke, especially with higher dose of oestrogen (Roach et al 2015 *[192]* ; Plu-Bureau 2013 *[193]*; Peragallo et al 2013 *[194]* Li et al 2019 *[196]*) . There is no difference between second and third generation contraceptives. No increased risk for intracerebral haemorrhage was found.

**Certainty of the Evidence**

Very Low

There is no high-level evidence, i.e. from randomised controlled trials, available, nor direct evidence on prevention of secondary stroke. Therefore, no definitive conclusion can be drawn from the current evidence.

**Preference and values**

Substantial variability is expected or uncertain

In the absence of high-quality evidence, patients' preferences are likely to vary.

**Resources and other considerations**

Important issues, or potential issues not investigated

Resources considerations

No literature to understand or describe the potential economic implications of this recommendation was identified.

### Rationale

There has been evidence from observational studies that oral contraception may be associated with increased risk of stroke for women of childbearing age. The risk appears to be even higher for high-dose combined oral contraceptives but risk should be considered in addition to usual stroke risk factors. It should also be considered that pregnancy also increases stroke risk. However, the quality of evidence is inadequate to draw a definitive conclusion. Therefore, women of child-bearing age with a history of stroke should be informed about potential risks and benefits of stroke with and without various hormonal and non-hormonal contraception alternatives.

## Clinical Question/ PICO

**Population:** All women in childbearing years
**Intervention:** Oral contraceptive use
**Comparator:** Control


### Summary

To date, there are no randomised controlled trials investigating the risk of stroke with the use of oral contraceptive. Peragallo Urrutia et al (2013) *[194]* pooled data from 50 observational studies and found twofold increased odds of ischaemic stroke but no difference in the odds of intracerebral haemorrhage.

Another systematic review Plu-Bureau et al (2013) *[193]* reported similar results. The risk of ischaemic arterial disease was found to be higher in first-generation pill users compared with second or third generation.

Roach et al (2015) *[192]* conducted a network meta-analysis and found oral contraception was not associated with higher risk of ischaemic stroke (OR: 1.0, 95%CI: 0.9 - 1.1). The risk did not vary according to the generation of progestogen or the type, however, the risk seemed to increase with higher doses of oestrogen (more than 50ug). Based on sensitivity analyses, it appears that the difference in results compared to other systematic reviews may be due to the stricter inclusion criteria used by Roach et al. Roach et al only included studies recruiting women younger than 50 years old, and excluded studies that did not report crude numbers of exposed or diseased cases and controls.

Another review by Li et al (2019) *[196]* included 6 cohort and 12 case-control studies (N=2,143,174 participants) found increased stroke risk with higher estrogen dosages (19% increase risk for each 10-µg increment in estrogen dosage) and longer duration of therapy (20% increase risk for every 5-years increment in duration of OCP use) with equivalent risk reduction 5-years post ceasing use although there was high heterogeneity. Effects were more pronounced for ischaemic stroke but evidence from prospective studies (OR 1.12; 95% CI, 1.01-1.24) was weaker than for retrospective studies (OR 1.30; 95% CI, 1.01-1.67).

Overall, the current evidence is insufficient to determine if oral contraceptive use increases the risk of subsequent stroke.


| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Control | Oral contraceptive use | **Certainty of the Evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| **Ischaemic stroke** | Odds Ratio 1.9 (CI 95% 1.24 - 2.91) Based on data from 49,804 patients in 7 studies. [1] (Observational (non-randomized)) | | | **Very Low** Due to serious indirectness, risk of bias (observational studies) and serious inconsistency [2] | We are uncertain whether oral contraceptive use increases or decreases ischaemic stroke |
| **Intracerebral haemorrhage** | Odds Ratio 1.03 (CI 95% 0.71 - 1.49) Based on data from 48,382 patients in 4 studies. (Observational (non-randomized)) | | | **Very Low** Due to serious indirectness and serious risk of bias [3] | We are uncertain whether oral contraceptive use increases or decreases haemorrhagic stroke |

1. Systematic review [194] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias: Serious.** observational studies. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high. **Indirectness: Serious.** Population didn't necessarily have previous stroke - indirect to secondary prevention. **Imprecision: No serious. Publication bias: No serious.**

3. **Risk of bias: Serious.** observational studies. **Inconsistency: No serious. Indirectness: Serious.** Population didn't necessarily have previous stroke - indirect to secondary prevention. **Imprecision: No serious. Publication bias: No serious.**

Practice Statement

**Consensus-based recommendation**
For women of child bearing age with a history of stroke or TIA, the decision to initiate or continue oral contraception should be discussed with the patient and based on an overall assessment of individual risk and benefit.

## Lifestyle modifications

Although the modification of lifestyle factors is recognised as extremely important for the management of secondary risk in stroke, the National Stroke Audit of Acute Services reported only 56% of patients with stroke received risk factor modification advice (Stroke Foundation 2015 *[197]*). Evidence for behaviour-changing strategies targeting lifestyle factors to prevent recurrence of stroke is limited and often derived from cohort studies of primary prevention. Specific guidelines focussing on each of the cardiovascular risk factors are available and these guidelines apply generically to the population including patientswith stroke. It is for this reason we have decided not to undertake a separate process to develop stroke-specific recommendations but rather refer to these overarching guidelines.

Recommendation Strength Not Set

**Practice point**
All patients with stroke or TIA (except those receiving palliative care) should be assessed and informed of their risk factors for recurrent stroke and strategies to modify identified risk factors. This should occur as soon as possible and prior to discharge from hospital.

## Smoking

Smoking is a major cause of stroke (Aldoori et al 1999 *[200]*). Fortunately, rates of daily smoking have continued to drop in Australia to 14.5% (2.6 million) of adults smoking in 2014-15, compared with 16.1% in 2011-12 and 22.4% in 2001 (ABS 2015 *[199]*). Indigenous Australians are still more than twice as likely as non-Indigenous Australians to be current daily smokers (AIHW 2011 *[201]*). Tobacco dependence is a chronic condition that typically requires repeated cessation treatment and ongoing care (RACGP 2014 *[202]*) so it is the role of every healthcare professional to support and assist people with stroke to quit. An Australian smoking cessation guideline developed by The Royal Australian College of General Practitioners recommends the 5As approach (ask, assess, advise, assist, and arrange follow-up) to enable healthcare professionals to provide the appropriate support for each smoker's level of motivation to quit (RACGP 2014 *[202]*).

Recommendation Strength Not Set

**Practice point**
Patients with stroke or TIA who smoke should be advised to stop and assisted to quit in line with existing guidelines, such as Supporting smoking cessation: a guide for health professionals. (RACGP 2014 *[202]*)

### Key Info

**Resources and other considerations**

Implementation considerations
There is a clinical indicator collected on provision of education regarding risk factor modification in the National Stroke Audit. Risk factors modification is also included in the Acute Stroke Clinical Care Standard.

## Diet

In 2014-15, nearly one in two (49.8%) adults met the Australian Dietary Guidelines for recommended daily serves of fruit, while 7.0% met the guidelines for serves of vegetables. Only one in twenty (5.1%) adults met both guidelines (ABS 2015 *[199]*). Diet has an impact on a number of risk factors and can provide additional benefits to pharmacological interventions in people with vascular disease. Reducing sodium in people with cardiovascular disease, especially in those with high BP, modestly reduces BP and may therefore help to prevent stroke (He 2013 *[204]*). A meta-analysis of cohort studies found a diet high in fruit and vegetables (more than five servings per day) reduced the risk of stroke (He et al 2006 *[205]*; Dauchet et al 2005 *[206]*). National dietary guidelines recommend achieving and maintaining a healthy weight; enjoying a wide variety of nutritious food and limiting the intake of foods containing saturated fat, added salt, added sugar and alcohol (NHMRC 2013 *[203]*).

Recommendation Strength Not Set

**Practice point**

- Patients with stroke or TIA should be advised to manage their dietary requirements in accordance with the Australian Dietary Guidelines. (NHMRC 2013 *[203]*)
- All patients with stroke should be referred to an Accredited Practising Dietitian who can provide individualised dietary advice.

### Key Info

**Resources and other considerations**

Implementation considerations
There is a clinical indicator collected on provision of education regarding risk factor modification in the National Stroke Audit. Risk factors modification is also included in the Acute Stroke Clinical Care Standard.

## Physical activity

Physical activity is any activity that gets your body moving, makes your breathing more rapid, and your heart beat faster (Commonwealth of Australia 2014 *[207]*). Being physically active is an important factor in preventing and managing stroke and other cardiovascular diseases (Warburton et al 2006 *[209]*).

In 2014-15, only about half (56%) of 18-64 year olds participated in sufficient physical activity in the last week (more than 150 minutes of moderate physical activity or more than 75 minutes of vigorous physical activity, or an equivalent combination of both). Nearly one in three (30%) were insufficiently active (less than 150 minutes in the last week) while 15% were inactive (no exercise in the last week) (ABS 2015 *[199]*). Older adults do even less physical activity. For the same period, one in four (25%) adults aged 65 years and over did at least 30 minutes of exercise on five or more days in the last week, while almost half (45%) had no days in which they exercised for more than 30 minutes (ABS 2015 *[199]*). For adults aged 18-64 years, physical activity guidelines recommend at least 150-300 minutes of moderate intensity or 75 minutes of vigorous intensity physical activity increasing to 300 minutes of moderate intensity or 150 minutes of vigorous intensity. The guidelines also recommend that adults aged 18-64 years do muscle-strengthening activities on at least 2 days of each week (Commonwealth of Australia *[207]*). For adults aged 65 years and over, guidelines recommend at least 30 minutes of moderate-intensity physical activity on most, but preferably all, days (Brown et al 2005 *[208]*). See also Cardiorespiratory fitness section in the Rehabilitation chapter for additional stroke specific guidelines for physical activity (Billinger et al 2014 *[210]*).

Recommendation Strength Not Set

**Practice point**

Patients with stroke or TIA should be advised and supported to undertake appropriate, regular physical activity as outlined in one of the following existing guidelines:

- Australia's Physical Activity & Sedentary Behaviour Guidelines for Adults (18-64 years) (Commonwealth of Australia 2014 *[207]*) OR
- Physical Activity Recommendations for Older Australians (65 years and older) (Commonwealth of Australia 2014 *[208]*).

### Key Info

**Resources and other considerations**

Implementation considerations
There is a clinical indicator collected on provision of education regarding risk factor modification in the National Stroke Audit. Risk factors modification is also included in the Acute Stroke Clinical Care Standard.

## Obesity

The prevalence of overweight and obesity among Australians has been steadily increasing for the past 30 years. In 2014-15, 63.4% of Australians aged 18 years and over were overweight or obese more than 25% of these fell into the obese category (ABS 2015 *[199]*). Overweight and obesity are associated with progressively increasing the risk of ischaemic stroke, at least in part, independently from age, lifestyle, and other cardiovascular risk factors (Strazzullo et al 2010 *[212]*). National guidelines recommend a three-pronged approach to weight managment - assessment, advice abut the health benefits of lifestyle change and weight loss and assistance to help adults lose weight through lifestyle interventions (NHMRC 2013 *[211]*).

Recommendation Strength Not Set

**Practice point**
Patients with stroke or TIA who are overweight or obese should be offered advice and support to aid weight loss as outlined in the Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults, Adolescents and Children in Australia (NHMRC 2013 *[211]*).

## Alcohol

In 2014-15, 17.4% of adults consumed more than the recommended two standard drinks per day on average (exceeding the National Health and Medical Research Council lifetime risk guidelines) (ABS 2015 *[199]*). Excessive alcohol consumption increases the risk of stroke (Ronskley et al 2011 *[213]*; Reynolds et al 2003 *[214]*), so reducing alcohol levels could be expected to modify the risk of further strokes although no studies specific to secondary stroke prevention have been found. Light intake of alcohol (1–2 standard drinks) may be protective against stroke events (Reynolds et al 2003 *[214]*). National guidelines recommend limiting alcohol consumption to two standard drinks per day to reduce the lifetime risk of harm (NHMRC 2009 *[215]*).

Recommendation Strength Not Set

**Practice point**
People with stroke or TIA should be advised to avoid excessive alcohol consumption (>2 standard drinks per day) in line with the Australian Guidelines to Reduce Health Risks from Drinking Alcohol. (NHMRC 2009 *[215]*)

### Key Info

**Resources and other considerations**

Implementation considerations
There is a clinical indicator collected on provision of education regarding risk factor modification in the National Stroke Audit. Risk factors modification is also included in the Acute Stroke Clinical Care Standard.

## Glossary and abbreviations

# Glossary

**Activities of daily living:** The basic elements of personal care such as eating, washing and showering, grooming, walking, standing up from a chair and using the toilet.
**Activity:** The execution of a task or action by an individual. Activity limitations are difficulties an individual may have in executing activities.
**Agnosia:** The inability to recognise sounds, smells, objects or body parts (other people's or one's own) despite having no primary sensory deficits.
**Aphasia:** Impairment of language, affecting the production or comprehension of speech and the ability to read and write.
**Apraxia:** Impaired planning and sequencing of movement that is not due to weakness, incoordination or sensory loss.
**Apraxia of speech:** Inability to produce clear speech due to impaired planning and sequencing of movement in the muscles used for speech.
**Atrial fibrillation:** Rapid, irregular beating of the heart.
**Augmentative and alternative communication:** Non-verbal communication, e.g. through gestures or by using computerised devices.
**Central register**: collection of large dataset related to patients' diagnoses, treatments and outcomes
**Cochrane review:** a comprehensive systematic review and meta-analysis published online in Cochrane library, internationally recognized as the highest standard in evidence-based health care resources
**Deep vein thrombosis:** Thrombosis (a clot of blood) in the deep veins of the leg, arm, or abdomen.
**Disability:** A defect in performing a normal activity or action (e.g. inability to dress or walk).
**Drip and ship:** A model of thrombolysis service provision that involves assessment of patients at a non-specialist centres with telemedicine support by stroke specialists, commencing thrombolysis (if deemed appropriate) and subsequent transfer to the stroke specialist centre.
**Dyad:** involvement of both patients and their caregivers
**Dysarthria:** Impaired ability to produce clear speech due to the impaired function of the speech muscles.
**Dysphagia:** Difficulty swallowing.
**Dysphasia:** Reduced ability to communicate using language (spoken, written or gesture).
**Emotionalism:** An increase in emotional behaviour—usually crying, but sometimes laughing that is outside normal control and may be unpredictable as a result of the stroke.
**Endovascular thrombectomy** (also called mechanical thrombectomy or endovascular clot retrieval): a minimally invasive procedure performed via angiogram, in which a catheter passes up into the brain to remove the clot in the blocked blood vessel.
**Enteral tube feeding:** Delivery of nutrients directly into the intestine via a tube.
**Executive function:** Cognitive functions usually associated with the frontal lobes including planning, reasoning, time perception, complex goal-directed behaviour, decision making and working memory.
**Family support / liaison worker:** A person who assists stroke survivors and their families to achieve improved quality of life by providing psychosocial support, information and referrals to other stroke service providers.
**Impairment:** A problem in the structure of the body (e.g. loss of a limb) or the way the body or a body part functions (e.g. hemiplegia).
**Infarction:** Death of cells in an organ (e.g. the brain or heart) due to lack of blood supply.
**Inpatient stroke care coordinator:** A person who works with people with stroke and with their carers to construct care plans and discharge plans and to help coordinate the use of healthcare services during recovery in hospital.
**Interdisciplinary team:** group of health care professionals (including doctors, nurses, therapists, social workers, psychologists and other health personnel) working collaboratively for the common good of the patient.
**Ischaemia:** An inadequate flow of blood to part of the body due to blockage or constriction of the arteries that supply it.
**Neglect:** The failure to attend or respond to or make movements towards one side of the environment.
**Participation:** Involvement in a life situation.
**Participation restrictions**: Problems an individual may experience in involvement in life situations.
**Penumbral-based imaging**: brain imaging that uses advanced MRI or CT angiography imaging to detect parts of the brain where the blood supply has been compromised but the tissue is still viable.
**Percutaneous endoscopic gastrostomy (PEG):** A form of enteral feeding in which nutrition is delivered via a tube that is surgically inserted into the stomach through the skin.
**Pharmaceutical Benefits Scheme (PBS):** A scheme whereby the costs of prescription medicine are subsidised by the Australian Government to make them more affordable.
**Phonological deficits:** Language deficits characterised by impaired recognition and/or selection of speech sounds.
**Pulmonary embolism:** Blockage of the pulmonary artery (which carries blood from the heart to the lungs) with a solid material, usually a blood clot or fat, that has travelled there via the circulatory system.
**Rehabilitation:** Restoration of the disabled person to optimal physical and psychological functional independence.
**Risk factor:** A characteristic of a person (or people) that is positively associated with a particular disease or condition.
**Stroke unit:** A section of a hospital dedicated to comprehensive acute and/or rehabilitation programs for people with a stroke.
**Stroke:** Sudden and unexpected damage to brain cells that causes symptoms that last for more than 24 hours in the parts of the body controlled by those cells. Stroke happens when the blood supply to part of the brain is suddenly disrupted, either by blockage of an artery or by bleeding within the brain.
**Task-specific training:** Training that involves repetition of a functional task or part of the task.
**Transient ischaemic attack:** Stroke-like symptoms that last less than 24 hours. While TIA is not actually a stroke, it has the same cause. A TIA may be the precursor to a stroke, and people who have had a TIA require urgent assessment and intervention to prevent stroke.

# Abbreviations

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| ADL | Activities of daily living |
| AF | Atrial fibrillation |
| AFO | Ankle foot orthosis |
| BAO | Basilar artery occlusion |
| BI | Barthel Index |
| BMI | Body mass index |
| BP | Blood pressure |
| CEA | Carotid endarterectomy |
| CEMRA | Contrast-enhanced magnetic resonance angiography |
| CI | Confidence interval |
| CIMT | Constraint induced movement therapy |
| CT | Computed tomography |
| CTA | Computed tomography angiography |
| CVD | Cardiovascular disease |
| DALY | Disability-adjusted life years |
| DBP | Diastolic blood pressure |
| DOAC | Direct oral anticoagulant |

| | |
|---|---|
| DSA | Digital subtraction angiography |
| DUS | Doppler ultrasonography |
| DVT | Deep vein thrombosis |
| DWI | Diffusion-weighted imaging |
| ECG | Electrocardiography |
| ECST | European Carotid Surgery Trial |
| ED | Emergency department |
| EMG | Electromyographic feedback |
| EMS | Emergency medical services |
| ESD | Early supported discharge |
| ESS | European Stroke Scale |
| FAST | Face, Arm, Speech, Time |
| FEES | Fibre-optic endoscopic examination of swallowing |
| FeSS | Fever, Sugar, Swallowing |
| FFP | Fresh frozen plasma |
| FIM | Functional independence measure |
| GP | General practitioner |
| HDL | High-density lipoprotein |
| HR | Hazard ratio |

| | |
|---|---|
| HRQOL | Health related quality of life |
| HRT | Hormone replacement therapy |
| IA | Intra-arterial |
| ICH | Intracerebral haemorrhage |
| ICU | Intensive care unit |
| INR | International normalised ratio |
| IPC | Intermittent pneumatic compression |
| IV | Intravenous |
| LDL | Low-density lipoprotein |
| LMWH | Low molecular weight heparin |
| LOS | Length of stay |
| MCA | Middle cerebral artery |
| MD | Mean difference |
| MI | Myocardial infarction |
| MNA | Mini Nutritional Assessment |
| MR | Magnetic resonance |
| MRA | Magnetic resonance angiography |
| MRI | Magnetic resonance imaging |
| mRS | Modified rankin scale |
| MST | Malnutrition screening tool |

| | |
|---|---|
| MUST | Malnutrition universal screening tool |
| N | Number of participants in a trial |
| NASCET | North American Symptomatic Carotid Endarterectomy Trial |
| NG | Nasogastric |
| NHMRC | National Health and Medical Research Council |
| NIHSS | National Institutes of Health Stroke Scale |
| NMES | Neuromuscular electrical stimulation |
| NNH | Numbers needed to harm |
| NNT | Numbers needed to treat |
| OR | Odds ratio |
| OT | Occupational therapist |
| PBS | Pharmaceutical Benefits Scheme |
| PE | Pulmonary embolism |
| PEG | Percutaneous endoscopic gastrostomy |
| PFO | Patent foramen ovale |
| PPV | Positive predictive value |
| QALYs | Quality-adjusted life years |
| QOL | Quality of life |
| RCT | Randomised controlled trial |

| | |
|---|---|
| rFVIIa | recombinant activated factor VII |
| RHS | Right hemisphere syndrome |
| ROC | Receiver operator curve |
| ROM | Range of motion |
| ROSIER | Recognition of stroke in the emergency room |
| RR | Relative risk |
| RRR | Relative risk reduction |
| rTMS | repetitive transcranial magnetic stimulation |
| rt-PA | Recombinant tissue plasminogen activator |
| SBP | Systolic blood pressure |
| SC | Subcutaneous |
| SD | Standard deviation |
| SE | Standard error |
| SES | Standardised effect size |
| SGA | Subjective global assessment |
| sICH | symptomatic intracerebral haemorrhage |
| SMD | Standardised mean difference |
| SSS | Scandinavian stroke scale |
| TEE | Transoesophageal echocardiography |
| TIA | Transient ischaemic attack |

| | |
|---|---|
| TOE | Transoesophageal echocardiography |
| TOR-BSST | Toronto Bedside Swallowing Screening test |
| tPA | Tissue plasmogen activator |
| TTE | Transthoracic echocardiography |
| UFH | Unfractionated heparin |
| UK | United Kingdom |
| UL | Upper limb |
| VF or VFS | Videofluoroscopy |
| VR | Virtual reality |
| VTE | Venous thromboembolism |
| WMD | Weighted mean difference |

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