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 in adults.

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Disclaimer

Sections

Summary of recommendations

Introduction

Methodology

Clinical questions

Secondary prevention - overview

Adherence to pharmacotherapy

Weak recommendation In review

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

Practice statement

Acute blood pressure management **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 *[50]*)

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*[53]*; Qureshi et al 2016*[52]*)

Weak recommendation

Pre-existing antihypertensive agents may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 *[50]*)

Strong recommendation

Long term blood pressure management

- 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. (Zonneveld et al 2018 *[55]*; Ettehad et al 2016 *[41]*)
- 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. (Zonneveld et al 2018 *[55]*; Ettehad et al 2016 *[41]*)
- 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. (Zonneveld et al 2018 *[55]*; Mukete et al 2015 *[43]*)

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 *[41]*; Kitagawa et al 2019 *[56]*; Katsanos et al 2017 *[54]*)
- 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. (Kitagawa et al 2019 *[56]*; Ettehad et al 2016 *[41]*)

Management of atrial fibrillation

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 *[72]*; Saxena 2004 *[73]*; Ruff et al 2014 *[57]*)
- 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 *[57]*)
- 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 *[86]*)

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.

Info Box

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.

Remark:
Third practice point has become a draft weak evidence -based recommendation as below. The wording has not changed.

Weak recommendation New

DRAFT RECOMMENDATION AUGUST 2020

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. (Osmancik et al 2020 *[90]*)

Remark:
Previously this was a practice point but is a draft evidence-based recommendation. The actual wording of recommendation has not changed. This draft has been submitted to the NHMRC for consideration of approval.

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 *[91]*; Niu et al 2016 *[92]*; Greving et al 2019 *[122]*)

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]*) (see Antithrombotic therapy in Acute medical and surgical management)

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 *[98]*; Greving et al 2019 *[122]*)

Strong recommendation against

Antiplatelet agents should not be used for stroke prevention in patients with atrial fibrillation. (Connolly et al 2011 *[101]*)

Weak recommendation New

In patients with spontaneous (or primary) intracerebral haemorrhage who were previously prescribed antithrombotic therapy for secondary prevention of cardiovascular and/or cerebrovascular disease, restarting antiplatelet therapy after the acute phase may be considered, although the optimal timing is undertermined (see practical information). (RESTART Collaboration 2019 *[121]*)

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 *[128]*; Tramacer et al 2019 *[139]*)

Strong recommendation New

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 *[133]*)

Weak recommendation against

Statins should not be used routinely for intracerebral haemorrhage. (Manktelow et al 2009 *[128]*; Amarenco et al 2006 *[129]*)

Weak recommendation against

Fibrates should not be used routinely for the secondary prevention of stroke. (Zhou et al 2013 *[125]*; Wang et al 2015 *[124]*)

Carotid surgery

Strong recommendation Updated evidence, no change in 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 *[152]*, Rerkasem et al 2020 *[166]*)

Weak recommendation Updated evidence, no change in 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.

(Muller et al. 2020 *[151]*)

Weak recommendation against Updated evidence, no change in recommendation

In patients with asymptomatic carotid stenosis, carotid endarterectomy or stenting should not be performed. (Galyfos et al 2019 *[173]*; Raman et al 2013 *[149]*; Muller et al 2020 *[151]*)

Strong recommendation against

In patients with symptomatic carotid occlusion, extracranial/ intracranial bypass is not recommended. (Powers et al 2011 *[153]*; Fluri et al 2010 *[156]*)

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 *[176]*)

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 *[185]*; Misra et al 2012 *[186]*; Afshari et al 2015 *[187]*)

Remark: Important note May 2021: This recommendation was drafted prior to the COVID-19 pandemic and vaccine related complications. Please refer to the practical information for information related to COVID-19 vaccines.

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

Info Box

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 *[210]*; Sagris et al 2019 *[209]*)

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 *[198]*, Saver et al 2018 *[200]*).

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 *[213]*; Yang et al 2013 *[214]*; Marjoribanks et al 2012 *[215]*; Nudy et al 2019 *[216]*)

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 *[217]*; Plu-Bureau 2013 *[218]*; Peragallo et al 2013 *[219]*; Li et al 2019 *[221]*)

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

Info Box

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.

Weak recommendation New

DRAFT RECOMMENDATION AUGUST 2021
Interventions addressing secondary stroke risk factors may be used for all people with stroke and TIA. Such interventions should include multiple components including individual (support and counselling) and organisational approaches (regular reviews by relevant health care professionals) and include exercise training as a component. (Bridgwood et al 2020 *[225]*; Liljehult et al 2020 *[227]*; Wang et al 2019 *[233]*; Deijle et al 2017*[231]*).

Remark:
Draft recommendation submitted to the NHMRC for consideration of approval.

Diet

Consensus recommendation New

DRAFT AUGUST 2021
All patients with stroke or TIA should be supported to follow a Mediterranean or similar style diet (high intake of plant-based foods such as fruit, vegetables, whole grain cereals, legumes and nuts, moderate intake of low fat dairy products, and low intake of processed and red meat and sugary foods, as well as olive oil as the main added dietary fat) to reduce the risk of recurrent stroke. (English et al 2021) *[235]*

Remark:
Current recommendation has completed public consultation and has been submitted to NHMRC for consideration of approval.

Info Box

Practice point

- **(To be deleted -see remarks below)** Patients with stroke or TIA should be advised to manage their dietary requirements in accordance with the Australian Dietary Guidelines. (NHMRC 2013 *[236]*)
- All patients with stroke should be referred to an Accredited Practising Dietitian who can provide individualised dietary advice.

Remark:
Suggested change to incorporate first practice point into background text of new draft recommendation on diet.

Physical activity

Info Box

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 *[245]*) OR
- Physical Activity Recommendations for Older Australians (65 years and older) (Commonwealth of Australia 2005 *[246]*).

Obesity

Info Box

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 *[249]*).

Smoking

Info Box

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 2019 *[253]*)

Alcohol

Info Box

Practice point
People with stroke or TIA should be advised to avoid excessive alcohol consumption (no more than 10 standard drinks per week and no more than 4 standard drinks on any one day) in line with the Australian Guidelines to Reduce Health Risks from Drinking Alcohol. (NHMRC 2020 *[255]*)

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.

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.

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 further 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

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), 7 November 2019 (updated recommendations for Thrombolysis, Acute antiplatelet therapy, and Patent foramen ovale management), and 11 February 2021 (updated recommendations for oxygen therapy, cholesterol lowering targets, new acute antiplatelet agent, shoulder pain and weakness) 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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The Stroke Foundation gratefully acknowledges the financial assistance provided by the Australian Government, Medical Research Future Fund. The development of the final recommendations has not been influenced by the views or interests of the funding body.

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Methodology

Development of questions

Questions have been extensively developed and reviewed over the four iterations of the guidelines. In this 'living' phase the Content Steering Group reviews the PICO questions on an annual basis. The clinical questions are listed at the start of each chapter. Individual PICOs (population, intervention/s, comparator, outcomes) are listed in the research evidence section as related to each topic or recommendation.

Literature identification

On a monthly basis, we monitor the literature for relevant, new evidence by screening all randomised controlled trials or systematic reviews related to stroke published in the Pubmed database. One member of the project team initially screens all abstracts and excludes clearly irrelevant studies. Potentially included studies are allocated to relevant topics covered by the guidelines and a second member of the project team reviews and confirms included studies prior to sending to the relevant working group members. In addition, each month new economic studies and studies related to patient values and preferences are also captured.

Clinical expert review

Where new evidence has been identified by the project team a summary is sent to content experts who review and make a final decision to include or exclude the study and also to assess the potential impact of the new evidence on current recommendations. As a result of this assessment one of two options will be communicated for each topic:

a. New evidence is unlikely to change current recommendations: review and potentially integrate information in the next review cycle; or
b. New relevant evidence may change current recommendations: rapidly review.

Data extraction, updating evidence summary and GRADE profile

For rapid updates, the project team incorporates the new evidence into the existing body of evidence by:

- Updating the Summary of Findings table including the risk of bias assessment
- Review any additional studies related to Preferences and values of patients on the topic

Concurrently members of the economic working group review newly published economic studies.

The project team then drafts changes to the overall summary (GRADE profile). This profile is then reviewed and modified by clinical content experts and people with relevant lived experience (consumers). Finally changes to the changes to the recommendation, rationale and practical considerations are considered, discussed and agreed.

Draft changes are then circulated to the wider expert working groups (including consumer panel) for internal review. Once signed off by the Steering Group a period of public consultation is undertaken. Feedback is then reviewed and any changes made in response to feedback before finally submitting to the National Health and Medical Research Council (NHMRC) for approval.

Brief summary of GRADE

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

GRADE 'evidence to decision' framework includes a minimum of 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 situation would want the suggested course of action, but many would not.
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 appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working 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 debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options 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?

4.12 What non-pharmacological interventions reduce risk factors for recurrent stroke?

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

In review

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]*).

Evidence To Decision

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

Resources considerations

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 or educational interventions designed to improve medication adherence/concordance
Comparator: Usual care or modified usual care

Summary

A Cochrane review by Bridgwood et al (2018)*[225]* included 42 randomised trials (n=33,840) and assessed education/ behavioural interventions or organisational interventions addressing secondary prevention with the aim to improve patient adherence with medication regimens and lifestyle advice. Out of the sixteen studies that used education or behavioural interventions, thirteen studies (n= 33,762) included outcomes related to medication adherence. Due to the heterogeneity in patient populations, interventions and outcome measures in studies, the review authors carried out a qualitative analysis. Most studies (n=10) found no significant differences between the intervention and control groups on any indicator of adherence (low quality of evidence).

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; 2 studies, n= 2756), as did statins (OR 2.53, 95% CI 2.15 to 2.97; 3 studies, n= 2636). There was no significant difference in antihypertensive adherence, (OR 0.93, 95% CI 0.76 to 1.13; 3 studies, n= 2028). 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.

Al AlShaikh et al. (2016)*[25]* assessed multimodal interventions to increase adherence to medication after stroke. The review identified 17 mixed method studies (7 RCT, 2 CCT, 8 pre-post studies) that included 3942 participants (2090 intervention in intervention arms and 824 in control arms). Included studies used a range of interventions including motivational interventions, pre-discharge education, simplication of drug regimen including use of dosettes, environmental cues and/or reminders or a combination. The effect on medication adherence overall was non-significantly higher(OR 1.96; 95% CI 0.50-7.67; 4 studies, n= 534; moderate heterogeneity I^2= 70%)). However, there was a significant adherence to blood pressure-lowering drugs (OR 2.21; 95% CI 1.63-2.98, p < 0.001; 6 studies, n= 1038; 3 matched studies), lipid-lowering drugs (OR 2.11; 95% CI 1.00-4.46; 3 studies, n= 477) and antithrombotic drugs (OR 2.32; 95% CI 1.18-4.56; 2 studies, n= 412) when considered separately.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care or modified usual care	**Intervention** Behavioural/ educational interventions	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Medication adherence 7 Critical	Based on data from: 33,762 patients in 13 studies. [1] (Randomized controlled)	Thirteen studies (n= 33,762) were identified to use education or behavioural interventions. Due to the heterogeneity in patient populations, interventions and outcome measures in studies, the review authors carried out a qualitative analysis. Most studies (n=10) measuring medication adherence outcomes found no significant differences between the intervention and control groups on any indicator of adherence (low quality of evidence).		**Low** Due to serious inconsistency, Due to serious indirectness [2]	Behavioural or educational interventions may have little or no difference on medication adherence

1. Systematic review [225].
2. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important). **Imprecision: No serious. Publication bias: No serious.**

Clinical Question/ PICO

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

Summary

A updated Cochrane review by Bridgwood et al (2018)*[225]* included twenty-six studies with organisational interventions addressing the secondary prevention aim to improve patient adherence with medication regimens and lifestyle advice. Data was not pulled for the 8 studies (5,384 participants) with medication adherence due to heterogeneity in the methods used to obtain outcome data. Most studies (4/6) measuring medication adherence outcomes found no significant differences between the intervention and control groups on any indicator of adherence (low quality evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Organisational interventions	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Medication adherence 7 Critical	Based on data from: 5,384 patients in 8 studies. [1] (Randomized controlled)	Most studies (4/6) measuring medication adherence outcomes found no significant differences between the intervention and control groups on any indicator of adherence.		**Low** Due to serious risk of bias, Due to serious indirectness [2]	Organisational interventions may have little or no difference on medication adherence

1. Systematic review [225].
2. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: No serious.** **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important).

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 *[45]*). Yet only 77% of eligible patients discharged from acute services, and 79% from in-patient rehabilitation services are prescribed with BP lowering therapy (Stroke Foundation 2019 *[222]* 2020 *[223]*). 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 *[50]*)

Evidence To Decision

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 *[50]*).

Certainty of the Evidence — High

The evidence has multiple high quality randomised controlled trials (Bath and Krishnan 2014 *[50]*).

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.

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*[53]*; Qureshi et al 2016*[52]*)

Evidence To Decision

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 acute ICH
Intervention: Blood pressure lowering
Comparator: Control

Summary

Systematic review by Bath et al (2014 *[50]*) , 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 *[52]*).

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention 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

Weak recommendation

Pre-existing antihypertensive agents may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 *[50]*)

Evidence To Decision

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 *[50]*). 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) *[50]* 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 Timeframe	**Study results and measurements**	**Comparator** Stop pre-stroke antihypertensives	**Intervention** Continue pre-stroke antihypertensives	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death or dependency [1] 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 per 1000	581 per 1000 Difference: **14 more** per 1000 (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. (Zonneveld et al 2018 *[55]*; Ettehad et al 2016 *[41]*)
- 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. (Zonneveld et al 2018 *[55]*; Ettehad et al 2016 *[41]*)
- 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. (Zonneveld et al 2018 *[55]*; Mukete et al 2015 *[43]*)

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 *[39]*). 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 *[35]*). 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 *[40]*, Ettehad 2016 *[41]*). 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**.

Evidence To Decision

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 *[35]*; Thomopoulos et al 2016 *[40]*; Ettehad et al 2016 *[41]*; Zonneveld et al 2018 *[55]*).

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 *[46]*). 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 *[47]*; PROGRESS Collaborative Group 2001 *[48]*). 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 *[37]*).

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 *[35]*). 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 *[39]*).

A meta-analysis reported better outcomes for patients with more intense BP lowering irrespective of baseline

levels (Thomopoulos et al 2016 *[40]*). Another 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 *[41]*).

A systematic review of 14 studies (n=42736) by Katsanos et al. (2017) *[54]* assessed the effect on blood pressure reduction in people with previous ischaemic stroke or TIA. A subgroup analysis found that in patients with stroke, achieving a SBP <130mmHg is associated with a lower prevalence of recurrent stroke (8.3%; 95% CI 7.0–9.8%, p=0.048) than achieving SBP 130-140 (9.2%; 95% CI 6.9–12.1%) or SBP >140 mmHg (11.7%; 95% CI 9.4–14.3%).

Kitagawa et al. (2019) *[56]* conducted a RCT in Japan to determine the optimum blood pressure (BP) target in secondary stroke prevention. Patients with prior history of stroke (n=1263; 1074 ischaemic stroke and 189 haemorrhagic stroke) were randomised to two groups; BP control <140/90mmHg (standard treatment) or to <120/80mmHg (intensive treatment). Patients received stepwise treatments orally every 4 weeks for 24 weeks until the BP target of the allocated group was achieved. After a mean follow up of 3.9 years (range, 0-5.5 years) the annualized rate of recurrent stroke in the standard treatment group was 2.26% versus 1.65% in the intensive treatment group (HR 0.73; 95% CI 0.49-1.11, p = 0.15). All cause death was also not significant (HR 0.80; 95% CI 0.49-1.29, p=0.36) but ICH was lower but actual numbers were low (11 v 1; HR 0.09 95%CI 0.01 to 0.70). The trial was stopped early due to funding and slow recruitment (planned for 2000 participants). Further, the authors combined these data with the outcome data of three previous RCTs (the SPS3 trial, the Prevention After Stroke–Blood Pressure [PAST-BP] trial, and the Prevention of Decline in Cognition After Stroke Trial [PODCAST]) to conduct a meta-analysis which favoured intensive BP control (RR 0.78; 95% CI 0.64-0.96, p=0.02) over the control group, with no evidence of heterogeneity. Number needed to treat to avoid one recurrent stroke was 67 (95%CI 39-250) with the benefit driven by reduction in ICH (RR 0.25, 95%CI 0.07 to 0.90) rather than ischemic stroke (RR 0.88, 95%CI 0.71 to 1.08).

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Higher target of blood pressure (130-149 mm Hg)	**Intervention** 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 effect 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			**Low** Due to serious imprecision, Due	Blood pressure target of less than 130 mm hg may decrease recurrent

Outcome Timeframe	**Study results and measurements**	**Comparator** Higher target of blood pressure (130-149 mm Hg)	**Intervention** Lower target of blood pressure (less than 130 mmHg)	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
8 Critical	patients in 1 studies. (Randomized controlled) Follow up: Mean follow-up of 3.7 years.			to serious risk of bias [4]	haemorrhagic stroke in patients with recent lacunar stroke
Adverse events [5] 7 Critical	Hazard Ratio 1.53 (CI 95% 0.8 — 2.93) Based on data from 3,020 patients in 1 studies. (Randomized controlled) Follow up: Mean follow-up of 3.7 years.			**Moderate** Due to serious imprecision [6]	Blood pressure target of less than 130 mm hg may have little or no effect 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 the most recent Cochrane review (11 RCTs, n=38,742) found that therapy to lower BPreduced recurrent stroke (pooled RR 0.81, 95% CI 0.70–0.93; 8 studies, n=35,110; moderate quality) and major vascular events (RR 0.90, 95% CI 0.78 to 1.06; 4 studies, n=28,630; high quality). (Zonneveld et al. 2018 *[55]*). Sensitivity analysis including trials of low risk of bias (five studies, n=29,082) had similar results for recurrent stroke (RR 0.86, 95%CI 0.75-1.00). Results were most favourable for ACE inhibitor or diuretics although significant heterogeneity was noted (I^2=72%). Intensive BP lowering (<130/85 mmHg vs <140-160/90-100 mmHg) appears to reduce recurrent stroke (RR 0.80, 95%CI 0.63 to 1.00; 3 studies, n=3632) although this just failed to reach statistical significance. Subgroup analysis (from 3 studies, n=6656) found reduce in recurrent strokes occurred only when mean baseline SBP was >140 mmHg (RR 0.65, 95%CI 0.51 to 0.83 for >160 mmHg; RR 0.71, 95%CI 0.57 to 0.89 for 140-160 mmHg; RR 0.86, 95%CI 0.67 to 1.12 for 120-140 mmHg; and RR 1.01, 95%CI 0.47 to 2.19 for <120 mmHg).

As noted by the Cochrane review 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 *[38]*). A 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 *[42]*). 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 *[43]*).

A systematic review of 14 studies (n=42,736) by Katsanos et al. (2017) *[54]* in people with previous ischaemic stroke or TIA found antihypertensive treatment was associated with a lower risk for recurrent stroke (RR 0.73; 95% CI 0.62-0.87) and death from a cardiovascular cause (RR 0.85; 95% CI 0.75–0.96). Overall, in metaregression analysis the reduction of SBP is linearly associated with the reduction of recurrent stroke (P=0.049), myocardial infarction (P=0.024), and cardiovascular death (P<0.001), and death from any cause (P=0.001). Similarly, reduction in DBP was linearly associated with recurrent stroke (P=0.026) and death from any cause (P=0.009). SBP was not found to relate to degree of SBP reduction and risk of disabling or fatal stroke (p=0.94). In sensitivity analysis while the use of thiazide diuretics in monotherapy or in combination therapy appeared to have a lower risk of recurrent stroke compared with other antihypertensive regimens the difference was not significant.

The large meta-analysis by Ettehad et al 2016 *[41]* synthesised results from 123 studies (primary and secondary stroke prevention) involving 613,815 participants in which BP lowering therapy was compared to placebo or other BP lowering therapy. 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.

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

1. Systematic review [36] . **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 [36] . **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).

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 *[41]*; Kitagawa et al 2019 *[56]*; Katsanos et al 2017 *[54]*)
- 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. (Kitagawa et al 2019 *[56]*; Ettehad et al 2016 *[41]*)

Evidence To Decision

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 *[35]*; Lakhan and Sapko 2009 *[36]*; Arima et al 2006 *[39]*; Thomopoulos et al 2016 *[40]*; Ettehad et al 2016 *[41]*).

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 *[46]*). 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 *[47]*; PROGRESS Collaborative Group 2001 *[48]*). 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 *[37]*).

<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 *[39]*). 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 *[35]*). 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 *[40]*, Ettehad 2016 *[41]*). 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 *[35]*). 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 *[39]*).

A meta-analysis reported better outcomes for patients with more intense BP lowering irrespective of baseline levels (Thomopoulos et al 2016 *[40]*). Another 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 *[41]*).

A systematic review of 14 studies (n=42736) by Katsanos et al. (2017) *[54]* assessed the effect on blood pressure reduction in people with previous ischaemic stroke or TIA. A subgroup analysis found that in patients with stroke, achieving a SBP <130mmHg is associated with a lower prevalence of recurrent stroke (8.3%; 95% CI 7.0–9.8%, p=0.048) than achieving SBP 130-140 (9.2%; 95% CI 6.9–12.1%) or SBP >140 mmHg (11.7%; 95% CI 9.4–14.3%).

Kitagawa et al. (2019) *[56]* conducted a RCT in Japan to determine the optimum blood pressure (BP) target in secondary stroke prevention. Patients with prior history of stroke (n=1263; 1074 ischaemic stroke and 189 haemorrhagic stroke) were randomised to two groups; BP control <140/90mmHg (standard treatment) or to <120/80mmHg (intensive treatment). Patients received stepwise treatments orally every 4 weeks for 24 weeks until the BP target of the allocated group was achieved. After a mean follow up of 3.9 years (range, 0-5.5 years) the annualized rate of recurrent stroke in the standard treatment group was 2.26% versus 1.65% in the intensive treatment group (HR 0.73; 95% CI 0.49-1.11, p = 0.15). All cause death was also not significant (HR 0.80; 95% CI 0.49-1.29, p=0.36) but ICH was lower but actual numbers were low (11 v 1; HR 0.09 95%CI 0.01 to 0.70). The trial was stopped early due to funding and slow recruitment (planned for 2000 participants). Further, the authors combined these data with the outcome data of three previous RCTs (the SPS3 trial, the Prevention After Stroke–Blood Pressure [PAST-BP] trial, and the Prevention of Decline in Cognition After Stroke Trial [PODCAST]) to conduct a meta-analysis which favoured intensive BP control (RR 0.78; 95% CI 0.64-0.96, p=0.02) over the control group, with no evidence of heterogeneity. Number needed to treat to avoid one recurrent stroke was 67 (95%CI 39-250) with the benefit driven by reduction in ICH (RR 0.25, 95%CI 0.07 to 0.90) rather than ischemic stroke (RR 0.88, 95%CI 0.71 to 1.08).

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Higher target of blood pressure (130-149 mm Hg)	**Intervention** 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 effect on death in patients with recent lacunar stroke

Outcome Timeframe	**Study results and measurements**	**Comparator** Higher target of blood pressure (130-149 mm Hg)	**Intervention** Lower target of blood pressure (less than 130 mmHg)	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 8 Critical	Hazard Ratio 0.61 (CI 95% 0.31 — 1.22) 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 [4]	Blood pressure target of less than 130 mm hg may decrease recurrent haemorrhagic stroke in patients with recent lacunar stroke
Adverse events [5] 7 Critical	Hazard Ratio 1.53 (CI 95% 0.8 — 2.93) Based on data from 3,020 patients in 1 studies. (Randomized controlled) Follow up: Mean follow-up of 3.7 years.			**Moderate** Due to serious imprecision [6]	Blood pressure target of less than 130 mm hg may have little or no effect 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.**
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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 the most recent Cochrane review (11 RCTs, n=38,742) found that therapy to lower BPreduced recurrent stroke (pooled RR 0.81, 95% CI 0.70–0.93; 8 studies, n=35,110; moderate quality) and major vascular events (RR 0.90, 95% CI 0.78 to 1.06; 4 studies, n=28,630; high quality). (Zonneveld et al. 2018 *[55]*). Sensitivity analysis including trials of low risk of bias (five studies, n=29,082) had similar results for recurrent stroke (RR 0.86, 95%CI 0.75-1.00). Results were most favourable for ACE inhibitor or diuretics although significant heterogeneity was noted (I^2=72%). Intensive BP lowering (<130/85 mmHg vs <140-160/90-100 mmHg) appears to reduce recurrent stroke (RR 0.80, 95%CI 0.63 to 1.00; 3 studies, n=3632) although this just failed to reach statistical significance. Subgroup analysis (from 3 studies, n=6656) found reduce in recurrent strokes occurred only when mean baseline SBP was >140 mmHg (RR 0.65, 95%CI 0.51 to 0.83 for >160 mmHg; RR 0.71, 95%CI 0.57 to 0.89 for 140-160 mmHg; RR 0.86, 95%CI 0.67 to 1.12 for 120-140 mmHg; and RR 1.01, 95%CI 0.47 to 2.19 for <120 mmHg).

As noted by the Cochrane review 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 *[38]*). A 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 *[42]*). 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 *[43]*).

A systematic review of 14 studies (n=42,736) by Katsanos et al. (2017) *[54]* in people with previous ischaemic stroke or TIA found antihypertensive treatment was associated with a lower risk for recurrent stroke (RR 0.73; 95% CI 0.62-0.87) and death from a cardiovascular cause (RR 0.85; 95% CI 0.75–0.96). Overall, in metaregression analysis the reduction of SBP is linearly associated with the reduction of recurrent stroke (P=0.049), myocardial infarction (P=0.024), and cardiovascular death (P<0.001), and death from any cause (P=0.001). Similarly, reduction in DBP was linearly associated with recurrent stroke (P=0.026) and death from any cause (P=0.009). SBP was not found to relate to degree of SBP reduction and risk of disabling or fatal stroke (p=0.94). In sensitivity analysis while the use of thiazide diuretics in monotherapy or in combination therapy appeared to have a lower risk of recurrent stroke compared with other antihypertensive regimens the difference was not significant.

The large meta-analysis by Ettehad et al 2016 *[41]* synthesised results from 123 studies (primary and secondary stroke prevention) involving 613,815 participants in which BP lowering therapy was compared to placebo or other BP lowering therapy. 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.

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Control/placebo	**Intervention** Blood pressure lowering	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
8 Critical	studies. [4] (Randomized controlled) Follow up: 1 to 5 years.	Difference: **28 fewer** per 1000 (CI 95% 41 fewer — 13 fewer)		and possible publication bias [5]	

1. Systematic review [36] . **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 [36] . **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).

Management of atrial fibrillation

Anticoagulation is used for long-term secondary prevention following cardioembolic stroke, particularly due to atrial fibrillation (AF). Twenty-seven percent of patients with stroke were admitted with AF in the last National Stroke Audit of Acute Services (Stroke Foundation 2019 *[222]*) and a further 6% were identified during the stroke admission. Only 74% of patients with AF were discharged on oral anticoagulation following ischaemic stroke (Stroke Foundation 2019 *[222]*). 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 *[72]*; Saxena 2004 *[73]*; Ruff et al 2014 *[57]*)
- 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 *[57]*)
- 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 *[86]*)

Practical Info

Valvular AF is defined as mechanical prosthetic valve or moderate-severe mitral stenosis (Di Biase et al 2016 *[87]*, Kirchhof et al 2016 *[88]*).

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 *[85]*). 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 *[84]*). 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).

Evidence To Decision

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 *[86]*). 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 *[57]*). 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 *[57]*). 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 *[61]*).

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 *[81]*). In overseas settings, warfarin has been found to more cost-effective when provided to patients at greater cardiovascular risk (Holloway et al 1999 *[74]*) or at an optimal dosage (Sorensen et al 2009 *[75]*).

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 *[76]*; Kamel et al 2012 *[77]*). 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 *[63]*; Chang et al 2013 *[64]*; Lee et al 2012 *[65]*; Zheng et al 2014 *[66]*). Two studies provided some evidence that DOACs were not cost-effective compared to warfarin (Canestaro et al 2013 *[67]*; Freeman et al 2011 *[68]*). 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 *[69]*; Davidson et al 2013 *[70]*; You 2014 *[71]*). 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 *[78]*).

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 *[85]*) and

andexenet alfa may become available for Xa inhibitors (Connolly et al 2016 *[84]*). 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) *[57]* 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) *[58]* 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) *[60]* 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 *[61]*) 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)*[89]* 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**	**Comparator** Warfarin	**Intervention** DOACs	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Stroke or systemic embolic events [1] 2 years 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 Difference: 8 fewer per 1000 (CI 95% 1 fewer — 14 fewer)	**High** [2]	DOACs decrease stroke or systemic embolic events
Major bleeding [3] 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 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: Anticoagulant
Comparator: Antiplatelets

Summary

In a Cochrane review, Saxena and Koudstaal (2004)*[72]* 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)*[73]* 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.

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 *[101]*). 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 *[102]*), 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 *[103]*). 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 *[57]*).

Diener et al. (2019) *[123]* conducted a multicentre RCT (n=5390) comparing dabigatran (150mg or 110 mg twice daily) to aspirin (100mg) in patients with embolic stroke of undetermined source. Patients were followed up a median 19 months. There was no significant reduction in recurrent stroke (HR 0.85, 95%CI 0.69 to 1.03) and no difference in major bleeding (HR 1.19, 95%CI 0.85 to 1.66). Non-major bleeding rates were higher in the dabigatran group (HR 1.73, 95%CI 1.17 to 2.54).

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

Outcome Timeframe	Study results and measurements	Comparator Antiplatelets	Intervention Anticoagulant	Certainty of the Evidence (Quality of evidence)	Plain text summary
7 Critical	Follow up: 1 to 2+ years.	(CI 95% 2 fewer — 26 more)			
Major extracranial bleed End of follow-up 7 Critical	Odds Ratio 5.16 (CI 95% 2.08 — 12.83) Based on data from 1,371 patients in 2 studies. [7] (Randomized controlled) Follow up: 1 to 2+ years.	3 per 1000 Difference: 12 more per 1000 (CI 95% 3 more — 34 more)	15 per 1000	**Moderate** Due to serious imprecision (few events) [8]	Vitamin K antagonists probably increase major extracranial bleeding

1. Systematic review [72] . **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 [72] . **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 [72] . **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 [72] . **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.

Info Box

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.

Third practice point has become a draft weak evidence -based recommendation as below. The wording has not changed.

Evidence To Decision

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 *[79]*; van Es et al 2002 *[80]*) . 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.

Weak recommendation

New

DRAFT RECOMMENDATION AUGUST 2020
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. (Osmancik et al 2020 *[90]*)

Previously this was a practice point but is a draft evidence-based recommendation. The actual wording of recommendation has not changed. This draft has been submitted to the NHMRC for consideration of approval.

Practical Info

The following must be considered in the decision-making process for an individual patient:

- the higher risk of procedural related complication in LAAC (1% mortality directly related to the device/procedure); and
- the potential increased risk of bleeding associated with long term oral anticoagulation.

Post LAAC the antithrombotic regime was individualised with the vast majority (82%) receiving dual antiplatelet therapy of aspirin (100mg/day) plus clopidogrel (75 mg/day) for 3 months followed indefinitely by single antiplatelet therapy (usually aspirin).

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Left atrial appendage closure (LAAC) plus antiplatelet therapy was noninferior to direct oral anticoagulants (DOAC) in high risk patients (Osmancik et al, 2020 *[90]*).

Certainty of the Evidence

Moderate

The evidence was a single RCT and the overall certainty is moderate.

Preference and values

Substantial variability is expected or uncertain

We expect there will be variation in the value of undertaking surgery plus medical therapy or medical therapy alone dependent on individual patient factors such as age and overall health. It will be important to carefully discuss the risks and benefits of treatment options with the patient and their family.

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

Surgery plus medical therapy will be more expensive than medical therapy alone but no published economic literature was identified.

Rationale

Mechanical left atrial appendage closure (LAAC) is a novel site-specific therapeutic alternative to traditional atrial fibrillation stroke prevention methods, like vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). The use of VKAs, like warfarin, are limited due to narrow therapeutical profile, diet-drug interactions and blood level monitoring. DOACs are known to decrease intracranial hemorrhage compared to VKAs and is more commonly used for further stroke prevention. A study in patients with high risk (CHAsDS2-VASc score median 4.7 +/- 1.5), of which about one-third of patients had stroke as a component of the score, found LAAC and antiplatelet therapy to be noninferior to DOAC in preventing major AF related cardiovascular, neurological and bleeding events, in patients at high risk for further stroke and increased risk of bleeding (Osmancik et al, 2020 *[90]*). Further trials are ongoing and further refinements in both operator technique and device technology are required to reduce safety concerns of LAAC.

Clinical Question/ PICO

Population: Adults with stroke with left atrial appendage occlusion
Intervention: Closure of left atrial appendage
Comparator: anticoagulant

Summary

Osmancik et al. (2020) *[90]* compared left atrial appendage closure (LAAC) versus direct oral anticoagulants (DOACs) in a multicenter RCT in high-risk patients (n=402) with atrial fibrillation (AF). The eligibility criteria included patients with nonvalvular AF indicated for oral anticoagulation (OAC) and had a history of bleeding requiring intervention or hospitalization and/or a history of a cardioembolic event while taking an OAC or a CHA_2DS_2-VASc of >2 and HAS-BLED of >2. About one-third of participants had a prior stroke. The median follow-up was 19.9 months. The LAAC procedure was successful in 90.0% patients. In the DOAC group, apixaban was used in 95.5% patients. The most common antithrombotic regimen in the LAAC group was aspirin and clopidogrel for 3 months followed by aspirin monotherapy. The primary composite outcome consisted of stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or nonmajor clinically relevant bleeding, or procedure-/device-related complication. The annual rate of the primary outcome was 10.99% with LAAC and 13.42% in the DOAC group (subdistribution hazard ratio [sHR] 0.84; 95% CI 0.53-1.31, p=0.44). Also, no significant difference was observed for the components of the composite outcome [e.g. all stroke/TIA sHR 1.00; 95% CI 0.40-2.51, clinically significant bleeding sHR 0.81; 95% CI 0.44-1.52, cardiovascular death sHR 0.75; 95% CI 0.34-1.62. The study reached pre-specified non-inferioriority levels.

Outcome Timeframe	**Study results and measurements**	**Comparator** anticoagulant	**Intervention** Closure of left atrial appendage	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Composite outcome (stroke, TIA, systemic embolism, CVD death, bleeding, procedure or device related complication) [1] 7 Critical	Hazard Ratio 0.84 (CI 95% 0.53 — 1.31) Based on data from 402 patients in 1 studies. (Randomized controlled) Follow up: median 19.9 months.	189 per 1000	161 per 1000 Difference: **28 fewer** per 1000 (CI 95% 84 fewer — 51 more)	**Moderate** Due to serious imprecision as only one study with very small number (15) of stroke events [2]	Closure of left atrial appendage followed by antiplatelet therapy probably has little or no difference on a composite outcome compared to direct oral anticoagulants (non-inferior)

1. Composite outcome (consists of incidence of stroke, TIA, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding, or procedure-/device-related complications)
2. **Risk of Bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious.** Ideally longer follow up than median 20 months is needed.

Imprecision: Serious. Only data from one study, Low number of patients.

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 98% of patients with acute ischaemic stroke by discharge (Stroke Foundation 2019 *[222]*) 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 *[105]*).

Commencement of secondary prevention medication prior to hospital discharge is important for improving rates of adherence long-term after stroke (Thrift et al 2014 *[45]*).

Several therapeutic options are 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 *[91]*; Niu et al 2016 *[92]*; Greving et al 2019 *[122]*)

Practical Info

Aspirin generally commences with initial loading dose of 300mg followed by daily low dose of 100-150mg.
Clopidogrel (Multiple generic brand names) 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; Diasp 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.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Aspirin, aspirin-dipyridamole and clopidogrel all reduce recurrent ischaemic events (Rothwell et al 2016 *[91]*; Niu et al 2016 *[92]*; Sandercock et al 2014 *[93]*; Kwok et al 2015 *[94]*; Malloy et al 2013 *[95]*; Greving et al 2019 *[122]*). 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 *[106]*; Jones et al 2004 *[107]*). 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 *[108]*) and cost effective at an additional cost of US$1,725 per QALY gained (cost reference year not reported) (Matchar et al 2005 *[109]*) 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 *[109]*) . 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 *[110]*); 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 *[109]*). 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 *[114]*; Marissal et al 2004 *[113]* ; Heeg et al 2007 *[108]*; Malinina et al 2007 *[106]*; Shah et al 2000 *[112]*); and more effective and cost saving (Sarasin et al 2000 *[111]*) 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 *[108]*; Malinina et al 2007 *[106]*) 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 *[109]*) . 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 *[112]*). 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 *[111]*); and cost-effective for high-risk patients (Heeg et al 2007 *[108]*).

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 *[93]*; Niu et al 2016 *[92]*; Greving et al 2019 *[122]*). 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) *[92]* 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) *[91]* 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) *[93]* 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) *[94]* 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.

Another recent network meta-analysis by Xiang et al (2019)*[119]* compared the efficacy and safety of multiple antiplatelet therapies for secondary prevention of ischemic stroke or transient ischemic attack. It included 45 RCTs with 173,131 patients involving eight antiplatelet therapies. The comparisons involved mono- or dual antiplatelet therapies; aspirin, clopidogrel, dipyridamole, ticlopidine and cilostazol, and placebo. The traditional meta-analysis of aspirin versus placebo reported significant reduction in stroke recurrence (OR 0.88; 95% CI 0.80-0.96) which was consistent with the network meta-analysis findings of (OR 0.82; 95% CI 0.73-0.93) in patients on aspirin.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Aspirin only	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Recurrent stroke - long term - low dose (75 - 162mg daily) 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 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** [3]	Aspirin decreases recurrent stroke in the short term
Bleeding - long term - low dose (75 - 162mg daily) 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

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Aspirin only	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Serious vascular events - long term - low dose (75 - 162mg daily) End of follow-up	Odds Ratio 0.83 (CI 95% 0.71 — 0.96) Based on data from 13,327 patients in 36 studies. [5] (Randomized controlled) Follow up: Mean follow-up of 27 months.			**High**	Low dose aspirin decreases serious vascular events in the long term
Death or dependence End of follow-up 9 Critical	Odds Ratio 0.95 (CI 95% 0.91 — 0.99) Based on data from 41,291 patients in 4 studies. (Randomized controlled) Follow up: 3 to 6 months.	462 per 1000	449 per 1000 Difference: **13 fewer** per 1000 (CI 95% 23 fewer — 2 fewer)	**High**	Aspirin decreases death or dependence
Death End of follow-up 9 Critical	Odds Ratio 0.92 (CI 95% 0.87 — 0.98) Based on data from 41,291 patients in 4 studies. (Randomized controlled) Follow up: 3 to 6 months.	129 per 1000	120 per 1000 Difference: **9 fewer** per 1000 (CI 95% 15 fewer — 2 fewer)	**High**	Aspirin decreases death
Symptomatic intracranial haemorrhage During treatment 8 Critical	Odds Ratio 1.22 (CI 95% 1 — 1.5) Based on data from 40,850 patients in 3 studies. (Randomized controlled) Follow up: 5 days to 3 months of treatment.	8 per 1000	10 per 1000 Difference: **2 more** per 1000 (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) Based on data from 15,778 patients in 12 studies. (Randomized controlled)	24 per 1000	10 per 1000 Difference: **14 fewer** per 1000 (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) Based on data from 15,778 patients in 12 studies. (Randomized controlled)	15 per 1000	4 per 1000 Difference: **11 fewer** per 1000 (CI 95% 12 fewer — 9 fewer)	**High**	Aspirin reduces 6 week risk of recurrent fatal or disabling stroke

1. Systematic review [92] . **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [91] . **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 [92] . **Baseline/comparator:** Control arm of reference used for intervention.

5. Systematic review [92] . **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) *[92]* 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) *[95]* 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.

Another network meta-analysis by Xiang et al. (2019)*[119]* compared the efficacy and safety of multiple antiplatelet therapies for secondary prevention of ischemic stroke or transient ischemic attack. It included 45 RCTs with 173,131 patients involving eight antiplatelet therapies. The traditional meta-analysis reported significantly less stroke recurrence in patients who were on dipyridamole and aspirin compared to patients who were on placebo (OR 0.55; 95% CI 0.47-0.65) that was confirmed by the network meta-analysis (OR 0.62; 95% CI 0.52-0.73).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** 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) Follow up: Mean follow-up of 27 months.			**High**	Low dose aspirin plus dipyridamole increases bleeding in the long term

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Aspirin plus dipyridamole	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 [92] . **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [92] . **Baseline/comparator:** Control arm of reference used for intervention.

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Aspirin plus dipyridamole
Comparator: Aspirin alone

Summary

Greving et al (2019) *[122]* conducted an individual patient meta-analysis from six trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, and PRoFESS) that analysed 43112 patients with a TIA or noncardioembolic stroke. When Aspirin+dipyridamole were compared with aspirin alone, there was less serious vascular events defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (RR 0.83, 95% CI 0.74 to 0.94), lower ischaemic stroke recurrence (RR 0.86, 95% CI 0.76 to 0.97), and no difference in major bleeding (RR 0.86, 95% CI 0.71 to1.05). Net clinical benefit (serious vascular events or major bleeding adjusted for age, sex, hypertension, diabetes, smoking and stroke type i.e. stroke vs TIA) was 0.87 (95%CI 0.80 to 0.95).

Another network meta-analysis by Xiang et al (2019) *[119]* compared the efficacy and safety of multiple antiplatelet therapies for secondary prevention of ischemic stroke or transient ischemic attack. It included 45 RCTs with 173,131 patients involving eight antiplatelet therapies. The comparisons involved mono- or dual antiplatelet therapies; aspirin, clopidogrel, dipyridamole, ticlopidine and cilostazol, and placebo. The network meta-analysis reported significant reduction in stroke recurrence in Aspirin plus dipyridamole group compared to patients on aspirin alone (OR 0.75, 95% CI 0.63 to 0.88). However, these results were inconsistent with the results of the traditional meta-analysis that reported no significant difference (OR 0.88; 95 % CI 0.57 to 1.34).

In a network meta-analysis of randomized controlled trials Huang et al (2017)*[118]* assessed the efficacy and safety of nine anti-platelet therapies, including aspirin, dipyridamole, clopidogrel, cilostazol, ticlopidine, terutroban, sarpogrelate triflusal, clopidogrel plus aspirin, dipyridamole plus aspirin, and ticlopidine plus aspirin, for patients with ischemic stroke or TIA. Primary outcome was composite vascular events. The evidence suggested that aspirin and, dipyridamole plus aspirin have significant reduction in incidence of vascular events, compared with placebo (OR = 0.85, 95 % CI 0.74 to 0.99; OR = 0.70, 95 % CI 0.56 to 0.88 respectively).

Outcome Timeframe	**Study results and measurements**	**Comparator** Aspirin alone	**Intervention** Aspirin plus dipyridamole	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Recurrent ischaemic stroke [1] End of follow-up	Relative risk 0.86 (CI 95% 0.71 — 0.97) Based on data from patients in 6 studies.	81 per 1000	70 per 1000	**High** [2]	Aspirin plus dipyridamole decreases recurrent stroke

Outcome Timeframe	**Study results and measurements**	**Comparator** Aspirin alone	**Intervention** Aspirin plus dipyridamole	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical	(Randomized controlled) Follow up: Mean 2 years (Range 1.5 - 3.5).	Difference: **11 fewer** per 1000 (CI 95% 23 fewer — 2 fewer)			
Serious vascular events (stroke, MI, or vascular death) End of follow-up 8 Critical	Relative risk 0.83 (CI 95% 0.74 — 0.94) Based on data from patients in 5 studies. (Randomized controlled) Follow up: Mean 2 years (range 1.5 - 3.5).	154 per 1000	128 per 1000 Difference: **26 fewer** per 1000 (CI 95% 40 fewer — 9 fewer)	**High** 3	Aspirin plus dipyridamole decreases serious vascular events (stroke, MI, or vascular death)
Major bleeding End of follow-up 8 Critical	Relative risk 0.86 (CI 95% 0.71 — 1.05) Based on data from patients in 6 studies. (Randomized controlled) Follow up: Mean of 2 years (range 1.5 - 3.5).	40 per 1000	34 per 1000 Difference: **6 fewer** per 1000 (CI 95% 12 fewer — 2 more)	**High**	Aspirin plus dipyridamole may reduce risk of major bleeding

1. Fatal and nonfatal stroke
2. **Inconsistency: No serious.** Some (non-significant) heterogeneity, I^2 = 39%. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** The search in the systematic review was not comprehensive/ did apply language restriction: only published, English studies reported.
3. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Wide confidence intervals. **Publication bias: No serious.** The search in the Systematic review was not comprehensive/ did apply language restriction: only published, English studies included.

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Clopidogrel
Comparator: Placebo

Summary

Niu et al (2016) *[92]* 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 *[115]*). 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 *[116]*). 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).

A network meta-analysis by Xiang et al (2019)*[119]* compared the efficacy and safety of multiple antiplatelet therapies for secondary prevention of ischemic stroke or transient ischemic attack. It included 45 RCTs with 173,131 patients involving eight antiplatelet therapies. The comparisons involved mono- or dual antiplatelet therapies; aspirin, clopidogrel, dipyridamole, ticlopidine and cilostazol, and placebo. The network meta-analysis reported significant reduction in stroke recurrence in patients who were on clopidogrel compared to placebo (OR 0.63; 95% CI 0.51-0.79).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** 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 24,607 patients in 33 studies. [1] (Randomized controlled) Follow up: Mean follow-up of 27 months.			**Moderate** Due to serious indirectness: the reported estimate is based on a network meta-analysis. No trial directly compared clopidogrel with placebo [2]	Clopidogrel probably decreases recurrent stroke
Bleeding End of follow-up	Odds Ratio 1.79 (CI 95% 1.23 — 2.78) Based on data from 24,607 patients in 30 studies. [3] (Randomized controlled) Follow up: Mean follow-up of 27 months.			**Moderate** 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 End of follow-up	Odds Ratio 0.74 (CI 95% 0.65 — 0.86) Based on data from 24,607 patients in 36 studies. [5] (Randomized controlled) Follow up: Mean follow-up of 27 months.			**Moderate** 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 [92] . **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 [92] . **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 [92] . **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]*) (see Antithrombotic therapy in Acute medical and surgical management)

Practical Info

Importantly, patients were given treatment within 12 or 24 hours of symptom onset in the trials, and the risk of recurrent stroke is highest in the first few days, hence treatment should commence within 24 hours of stroke onset. 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.

Evidence To Decision

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

Resources considerations

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

Greving et al. (2019) [75] conducted an individual patient meta-analysis from six trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, and PRoFESS) that included 48 023 patients with a TIA or ischemic stroke. When Aspirin+clopidogrel were compared with aspirin alone, it identified significantly less serious vascular events (RR 0.83; 95% CI 0.71-0.96) and incidence of ischaemic stroke (RR 0.83; 95% CI 0.71-0.97) but incidence of major bleeding was significantly high in Aspirin+clopidogrel group (RR 1.63; 95% CI 1.29-2.07).

Greving et al. (2019) [75] also compared Aspirin+clopidogrel with clopidogrel alone. Both serious vascular events and ischaemic stroke incidence were not significant (RR 0.94; 95% CI 0.82-1.08 & RR 0.91; 95% CI 0.80-1.04) but significant major bleeding was observed in Aspirin+clopidogrel group (RR 2.16; 95% CI 1.72-2.71).

Outcome Timeframe	**Study results and measurements**	**Comparator** Aspirin or clopidogrel alone	**Intervention** Aspirin plus clopidogrel	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Secondary stroke - short term treatment [1] less than 3 months	Relative risk 0.69 (CI 95% 0.59 — 0.81) Based on data from 5,789 patients in 5 studies. (Randomized controlled)	114 per 1000	79 per 1000 Difference: 35 fewer per 1000	High [2]	Short term treatment with aspirin plus clopidogrel decreases secondary stroke

Outcome Timeframe	**Study results and measurements**	**Comparator** Aspirin or clopidogrel alone	**Intervention** Aspirin plus clopidogrel	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
7 Critical	Follow up: 7 days to 3.4 years.	(CI 95% 22 fewer — 47 fewer)			
Secondary stroke - long term treatment [3] more than one year 7 Critical	Relative risk 0.92 (CI 95% 0.83 — 1.03) Based on data from 14,939 patients in 3 studies. (Randomized controlled) Follow up: 7 days to 3.4 years.	82 per 1000	75 per 1000 Difference: **7 fewer** per 1000 (CI 95% 2 more — 14 fewer)	**Moderate** Due to serious imprecision [4]	Long term treatment with aspirin plus clopidogrel may decrease secondary stroke slightly
Major bleeding - short term treatment [5] less than 3 months 7 Critical	Relative risk 2.17 (CI 95% 0.18 — 25.71) Based on data from 5,789 patients in 5 studies. (Randomized controlled) Follow up: 7 days to 3.4 years.	3 per 1000	7 per 1000 Difference: **4 more** per 1000 (CI 95% 74 more — 2 fewer)	**Low** 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] more than one year 7 Critical	Relative risk 1.9 (CI 95% 1.46 — 2.48) Based on data from 14,939 patients in 3 studies. (Randomized controlled) Follow up: 7 days to 3.4 years.	25 per 1000	48 per 1000 Difference: **23 more** per 1000 (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] less than 3 months 8 Critical	Relative risk 0.7 (CI 95% 0.6 — 0.82) Based on data from 5,789 patients in 5 studies. (Randomized controlled) Follow up: 7 days to 3.4 years.	116 per 1000	81 per 1000 Difference: **35 fewer** per 1000 (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 treatment [11] more than one year 8 Critical	Relative risk 0.92 (CI 95% 0.84 — 1.01) Based on data from 14,939 patients in 3 studies. (Randomized controlled) Follow up: 7 days to 3.4 years.	117 per 1000	108 per 1000 Difference: **9 fewer** per 1000 (CI 95% 1 more — 19 fewer)	**Moderate** 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

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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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 *[98]*; Greving et al 2019 *[122]*)

Evidence To Decision

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 *[98]*).

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

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

<u>Implementation considerations</u>
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 *[98]*; Greving et al 2019 *[122]*). 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

Greving et al. (2019) [75] conducted an individual patient meta-analysis from six trials (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, and PRoFESS) that included 48 023 patients with a TIA or ischemic stroke. When Aspirin+clopidogrel were compared with aspirin alone, it identified significantly less serious vascular events (RR 0.83; 95% CI 0.71-0.96) and incidence of ischaemic stroke (RR 0.83; 95% CI 0.71-0.97) but incidence of major bleeding was significantly high in Aspirin+clopidogrel group (RR 1.63; 95% CI 1.29-2.07).

Greving et al. (2019) [75] also compared Aspirin+clopidogrel with clopidogrel alone. Both serious vascular events and ischaemic stroke incidence were not significant (RR 0.94; 95% CI 0.82-1.08 & RR 0.91; 95% CI 0.80-1.04) but significant major bleeding was observed in Aspirin+clopidogrel group (RR 2.16; 95% CI 1.72-2.71).

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Aspirin or clopidogrel alone	**Intervention** Aspirin plus clopidogrel	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
7 Critical	Follow up: 7 days to 3.4 years.				
Secondary stroke, MI or vascular death - short term treatment [9] less than 3 months 8 Critical	Relative risk 0.7 (CI 95% 0.6 — 0.82) Based on data from 5,789 patients in 5 studies. (Randomized controlled) Follow up: 7 days to 3.4 years.	116 per 1000	81 per 1000 Difference: **35 fewer** per 1000 (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 treatment [11] more than one year 8 Critical	Relative risk 0.92 (CI 95% 0.84 — 1.01) Based on data from 14,939 patients in 3 studies. (Randomized controlled) Follow up: 7 days to 3.4 years.	117 per 1000	108 per 1000 Difference: **9 fewer** per 1000 (CI 95% 1 more — 19 fewer)	**Moderate** 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
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.
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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 *[101]*)

Evidence To Decision

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 *[101]*).

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 *[101]*). 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 *[102]*), 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 *[103]*). 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 *[57]*).

Outcome Timeframe	**Study results and measurements**	**Comparator** Aspirin	**Intervention** Factor Xa inhibitor	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
All-case death 1 year 9 Critical	Hazard Ratio 0.79 (CI 95% 0.62 — 1.02) Based on data from 5,599 patients in 1 studies. (Randomized controlled) Follow up: mean 1.1 year.	44 per 1000	35 per 1000 Difference: **9 fewer** per 1000 (CI 95% 1 more — 17 fewer)	**Moderate** Due to serious imprecision [1]	Factor Xa inhibitors probably decrease all-case death
Stroke and systemic embolism 1 year 8 Critical	Relative risk 0.45 (CI 95% 0.32 — 0.62) Based on data from 5,599 patients in 1 studies. (Randomized controlled) Follow up: mean 1.1 year.	37 per 1000	16 per 1000 Difference: **21 fewer** per 1000 (CI 95% 14 fewer — 25 fewer)	**High** 2	Factor Xa inhibitors decrease stroke and systemic embolism
Major bleeding [3] 1 year 8 Critical	Hazard Ratio 1.13 (CI 95% 0.74 — 1.75) Based on data from 5,599 patients in 1 studies. (Randomized controlled) Follow up: mean 1.1 year.	12 per 1000	14 per 1000 Difference: **2 more** per 1000 (CI 95% 9 more — 3 fewer)	**High** 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.**

Weak recommendation

New

In patients with spontaneous (or primary) intracerebral haemorrhage who were previously prescribed antithrombotic therapy for secondary prevention of cardiovascular and/or cerebrovascular disease, restarting antiplatelet therapy after the acute phase may be considered, although the optimal timing is undertermined (see practical information). (RESTART Collaboration 2019 *[121]*)

Practical Info

Although there was no increase in harm evident in the RESTART trial, the benefits remain unclear. The trend to reduced recurrent intracerebral haemorrhage was an unexpected result and further trials are underway. Therefore, careful consideration and discussion of risk and benefits with the patient and their family is needed. In those with higher risk, such as patients with unstable angina or recent coronary stent, the benefits with restarting antiplatelets may outweigh any possible risk.

Only around 10% of patients in the trial underwent MRI and met modified Boston diagnostic criteria for cerebral amyloid angiopathy and hence there is significant residual uncertainty regarding the potential benefits and harms of antiplatelet resumption in this group.

In the RESTART trial the median time from heamorrhage onset to recruitment was 76 days (IQR 29–146) and only 4% were recruited within the first week. In general, intracerebral haemorrhage expansion occurs in the first 24h and it is suggested to delay restarting antiplatelet medication for one week or more.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Restarting antiplatelet therapy did not increase subsequent harms (recurrent ICH, major haemorrhage, or major occlusive vascular events) compared to no antiplatelet therapy in people after ICH. (RESTART Collaboration 2019 *[121]*) The median time to commencement was 76 days in the RESTART study. The benefits of antiplatelet therapy in reducing recurrent ischaemic strokes are also well-known.

Certainty of the Evidence

Moderate

Overall certainty is moderate based on a single well-conducted study in the UK.

Preference and values

Substantial variability is expected or uncertain

Harms appear similar with or without therapy but, based on this single study, people following stroke may have different preferences for commencing or avoiding therapy depending on individual circumstances and attitude to risk.

Resources and other considerations

No important issues with the recommended alternative

Antiplatelet therapy is cost-effective in people with ischaemic stroke and as there appears to be no increase in harms it is also likely to be cost-effective in people following ICH.

Rationale

Recommencing antiplatelet therapy at a median 76 days post intracerebral haemorrhage (ICH) did not increase recurrent ICH, based on a single multicentre trial in the UK. The decision to restart antiplatelet therapy should carefully consider individual patient factors to ensure any potential benefits clearly outweigh the risks. The appropriate time to restart antiplatelets remains uncertain (see Practical Information). Further studies are underway.

Clinical Question/ PICO

Population: Adults with stroke due to ICH

Intervention: Antiplatelet therapy
Comparator: Avoid anti-platelet therapy

Summary

The RESTART collaboration (2019)*[121]* conducted a multicentre RCT (n=537 participants) across the UK. Participants had developed spontaneous (primary) ICH while taking antithrombotic therapy, with therapy discontinued. Those who survived 24 hours were randomised to start or avoid restarting antiplatelet therapy and followed up for up to 5 years (median 2 years). Median timeframe from initial stroke was 76 days. The primary outcome of recurrent symptomatic ICH was non-significantly lower in those who restarted antiplatelet therapy (HR 0.51, 95%CI 0.25 to 1.03). Sensitivity analysis of recurrent ICH or stroke of uncertain type did reach significance (p=0.044) along with recurrent ICH or death of undetermined cause (p=0.048). Most secondary outcomes were similar between groups except for major vascular events which were lower in the group restarting therapy (HR 0.65, 95%CI 0.44 to 0.95). Longer term follow-up of participants is being undertaken. Results of two other trials are yet to be published.

Outcome Timeframe	**Study results and measurements**	**Comparator** No anti-platelet therapy	**Intervention** Antiplatelet therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Recurrence of intracerebral haemorrhage median 2 years 9 Critical	Hazard Ratio 0.51 (CI 95% 0.25 — 1.03) Based on data from 537 patients in 1 studies. [1] (Randomized controlled) Follow up: median 2 years.	86 per 1000	45 per 1000 Difference: 41 fewer per 1000 (CI 95% 64 fewer — 2 more)	**Moderate** Due to serious imprecision, Due to Risk of bias [2]	Antiplatelet therapy probably has little or no difference on recurrence of intracerebral haemorrhage
Major haemorrhagic events median 2 years 8 Critical	Hazard Ratio 0.71 (CI 95% 0.39 — 1.3) Based on data from 536 patients in 1 studies. (Randomized controlled) Follow up: Median 2 years.	93 per 1000	67 per 1000 Difference: 26 fewer per 1000 (CI 95% 56 fewer — 26 more)	**Moderate** Due to serious imprecision, Due to risk of bias [3]	Antiplatelet therapy probably has little or no difference on major haemorrhagic events
All major occlusive vascular events median 2 years 7 Critical	Hazard Ratio 1.02 (CI 95% 0.65 — 1.6) Based on data from 536 patients in 1 studies. [4] (Randomized controlled) Follow up: median 2 years.	142 per 1000	145 per 1000 Difference: 3 more per 1000 (CI 95% 47 fewer — 75 more)	**Moderate** Due to serious imprecision, Due to risk of bias [5]	Antiplatelet therapy probably has little or no difference on all major occlusive vascular events

1. Primary study. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [121],
2. **Risk of Bias: No serious.** No blinding of participants and personnel. Trial recruited 562 of planned 720 but offset this by increasing time of follow up to accrue planned numbers of person-years of follow up and outcome events.. **Imprecision: Serious.** Only data from one study, Wide confidence intervals.
3. **Risk of Bias: No serious.** No blinding of participants and personnel. Trial recruited 562 of planned 720 but offset this by increasing time of follow up to accrue planned numbers of person-years of follow up and outcome events.. **Imprecision: Serious.** Only data from one study.
4. Primary study. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [121],
5. **Imprecision: Serious.** Only data from one study.

Cholesterol lowering therapy

The most recent National Stroke Audit showed that around 88% of eligible patients with ischaemic stroke were on lipid-lowering therapy on discharge from hospital (Stroke Foundation 2020 *[223]*). Records from a large Australian GP registry indicate that in the community this rate fell to 65 % (Reid et al 2008 *[105]*). 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 *[45]*).

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 *[128]*; Tramacer et al 2019 *[139]*)

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.

Evidence To Decision

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 *[128]*).

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 *[128]*). 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 *[129]*).

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 *[126]*). 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 *[127]*). Historically, the price of statins in Australia has been considerably higher than in comparable countries such as New Zealand (Simeons et al 2011 *[131]*; Cobiac et al 2012 *[132]*). However, the price of statins in Australia is expected to fall with the expiry of patent protections on statins (Clarke and Fitzgerald 2010 *[130]*), 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) *[128]* 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 *[139]*) included nine trials (N=10,741 patients). Similar results were reported with the 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 haemorrhage 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 *[136]*).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Statins	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Secondary intracerebral haemorrhage End of follow-up 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 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 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 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 effect 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 9,224	121 per 1000	108 per 1000	**Moderate** Due to serious imprecision:	Statins probably decrease overall secondary strokes (net impact on ischaemic

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Statins	Certainty of the Evidence (Quality of evidence)	Plain text summary
8 Critical	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]	and haemorrhagic)
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 Difference: **20 fewer** per 1000 (CI 95% 30 fewer — 7 fewer)	**79** per 1000	**High** [10]	Statins slightly decrease secondary ischaemic stroke

1. Systematic review [128] with included studies: HPS, SPARCL. **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 [128] 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 [128] with included studies: HPS, FASTER, LIPID, CARE, 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 [128] with included studies: HPS, SPARCL. **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

New

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 *[133]*)

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 *[133]*; Zhan et al 2018 *[135]*) 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 *[134]*) 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.

Patient information (developed in co-design with members of consumer panel) is available from: https://strokefoundation.org.au/cholesterol-lowering

Evidence To Decision

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 *[133]*) 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 *[140]*).

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

<u>Resources considerations</u>

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 *[144]* 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 *[144]*).

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 *[143]* 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 *[141]*). 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 *[142]*).

<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

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*[145]*). The Treat Stroke to Target trial (Amarenco et al 2020) *[133]* 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 *[134]*) 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) *[133]* 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)*[134]* 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**	**Comparator** less intense LDL-C lowering	**Intervention** 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 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 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	Hazard Ratio 0.78 (CI 95% 0.61 — 0.98) Based on data from 2,860	**109**	**86**	**Moderate** Due to serious	More intense LDL-C lowering (<1.8 mmol/l) probably improves major

Outcome Timeframe	Study results and measurements	Comparator less intense LDL-C lowering	Intervention more intense LDL-C lowering (<1.8 mmol/L)	Certainty of the Evidence (Quality of evidence)	Plain text summary
event [3] 3.5 years 8 Critical	patients in 1 studies. [4] (Randomized controlled) Follow up: 3.5 years.	per 1000	per 1000 Difference: **23 fewer** per 1000 (CI 95% 41 fewer — 2 fewer)	imprecision [5]	cardiovascular event

1. Primary study. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [133],
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:** [133],
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 *[128]*; Amarenco et al 2006 *[129]*)

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.

Evidence To Decision

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 *[128]*).

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 *[129]*).

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 *[126]*;

Kongnakorn et al 2009 *[127]*). The price of statins in Australia is expected to fall with the expiry of patent protections on statins (Clarke and Fitzgerald 2010 *[130]*), 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) *[128]* 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 *[139]*) included nine trials (N=10,741 patients). Similar results were reported with the 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 haemorrhage 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 *[136]*).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Statins	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Secondary intracerebral haemorrhage End of follow-up 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 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 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	89 per 1000	91 per 1000 Difference: 2 more per 1000 (CI 95% 13 fewer — 20 more)	Moderate Due to indirectness and imprecision: only one study that excluded patients	Statins probably have little or no effect on all-cause mortality

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Statins	Certainty of the Evidence (Quality of evidence)	Plain text summary
	approximately 5 years.			with cardio-embolic stroke [5]	
Secondary stroke - all [6] End of follow-up 8 Critical	Odds Ratio 0.88 (CI 95% 0.77 — 1) Based on data from 9,224 patients in 5 studies. [7] (Randomized controlled) Follow up: 90 days to 6 years.	121 per 1000	108 per 1000 Difference: **13 fewer** per 1000 (CI 95% 25 fewer — 0 fewer)	**Moderate** Due to serious imprecision: confidence interval includes null effect [8]	Statins probably decrease overall secondary strokes (net impact on ischaemic and haemorrhagic)
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 [128] with included studies: HPS, SPARCL. **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 [128] 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 [128] with included studies: HPS, FASTER, LIPID, CARE, 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 [128] with included studies: HPS, SPARCL. **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 *[125]*; Wang et al 2015 *[124]*)

Evidence To Decision

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 *[125]*). 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 *[125]*).

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 *[125]*). 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) *[125]* 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) *[124]* 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**	**Comparator** Control	**Intervention** Fibrates	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Secondary stroke 9 Critical	Relative risk 1.28 (CI 95% 0.86 — 1.9) Based on data from 627 patients in 10 studies. [1] (Randomized controlled) Follow up: variable (30-104 months).	144 per 1000	184 per 1000 Difference: 40 more per 1000 (CI 95% 20 fewer — 130 more)	**Moderate** Due to serious risk of bias [2]	Fibrate therapy probably has little or no effect on secondary stroke.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Fibrates	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 [124] . 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

Updated evidence, no change in 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 *[152]*, Rerkasem et al 2020 *[166]*)

Practical Info

Symptomatic is defined as symptoms of a focal neurological event compatible with transient ischaemic attack or stroke affecting the the territory of the stenosed carotid artery. Beyond 3 months after an event the risk of stroke reduces substantially to levels similar to asymptomatic carotid stenosis.

Optimal medical management of atherosclerosis should be provided to all patients as outlined in this chapter. This may include cholesterol lowering therapy (aiming for LDL<1.8mmol/L), anti-platelet therapy, blood pressure control and lifestyle modification including smoking cessation, dietary advice, exercise advice, and alcohol intake. Diabetes management should also be considered.

NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria
The diameter of the arterial lumen at the tightest region of stenosis is compared with the lumen of the non-stenosed 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.

Evidence To Decision

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 et al 2020 *[166]*). 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 *[152]*).

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 *[163]*; Henriksson et al 2008 *[157]*). 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 *[147]*).

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 et al 2020 *[166]*). 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 et al 2020 *[166]*). 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 et al 2020 *[166]*). 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 symptomatic carotid stenosis
Intervention: Endarterectomy
Comparator: no endarterectomy

Summary

Three RCTs relevant to current practice have been published: 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 (2020) *[166]* 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**	**Comparator** no endarterectomy	**Intervention** 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)	**Moderate** [2]	surgery has little or no difference on any stroke or operative death in patients near occlusion

Outcome Timeframe	Study results and measurements	Comparator no endarterectomy	Intervention Endarterectomy	Certainty of the Evidence (Quality of evidence)	Plain text summary
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. [3] (Randomized controlled)	292 per 1000	155 per 1000 Difference: 137 fewer per 1000 (CI 95% 169 fewer — 96 fewer)	Moderate [4]	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. [5] (Randomized controlled)	232 per 1000	179 per 1000 Difference: 53 fewer per 1000 (CI 95% 86 fewer — 14 fewer)	Moderate	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 studies. [6] (Randomized controlled)	211 per 1000	205 per 1000 Difference: 6 fewer per 1000 (CI 95% 44 fewer — 40 more)	High	surgery has little or no difference on any stroke or operative death in patients with 30% to 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. [7] (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 [166] with included studies: NASCET, ECST. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Low number of patient outcomes. **Publication bias: No serious.**
3. Systematic review [166] with included studies: VACSP, NASCET, ECST. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious.** The magnitude of statistical heterogeneity was high, with I^2:68%.. **Indirectness: No serious. Imprecision: No serious.**
5. Systematic review [166] with included studies: VACSP, NASCET, ECST. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [166] with included studies: NASCET, ECST. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [166] with included studies: ECST, NASCET. **Baseline/comparator:** Control arm of reference used for intervention.

Weak recommendation

Updated evidence, no change in 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.

(Muller et al. 2020 *[151]*)

Practical Info

Experience in carotid stenting may be an important consideration. With sites with less experience (<10 procedures) the chance of adverse outcomes was higher (OR 2.21, 95%CI 1.56 to 3.13; 3 trials) whereas at sites with more experience (>10 procedures) the risk of adverse outcomes was non-significant (OR 1.37; 95%CI 0.98 to 1.94; four trials). The difference between groups however, was not significant. (Muller et al. 2020 *[151]*)

Evidence To Decision

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 (Muller et al. 2020 *[151]*). 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, well conducted 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

<u>Resources considerations</u>
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 *[150]*; Almekhlati et al 2014 *[158]*; Young et al 2014 *[159]*). However, carotid arterial stenting was cost-effective for patients with high surgical risk (Almekhlati et al 2014 *[158]*).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 *[154]*). 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 *[155]*).

Rationale

A number of trials have compared carotid stenting to carotid endarterectomy. Meta-analyses of these trials indicate that the perioperative stroke rate or death is significantly higher with carotid stenting than carotid endarterectomy (Bangalore et al. 2011 *[152]*; Muller et al. 2020 *[151]*), 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 over endarterectomy 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 found the higher risk is mostly related to minor, non-disabling stroke in those over the age of 70 years and the outcomes are similar beyond the periprocedural period (Muller et al. 2020 *[151]*). This recommendation does not apply to the context of carotid stenting during an emergency thrombectomy procedure in order to secure access to the intracranial circulation. Treatment of tandem extracranial carotid and intracranial occlusions in this way was shown to be beneficial in trials of endovascular thrombectomy.

Clinical Question/ PICO

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

Summary

In an updated Cochrane review Muller et al (2020)*[151]* included 22 studies (9753 participants) comparing carotid stenting to endarterectomy. In participants with symptomatic carotid stenosis, stenting was associated with a higher risk of periprocedural death or stroke (OR 1.70, 95%CI 1.31 to 2.19; 10 trials, 5396 participants; high-certainty evidence) and periprocedural death, stroke, or myocardial infarction (OR 1.43, 95%CI 1.14 to 1.80; 6 trials, 4861 participants; high-certainty evidence). Harm was more evident in people over 70 years old (OR 2.23, 95% CI 1.61 to 3.08). There was no difference in safety outcome for younger patients (<70 years) (OR 1.11, 95%CI 0.74 to 1.64; interaction P = 0.007). Stenting was associated with lower risks of myocardial infarction (OR 0.47, 95% CI 0.24 to 0.94), cranial nerve palsy (OR 0.09, 95% CI 0.06 to 0.16), and access site haematoma (OR 0.32, 95% CI 0.15 to 0.68). The combination of periprocedural death or stroke or ipsilateral stroke during follow-up favoured endarterectomy (OR 1.51, 95% CI 1.24 to 1.85; 8 trials, 5080 participants; high-certainty evidence).

These results are similar to previous reviews (Bangalore et al. 2011 *[152]*; Luebke and Brunkwell 2016 *[168]*; Sardar et al. 2017 *[167]*; Li et al. 2017*[169]*).

Furthermore, outcomes of carotid stenting in administrative datasets analysed by Paraskevas et al (2016) *[146]* suggest that in routine practice carotid stenting is associated with a higher stroke rate than carotid endarterectomy.

Outcome Timeframe	**Study results and measurements**	**Comparator** Carotid endarterectomy	**Intervention** Carotid artery stenting	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Periprocedural stroke	Odds Ratio 1.78 (CI 95% 1.38 — 2.29) Based on data from 5,113 patients in 8 studies. [1] (Randomized controlled) Follow up: 30 days.	40 per 1000	69 per 1000 Difference: 29 more per 1000 (CI 95% 14 more — 47 more)	High	Carotid artery stenting increases periprocedural stroke
Stroke - long term (periprocedural period excluded)	Odds Ratio 1.15 (CI 95% 0.82 — 1.62) Based on data from 4,837 patients in 6 studies. [2] (Randomized controlled) Follow up: >18 months.	59 per 1000	67 per 1000 Difference: 8 more per 1000 (CI 95% 10 fewer — 33 more)	High	There is little or no difference in long term stroke risk (after the periprocedural phase) between carotid stenting and endarterectomy
Periprocedural death or stroke	Odds Ratio 1.7 (CI 95% 1.31 — 2.19) Based on data from 5,396 patients in 10 studies. [3] (Randomized controlled) Follow up: perioperative (within 30 days).	44 per 1000	72 per 1000 Difference: 28 more per 1000 (CI 95% 47 more — 12 more)	High [4]	Carotid artery stenting increases periprocedural death or stroke
Death or stroke - Long term From randomisation to end of follow up 6 months to >4 years	Odds Ratio 1.23 (CI 95% 1.03 — 1.46) Based on data from 5,292 patients in 9 studies. [5] (Randomized controlled) Follow up: >6 months.	246 per 1000	286 per 1000 Difference: 40 more per 1000 (CI 95% 6 more — 77 more)	High	Carotid artery stenting probably increases death or stroke - long term

Outcome Timeframe	Study results and measurements	Comparator Carotid endarterectomy	Intervention Carotid artery stenting	Certainty of the Evidence (Quality of evidence)	Plain text summary

1. Systematic review [151] . **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [151] . **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [151] . **Baseline/comparator:** Control arm of reference used for intervention.
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.**
5. Systematic review [151] . **Baseline/comparator:** Control arm of reference used for intervention.

Weak recommendation against

Updated evidence, no change in recommendation

In patients with asymptomatic carotid stenosis, carotid endarterectomy or stenting should not be performed. (Galyfos et al 2019 *[173]*; Raman et al 2013 *[149]*; Muller et al 2020 *[151]*)

Practical Info

Optimal medical management of atherosclerosis should be provided as outlined in this chapter. This may include cholesterol lowering therapy (aiming for LDL<1.8mmol/L), anti-platelet therapy, blood pressure control and lifestyle modification including smoking cessation, dietary advice, exercise advice, and alcohol intake. Diabetes management should also be considered.

There is considerable debate as to whether those at higher risk can be identified and considered for surgery. The presence of high-risk plaques is common (26.5%) and leads to higher incidence of ipsilateral ischaemic strokes. (Kamtchum-Tatuene et al 2020 *[175]*) There is also no clear link between amount of narrowing and the presence of high-risk plaques. Further evidence is needed to confirm if using multimodal neurovascular imaging for risk stratification and therapy selection does in fact improve outcomes above best medical therapy alone.

Evidence To Decision

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 *[149]*). The benefit, however, comes with an increased risk of periprocedural stroke and other complications (Galyfos et al. 2019 *[173]*). 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 *[160]*).

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 an increase in periprocedural stroke or death with stenting compared to endarterectomy but there was no difference when ipsilateral stroke on follow up was also included (Muller et al. 2020 *[151]*). 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 *[146]*).

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

Surgery is more costly than best medical care alone.

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

Muller et al. (2020)*[151]* included 22 studies (9753 participants) in a Cochrane Review comparing carotid stenting to endarterectomy. In people with asymptomatic carotid stenosis, there was a borderline significant increase in periprocedural death or stroke with stenting compared with endarterectomy (OR 1.72, 95% CI 1.00 to 2.97; 7 trials, 3378 participants; moderate-certainty evidence). The risk of periprocedural death or stroke or ipsilateral stroke during follow-up did not differ between treatments (OR 1.27, 95% CI 0.87 to 1.84; 6 trials, 3315 participants; moderate-certainty evidence). There was a non-significant reduction in myocardial infarction in periprocedural period with stenting compared with endarterectomy (OR 0.53, 95% CI 0.24 to 1.15).

Previous reviews reported similar findings. Yuan et al (2018)*[172]* included five studies of asymptomatic but signficant stenosis (>50%) and found stenting reduced risk of myocardial infarction but may increase risk of stroke (RR1.69, 95%CI 0.97 to 2.92). There was no difference in death.

Kakkos et al. (2017)*[170]* included nine studies (n=3709). Stenting increased death or stroke within 30 days (OR 1.57, 95% CI 1.01 to 2.44). Including ipsilateral stroke at 1 year along with periprocedural death or stroke remained higher with stenting compared to endarterectomy (OR1.51, 95% CI 1.02 to 2.24). The quality of evidence was rated as moderate by authors.

Moresoli et al. (2017)*[171]* included 5 trials (n=3019). Stenting led to non-significant increase in periprocedural stroke (RR1.84, 95%CI 0.99 to 3.40) and periprocedural stroke or death (RR1.72, 95%CI 0.95 to 3.11). No difference in long term stroke was found (RR1.24, 95%CI 0.76 to 2.03).

Bangalore et al. (2011)*[152]* reported a non-significant increase in periprocedural strokes with the stenting compared to the endarterectomy (OR 1.75, 95%CI 0.88 to 3.49; 3 studies, n=1503).

The data is in keeping with findings 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). However, 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 *[162]*).

Outcome Timeframe	**Study results and measurements**	**Comparator** Carotid endarterectomy	**Intervention** 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 imprecision [3]	We are uncertain whether carotid artery stenting increases or decreases death or stroke - long term
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 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.**

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) *[149]* 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 *[149]*. This is consistent with two more recent reviews.

Galyfos et al (2019) *[173]* found periprocedural risks of stroke, death and myocardial infaction were higher with endarterectomy compared to best medical therapy but ipsilateral stroke risk was lower (OR 0.46, CI 95%CI 0.36 to 0.60).

Barkat et al (2018)*[174]* also found higher periprocedural risk of death or stroke with either stenting or endarterectomy compared to medical therapy alone but lower risk of ipsilateral stroke for endarterectomy than medical therapy although the authors do note there are few large trials recruiting patients in the last 10 years and the long term conclusions favouring endarterectomy are less conclusive.

Medical therapy has improved since earlier trials in these reviews and recent series reporting the outcome of medical therapy alone suggest annual stroke rates associated with asymptomatic carotid stenosis are <1%/ year (Abbott 2009 *[160]*). 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 *[161]*). 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**	**Comparator** Medical therapy alone	**Intervention** 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 *[153]*; Fluri et al 2010 *[156]*)

Practical Info

Optimal medical management of atherosclerosis should be provided as outlined in this chapter. This includes cholesterol lowering

therapy (aiming for LDL<1.8mmol/L), anti-platelet therapy, blood pressure control and lifestyle modification including smoking cessation (if relevant).

Evidence To Decision

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 *[153]*; Fluri et al 2010 *[156]*). The perioperative stroke rate associated with extracranial/ intracranial bypass is substantial - 14.3% in the most recent trial (Powers et al 2011 *[153]*). 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) *[156]* 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) *[153]* 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**	**Comparator** Medical therapy alone	**Intervention** 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

Outcome Timeframe	**Study results and measurements**	**Comparator** Medical therapy alone	**Intervention** Extracranial-intracranial arterial bypass surgery	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 stroke 30 days 9 Critical	n/a Based on data from 195 patients in 1 studies. (Randomized controlled) Follow up: 2 years.	20 per 1000	144 per 1000 Difference: **124 more** per 1000	**Moderate** Due to serious risk of bias, Due to very serious risk of bias, Upgraded due to Large magnitude of effect [4]	Extracranial-intracranial arterial bypass surgery 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 *[180]*). 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 *[180]*). 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 *[181]*; Beletsky et al 2003 *[182]*), while others report a much lower rate at 3% (Kennedy et al 2012 *[183]*). 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 *[178]*), and by the brain imaging results suggesting an embolic pattern (Benninger et al 2004 *[179]*). 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 *[176]*)

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.

Evidence To Decision

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 *[176]*; Markus et al 2019 *[184]*). Further, the rate of recanalisation is similar between antiplatelets and anticoagulants (Markus et al 2019 *[184]*).

Certainty of the Evidence — Moderate

The quality of evidence is moderate. There is a single randomised controlled trial (CADISS 2015 *[176]*). In addition, there are several meta-analyses of observational and largely low-quality studies (Sarikaya et al 2013 *[177]*).

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 *[176]*). 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*[184]*). There was no difference in residual narrowing between treatments between baseline and 3 months (Markus et al 2019*[184]*).

A prior meta-analysis (Sarikaya et al 2013 *[177]*) 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**	**Comparator** Antiplatelet	**Intervention** Anticoagulant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Stroke or death 3 months 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 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 9 Critical	Odds Ratio Based on data from 250 patients in 1 studies. (Randomized controlled) Follow up: 3 months.	0 per 1000	0 per 1000 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 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 Difference: **16 fewer** per 1000 (CI 95% 24 fewer — 70 more)	**Moderate** Due to only a single study, small patient number, incomplete blinding, and heterogeneity of patients studied. [4]	This RCT provides evidence that anticoagulants are not significantly superior to antiplatelets in the secondary prevention of stroke following cervical dissection.
Major bleeding 8 Critical	Odds Ratio Based on data from 250 patients in 1 studies.	0 per 1000	8 per 1000	**Moderate** Due to only a single study, small patient number,	This RCT found a higher number of major bleeding episodes per 1000 in the anticoagulation compared

Outcome Timeframe	**Study results and measurements**	**Comparator** Antiplatelet	**Intervention** Anticoagulant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
	(Randomized controlled) Follow up: 3 months.	Difference: **8 more** per 1000 CI 95%		incomplete blinding, and heterogeneity of patients studied [5]	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 *[189]*). 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 *[190]*). The overall risk of recurrence of any thrombotic event after a CVST is around 6.5% (Saposnik et al 2011 *[190]*). Approximately 3% to 15% of patients die in the acute phase of the disorder (Saposnik et al 2011 *[190]*). 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 *[188]*).

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 *[185]*; Misra et al 2012 *[186]*; Afshari et al 2015 *[187]*)

Important note May 2021: This recommendation was drafted prior to the COVID-19 pandemic and vaccine related complications. Please refer to the practical information for information related to COVID-19 vaccines.

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 *[191]*; Einhaupl et al 2010 *[192]*).

ADVICE RELATED TO COVID-19 VACCINES

A rare syndrome of immune-mediated thrombosis and thrombocytopenia has been reported after adenovirus-vector COVID-19 vaccination (AstraZeneca and Johnson&Johnson/Janssen vaccines). The commonest neurological presentation is with cerebral venous sinus thrombosis, often with associated intracerebral haemorrhage. Cases are reported between days 4-30 post-vaccine, maximally day 6-10. All reported cases included thrombosis, varying levels of thrombocytopenia (usually less than $150x10^9$/L but occasionally between 150-200), positive D-dimer (usually >5-fold elevation) and (almost always) the presence of pathogenic anti-Platelet Factor 4 platelet activating antibodies on functional testing.

The syndrome bears similarity to heparin induced thrombocytopenia (HIT), in particular the rare entity ‘spontaneous auto-immune HIT’ but with a distinct profile on immunological and functional testing of platelets. This syndrome currently has several labels: “VIPIT”: vaccine induced prothrombotic immune thrombocytopenia; “VATT”: vaccine associated thrombosis and thrombocytopenia; “TTS”: thrombosis with thrombocytopenia syndrome and “VITT”: vaccine induced immune thrombotic thrombocytopenia.

If cerebral venous sinus thrombosis occurs after the COVID-19 vaccine, then advice must be sought from local Haematologists to treat as per the most current guidelines since the situation continues to evolve. The main principles of treatment currently are therapeutic anticoagulation with a NON-heparin agent as per local HIT protocols (e.g. argatroban, fondaparinux, apixaban, rivaroxaban and dabigatran), IVIG 1-2g/kg in 2 doses and avoidance of platelet transfusion. High-dose corticosteroids and plasma exchange are potential second-line treatments.

Advice is currently that previous stroke or TIA does NOT increase the risk of complications following the astrazeneca vaccine.

For more information please see:
https://www.health.gov.au/news/joint-statement-from-atagi-and-thanz-on-thrombosis-with-thrombocytopenia-syndrome-tts-and-the-use-of-covid-19-vaccine-astrazeneca

Other references:
https://www.thanz.org.au/news/vitt-multidisciplinary-guideline-for-doctors
https://www.thanz.org.au/documents/item/577
https://b-s-h.org.uk/about-us/news/covid-19-updates/
https://b-s-h.org.uk/media/19590/guidance-version-17-on-mngmt-of-vitt-20210420.pdf
https://www.tga.gov.au/alert/astrazeneca-chadox1-s-covid-19-vaccine-3

Evidence To Decision

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 *[185]*).

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 *[186]*; Afshari et al 2015 *[187]*).

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) *[185]* 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) *[186]* 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) *[187]* 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**	**Comparator** Control	**Intervention** 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 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 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 9 Critical	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 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
Symptomatic intracerebral haemorrhage (new or increased) 3 months 8 Critical	n/a Based on data from 79 patients in 2 studies. [5] (Randomized controlled) Follow up: 3 months.			**Low** 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 3 months 7 Critical	Relative risk 2.9 (CI 95% 0.12 — 68.5) Based on data from 79 patients in 2 studies. [7] (Randomized controlled) Follow up: 3 months.	0 per 1000	25 per 1000 Difference: **0 fewer** per 1000 (CI 95% 0 fewer — 0 fewer)	**Low** Due to very serious imprecision [8]	anticoagulation (heparin) may increase any severe haemorrhage

1. Systematic review [185] with included studies: CVST Group 1999, Einhaupl 1991. **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 [185] with included studies: CVST Group 1999, Einhaupl 1991. **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 [185] with included studies: CVST Group 1999, Einhaupl 1991. **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 [185] with included studies: CVST Group 1999, Einhaupl 1991. **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) *[187]* was powered to detect statistical significance whereas Misra et al (2012) *[186]* was not.

Outcome Timeframe	**Study results and measurements**	**Comparator** Unfractionated heparin	**Intervention** Low molecular weight heparin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death During hospital stay	n/a Based on data from 52 patients in 1 studies. [1] (Randomized controlled)	56 per 1000	38 per 1000 Difference: **18 fewer** per 1000 CI 95%	**Low** 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 30 days to 3 months 5 Important	Relative risk Based on data from 110 patients in 2 studies. [3] Follow up: 30 days to 3 months.	100 per 1000	67 per 1000 CI 95%	**Moderate** 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 1 month to 3 months 6 Important	Relative risk Based on data from 66 patients in 1 studies. Follow up: 3 months.	125 per 1000	0 per 1000 Difference: **125 fewer** per 1000 (CI 95% 0 fewer — 0 fewer)	**Low** 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	The choice of anticoagulant probably has little or no difference to the incidence of adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Unfractionated heparin	**Intervention** Low molecular weight heparin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
				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]	

1. Primary study[187], [186]. **Baseline/comparator:** Control arm of reference used for intervention[186], [187].
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: [187], [186]. **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 *[193]*) 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.

Info Box

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 *[197]*) 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 *[196]*) 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 *[210]*; Sagris et al 2019 *[209]*)

Evidence To Decision

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*[210]*; Sagris et al 2019*[209]*). 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)*[210]* 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)*[209]* 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).

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**	**Comparator** Antiplatelet therapy	**Intervention** Anticoagulation therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Ischaemic stroke 1-5 years 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 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 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 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 *[198]*, Saver et al 2018 *[200]*).

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.

Evidence To Decision

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 *[198]*). 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

Resource considerations

There is evidence from modelling studies conducted for UK and USA healthcare perspectives that PFO closure becomes cost-effective at between two to four years after the procedure compared to management with antithrombotic medications (Picket et al. 2014 *[211]*, Hildick-Smith et al. 2019 *[205]*, Tirschwell et al. 2018 *[206]*, Picket et al. 2018*[212]*, Volpi et al 2019 *[208]*). In the longer term, there is evidence that PFO closure is potentially more effective and cost saving compared to management with antithrombotic medications (Leppert et al 2018 *[207]*).

Rationale

Endovascular closure of PFO has been a controversial field. With the publication of the GORE-REDUCE(*[203]*), CLOSE(*[201]*) and DEFENSE-PFO (*[204]*) trials, and long term follow-up of the RESPECT(*[202]*) 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 *[195]*. 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(*[203]*), CLOSE(*[201]*) and DEFENSE-PFO (*[204]*) trials, and long term follow-up of the RESPECT(*[202]*) 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 *[195]*. 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**	**Comparator** Medical therapy	**Intervention** 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 [195] . **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 [195] . **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 [195] . **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 *[213]*). The effect of HRT on stroke and TIA risk is present in younger women and increases with age (Nudy et al 2019 *[216]*). HRT significantly increases the risk of VTE and PE (Boardman et al 2015 *[213]*).

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 *[213]*; Yang et al 2013 *[214]*; Marjoribanks et al 2012 *[215]*; Nudy et al 2019 *[216]*)

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.

Evidence To Decision

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 *[213]*). However, systematic reviews of between 10-31 studies (mostly primary prevention) found consistent increase in stroke of approximately 25-50% (Yang et al 2013 *[214]*; Marjoribanks et al 2012 *[215]*; Nudy et al 2019*[216]*).

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 *[213]*). 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 *[214]*; Marjoribanks et al 2012 *[215]*). 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 *[213]*). 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 *[214]*; Marjoribanks et al 2012 *[215]*; Nudy et al 2019 *[216]*).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hormone therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Secondary stroke if pre-existing CVD 8 Critical	Relative risk 1.09 (CI 95% 0.89 — 1.33) Based on data from 5,172 patients in 5 studies. (Randomized controlled) Follow up: Varied - 2 to 4.1 years.	65 per 1000	71 per 1000 Difference: 6 more per 1000 (CI 95% 7 fewer — 21 more)	High 1	hormone therapy has little or no difference on secondary stroke
All-cause death 9 Critical	Relative risk 1.04 (CI 95% 0.87 — 1.24) Based on data from 5,445 patients in 7 studies. (Randomized controlled) Follow up: Varied - 0.5 to 4.1 years.	84 per 1000	87 per 1000 Difference: 3 more per 1000 (CI 95% 11 fewer — 20 more)	High 2	hormone therapy has little or no difference on all-cause death
Stroke, TIA and systemic embolism (all populations) 8 Critical	Odds Ratio 1.52 (CI 95% 1.38 — 1.67) Based on data from 36,844 patients in 18 studies. (Randomized controlled) Follow up: Average 4.13 years.	41 per 1000	61 per 1000 Difference: 20 more per 1000 (CI 95% 15 more — 26 more)	High 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 *[220]*). 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 *[217]*, Peragallo et al 2013 *[219]*). 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 *[217]*; Plu-Bureau 2013 *[218]*; Peragallo et al 2013 *[219]*; Li et al 2019 *[221]*)

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.

Evidence To Decision

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 *[217]* ; Plu-Bureau 2013 *[218]*; Peragallo et al 2013 *[219]* Li et al 2019 *[221]*) . 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) *[219]* 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) *[218]* 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) *[217]* 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) *[221]* 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**	**Comparator** Control	**Intervention** 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 [219] . **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 72% of patients with stroke received risk factor modification advice (Stroke Foundation 2019 *[222]*). 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 focusing on each of the cardiovascular risk factors are available and these guidelines apply generically to the population including patients with 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.

Info Box

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.

Weak recommendation

New

DRAFT RECOMMENDATION AUGUST 2021
Interventions addressing secondary stroke risk factors may be used for all people with stroke and TIA. Such interventions should include multiple components including individual (support and counselling) and organisational approaches (regular reviews by relevant health care professionals) and include exercise training as a component. (Bridgwood et al 2020 *[225]*; Liljehult et al 2020 *[227]*; Wang et al 2019 *[233]*; Deijle et al 2017*[231]*).

Draft recommendation submitted to the NHMRC for consideration of approval.

Practical Info

Multimodal interventions commonly include education (written/verbal), taking a counselling approach, and includes supervised/ active exercise (aerobic or mixed aerobic/strengthening) as a component. Counselling should be supportive, non-judgemental and collaborative, where the clinician and patient enter into a mutual relationship to encourage the patient to undertake health behaviour change. Counselling includes (but is not limited to) identifying barriers, setting goals and priorities, creating action plans or strategies to change, and self-monitoring activities. It could include using approaches to behaviour change such as motivational interviewing, the health belief model or cognitive behaviour therapy.

The person's personal living circumstances should be taken into account, as the other people in their living environment can influence their undertaking of behaviour changes. If a person has aphasia, this should be taken into account when communicating and when deciding on the best way to present educational and counselling information.

It appears important to ensure any intervention is commenced early after hospital discharge (within first 6 months after stroke/TIA) and ensure organised processes occur (e.g. follow up visits by health professionals/teams).

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Several systematic reviews found small reductions in some risk factors (particularly lower blood pressure) with mostly multimodal interventions which included a focus on physical activity. No adverse reports were reported.

Certainty of the Evidence

Moderate

Overall certainty of evidence was low to moderate.

Preference and values

No substantial variability expected

We expect all people will want to prevent a future stroke. However, given the benefits of various lifestyle interventions are small, preferences and values of patients should be taken into consideration as there is likely to be some variation in following advice on specific risk factor modifications in some cases.

Resources and other considerations

Important issues, or potential issues not investigated

Implementation considerations

There is a clinical indicator collected in the National Stroke Audit regarding the provision of education for reducing lifestyle risk factors. Risk factors modification is also included in the Acute Stroke Clinical Care Standard.

No formal cost effectiveness studies have been identified.

Rationale

There is conflicting evidence for the effect of non-medical interventions to improve recurrent stroke risk factors. However, the most recent systematic review found that structured approaches targeting the organisation of services (such as education for health professionals, decision support tools and follow up pathways for patients to be reviewed) may be effective. The inclusion of exercise training also appears important for multimodal approaches to be effective, particularly for blood pressure lowering. We have therefore provided a weak recommendation for such interventions to be implemented.

Clinical Question/ PICO

Population: People recovering from stroke
Intervention: Educational or behavioural interventions for patients
Comparator: usual care

Summary

Bridgwood et al. (2018)*[225]* included 42 studies (n=33,849) and looked predominantly at organisational interventions (26 studies) but also reported on educational and behavioural interventions (16 studies) aimed at secondary stroke prevention and modifiable risk factor control. Educational and behavioral interventions (targeted at patients) had no effect on risk factors (BP, lipids, BMI, HbA1c targets, medication adherence or CVD events). Most studies were multifaceted and all of the interventions were based on education, counselling and goal setting types of interventions but it is difficult to unpack the most effective intervention components. No trials included supervised exercise training.

Another review by Liljehult et al. (2020)*[227]* included 29 trials of counselling or educational interventions. Pooling of 14 trials (n=2,222) found significant reduction of BP (-3.85mmHg, 95%CI -6.43 to -1.28). The effect was greatest in four trials (n=174) that included supervised exercise training (-9.83 mmHg, 95%CI -16.56 to -3.09).

Sakakibara et al. (2017) included 14 studies that looked at self-management interventions to improve risk factor control. Multimodal interventions did not significantly change combined risk factors (SMD 0.06, 95%CI -0.02 to 0.14). However, in sensitivity analysis there was a very small improvement in risk factor control when four low-quality studies were removed (SMD 0.10, 95 %CI 0.02 to 0.17). Subgroup analyses also found interventions improved lifestyle behaviour risk factors (SMD 0.15, 95 %CI 0.04 to 0.25) due primarily to greater medication adherence (SMD 0.31, 95%CI 0.06 to 0.56; 5 trials, n=802). No other individual risk factor was found to be significantly improved.

Ahmadi et al (2020)*[226]* conducted a large RCT (n=2098) in which the intervention included a support program involving motivational counselling during 8 outpatient visits over 2 years. There was no difference in major vascular events (HR 0·92, 95%CI 0·75 to 1·14). Significantly more patients in the support program achieved secondary prevention targets at 1 year follow up (52% vs 42% for blood pressure, 62% vs 54% for LDL, 33% vs 19% for physical activity, and 51% vs 34% for smoking cessation).

Another study by Willeit et al (2020)*[229]* included 2149 patients with ischaemic stroke or high risk TIA. The intervention involved a 3 month follow-up appointment with a multidisciplinary team to assess risk factors and optimise management along with access to a web-based resource focusing on risk factor management, education and self-empowerment. At 12 month follow up significantly less major CVD events were found (5.4% vs 8.3%; HR 0.63, 95%CI 0.45 to 0.88, NNT = 35) and higher patient reported quality of life overall. The proportion of patients achieving target risk factor levels at 12 months did not differ significantly.

Outcome Timeframe	**Study results and measurements**	**Comparator** usual care	**Intervention** Educational or behavioural interventions for patients	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Blood pressure target achievement	Odds Ratio 0.74 (CI 95% 0.39 — 1.44) Based on data from 266 patients in 3 studies. [1]	385 per 1000	316 per 1000 Difference: 68 fewer per 1000 (CI 95% 189 fewer — 89 more)	Moderate	Educational or behavioural interventions for patients probably has little or no difference on blood pressure target achievement
Proporation of participants with secondary stroke	Odds Ratio 0.82 (CI 95% 0.37 — 1.84) Based on data from 4,333 patients in 4 studies. [2] (Randomized controlled)	21 per 1000	17 per 1000 Difference: 4 fewer per 1000 (CI 95% 13 fewer — 17 more)	Moderate	Educational or behavioural interventions for patients probably has little or no difference on proporation of participants with secondary stroke
Number of cardiovascular deaths	Odds Ratio 1.34 (CI 95% 0.3 — 6.07) Based on data from 386 patients in 1 studies. [3]	16 per 1000	21 per 1000 Difference: 5 more per 1000 (CI 95% 11 fewer — 74 more)	Low Due to serious imprecision [4]	Educational or behavioural interventions for patients may have little or no difference on number of cardiovascular deaths
Mean systolic blood pressure	Based on data from: 1,398 patients in 11 studies. [5]	Difference: MD 2.81 lower (CI 95% 7.02 lower — 1.39 higher)		Moderate	Educational or behavioural interventions for patients probably has little or no difference on mean systolic blood pressure
Mean diastolic blood pressure	Based on data from: 1,398 patients in 11 studies. [6]	Difference: MD 0.83 lower (CI 95% 2.8 lower — 1.13 higher)		Moderate	Educational or behavioural interventions for patients probably has little or no difference on mean diastolic blood pressure
Mean low density lipoprotein	Based on data from: 495 patients in 4 studies. [7]	Difference: MD 0.13 lower (CI 95% 0.28 lower — 0.02 higher)		Moderate	Educational or behavioural interventions for patients probably has little or no difference on mean low density lipoprotein
Mean HbA1c	Based on data from: 70 patients in 1 studies. [8]	Difference: MD 0.11 lower (CI 95% 0.39 lower — 0.17 higher)		Low	Educational or behavioural interventions for patients may have little or no difference on mean HbA1c
Mean BMI	Based on data from: 127 patients in 2 studies. [9]	Difference: MD 0.22 higher (CI 95% 0.85 lower — 1.29 higher)		Moderate	Educational or behavioural interventions for patients probably has little or no difference on mean BMI

1. Systematic review [225] with included studies: MacKenzie 2013, Adie 2010, Chiu 2008. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [225] with included studies: MacKenzie 2013, Kono 2013, MIST 2014, Peng 2014. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [225] with included studies: MIST 2014. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious.** Point estimates vary widely. **Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
5. Systematic review [225] with included studies: MIST 2014, O'Carroll 2011, Maasland 2007, Slark 2013, Chiu 2008, MacKenzie 2013, Mant 2016, Kono 2013, Chanruengvanich 2006, Adie 2010, Lowe 2007. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [225] with included studies: O'Carroll 2011, MIST 2014, Kono 2013, Chanruengvanich 2006, Mant 2016, Lowe 2007, MacKenzie 2013, Slark 2013, Chiu 2008, Adie 2010, Maasland 2007. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [225] with included studies: MIST 2014, Maasland 2007, Chiu 2008, Kono 2013. **Baseline/comparator:** Control arm of reference used for intervention.
8. Systematic review [225] with included studies: Kono 2013. **Baseline/comparator:** Control arm of reference used for intervention.
9. Systematic review [225] with included studies: Maasland 2007, Kono 2013. **Baseline/comparator:** Control arm of reference used for intervention.

Clinical Question/ PICO

Population: People recovering from stroke
Intervention: Organisational interventions
Comparator: usual care

Summary

Brigwood et al. (2018) included 42 studies (n=33,849) and looked predominantly at organisational interventions (26 studies) but also reported on educational and behavioural interventions (16 studies) aimed at interventions for secondary stroke prevention and modifiable risk factor control. Organisational interventions improve blood pressure control (OR 1.44, 95%CI 1.09 to 1.90; 13 trials, n=23,631; moderate quality evidence) but didn't significantly reduce mean blood pressure or other outcomes. Interventions included were similar in content with some including education for health professionals alone (e.g. decision tools for GPs).

Outcome Timeframe	**Study results and measurements**	**Comparator** usual care	**Intervention** Organisational interventions	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Blood pressure target achievement	Odds Ratio 0.7 (CI 95% 0.53 — 0.92) Based on data from 23,631 patients in 13 studies. [1]	391 per 1000	310 per 1000 Difference: 81 fewer per 1000 (CI 95% 137 fewer — 20 fewer)	Moderate	Organisational interventions probably improves blood pressure target achievement
Low density lipoprotein target achievement	Odds Ratio 0.73 (CI 95% 0.47 — 1.13) Based on data from 1,790 patients in 5 studies. [2]	340 per 1000	273 per 1000 Difference: 67 fewer per 1000 (CI 95% 145 fewer — 28 more)	Moderate	Organisational interventions probably has little or no difference on low density lipoprotein target achievement

Outcome Timeframe	**Study results and measurements**	**Comparator** usual care	**Intervention** Organisational interventions	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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]	175 per 1000	122 per 1000 Difference: 52 fewer per 1000 (CI 95% 128 fewer — 108 more)	**Moderate**	Organisational interventions probably has little or no difference on proportion of participants with secondary stroke or tia
Mean systolic blood pressure	Based on data from: 17,490 patients in 16 studies. [4]		Difference: MD 1.58 lower (CI 95% 4.66 lower — 1.51 higher)	**Moderate**	Organisational interventions probably has little or no difference on mean systolic blood pressure
Mean diastolic blood pressure	Based on data from: 17,178 patients in 14 studies. [5]		Difference: MD 0.91 lower (CI 95% 2.75 lower — 0.93 higher)	**Moderate**	Organisational interventions probably has little or no difference on mean diastolic blood pressure
Mean low density lipoprotein	Based on data from: 1,154 patients in 5 studies. [6]		Difference: MD 0.19 lower (CI 95% 0.3 lower — 0.09 lower)	**Moderate**	Organisational interventions may decrease mean low density lipoprotein slightly
Mean HbA1C	Based on data from: 554 patients in 4 studies. [7]		Difference: MD 0.2 lower (CI 95% 0.98 lower — 0.59 higher)	**Low**	Organisational interventions may have little or no difference on mean hba1c
Mean BMI	Based on data from: 1,089 patients in 5 studies. [8]		Difference: MD 0.47 lower (CI 95% 1.24 lower — 0.3 higher)	**Low**	Organisational interventions may have little or no difference on mean bmi

1. Systematic review [225] with included studies: Flemming 2013, McAlister 2014, Wang 2005, Nailed Stroke 2010, Johnston 2010, Allen 2009, Joubert 2009, Jönsson 2014, Brotons 2011, Pergola 2014, Hornnes 2011, Dregan 2014, Kronish 2014. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [225] with included studies: Nailed Stroke 2010, Flemming 2013, Kronish 2014, McAlister 2014, Jönsson 2014. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [225] with included studies: Kerry 2013, Wang 2005, Welin 2010, Allen 2002. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [225] with included studies: Ellis 2005, McAlister 2014, Brotons 2011, Jönsson 2014, Joubert 2009, Welin 2010, Mant 2016, Evans 2010, Flemming 2013, Kerry 2013, Hornnes 2011, Nailed Stroke 2010, Dregan 2014, Pergola 2014, McManus 2014, Hanley 2015. **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [225] with included studies: Kerry 2013, Evans 2010, Jönsson 2014, Joubert 2009, McManus 2014, Nailed Stroke 2010, Welin 2010, Mant 2016, Hornnes 2011, Ellis 2005, Hanley 2015, Brotons 2011, Pergola 2014, Dregan 2014. **Baseline/comparator:** Control arm of reference used for intervention.
6. Systematic review [225] with included studies: Nailed Stroke 2010, Brotons 2011, Flemming 2013, McAlister 2014, Evans 2010. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [225] with included studies: Jönsson 2014, Ellis 2005, Flemming 2013, Evans 2010. **Baseline/**

comparator: Control arm of reference used for intervention.
8. Systematic review [225] with included studies: Flemming 2013, McAlister 2014, Joubert 2009, Jönsson 2014, Brotons 2011. **Baseline/comparator:** Control arm of reference used for intervention.

Clinical Question/ PICO

Population: People recovery from stroke or TIA
Intervention: Physical activity interventions
Comparator: control

Summary

Wang et al (2019)*[233]* included 20 studies (n=1031) of exercise interventions to reduce secondary vascular risk and recurrent stroke. Exercise interventions (resulted in significant reductions in systolic blood pressure (MD -4.30 mmHg, 95%CI -6.77 to -1.83) and diastolic blood pressure (MD -2.58 mmHg, 95%CI -4.7 to -0.46) compared with control at the end of the intervention (6 weeks to 6 months duration). Reduction in BP was most evident when commenced within 6 months of initial event (-8.46 mmHg early vs -2.33 mm Hg), and in studies including an educational component (-7.81 mm Hg vs -2.78 mm Hg). Exercise was also associated with reductions in total cholesterol (-0.27 mmol/L, 95% CI -0.54 to 0.00), but not fasting glucose or body mass index. Only one underpowered trial reported reductions in secondary vascular events with exercise.

Liljehult et al (2020)*[227]* included 29 studies of counselling or educational interventions. Eight studies included counselling on physical activity with four of these studies (n=174) including supervised exercise (aerobic and strength training) which was found to have the strongest effect on lowering blood pressure (-9.83 mmHg, 95%CI -16.56 to -3.09; low-quality evidence).

Deijle et al (2017)*[231]* included 22 studies (n=2574) of lifestyle interventions with or without exercise. Meta-analysis of 10 studies (n=650) found a significant reduction in systolic blood pressure (MD -3.6 mmHg; 95%CI, -5.6 to -1.6). No difference was found on cardiovascular events, mortality, diastolic blood pressure, or cholesterol. Trials with fitness training were found to be an important component of BP reduction. Trials with longer interventions (>4 months) and interventions that used >3 behavior change techniques were more effective in reducing systolic blood pressure.

D'Isabella et al (2017)*[232]* included 18 studies (n=930). Based on 14 studies (n=720) exercise interventions significantly reduced systolic blood pressure (MD -5.32 mmHg, 95%CI -9.46 to -1.18), fasting glucose (MD -0.11 mmol/L, 95%CI -0.17 to -0.06), and fasting insulin (MD -17.14 mmol/L, 95%CI -32.90 to -1.38), and increased high-density lipoprotein cholesterol (MD 0.10 mmol/L, 95%CI 0.03 to 0.18).

Hendrickx et al (2020)*[234]* included 11 studies and reported moderate quality evidence that general lifestyle interventions did not significantly increase self-reported physical activity compared to controls. However, physical activity may increase when the intervention specifically focuses on physical activity as part of the intervention (low-quality evidence; three studies).

Brouwer et al (2019)*[230]* included nine studies (11 comparisons) of aerobic training on risk factors. A significant reduction in systolic blood pressure (-3.59 mmHg, 95%CI -6.14 to -1.05) and fasting glucose (-0.12 mmol/l, 95%CI -0.23 to -0.02) was found.

Overall there is consistency from multiple systematic reviews on the beneficial effects of physical activity (especially when aerobic training is included) on vascular risk factors. However, there is less evidence to confirm this subsequently reduces further strokes and the long-term effects after the end of interventions is less clear.

Outcome Timeframe	**Study results and measurements**	**Comparator** control	**Intervention** Physical activity	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Systolic blood pressure End of	Measured by: SBP Lower better Based on data from: 606 patients in 12 studies. [1]	Difference: **MD 4.3 lower** (CI 95% 6.77 lower — 1.83 lower)		**Moderate** Due to serious risk of bias [2]	Physical activity probably decreases systolic blood pressure

Outcome Timeframe	**Study results and measurements**	**Comparator** control	**Intervention** Physical activity	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
intervention 7 Critical	(Randomized controlled) Follow up: End of intervention.				
Diastolic blood pressure End of intervention 7 Critical	Measured by: DBP Lower better Based on data from: 606 patients in 12 studies. [3] (Randomized controlled) Follow up: End of intervention.	Difference: **MD 3.12 lower** (CI 95% 4.89 lower — 1.34 lower)		**Low** Due to serious risk of bias, Due to serious inconsistency, Due to serious publication bias [4]	Physical activity may decrease diastolic blood pressure
LDL cholesterol End of intervention 7 Critical	Measured by: LDL-C Lower better Based on data from: 303 patients in 7 studies. [5] (Randomized controlled) Follow up: End of intervention.	Difference: **MD 0.28 lower** (CI 95% 0.63 lower — 0.07 higher)		**Very low** Due to serious inconsistency, Serious risk of bias [6]	We are uncertain whether physical activity increases or decreases LDL cholesterol. Subgroup analysis reported LDL-C was lower among interventions involving education
Fasting blood glucose End of intervention 7 Critical	Measured by: Blood glucose Lower better Based on data from: 364 patients in 7 studies. [7] (Randomized controlled) Follow up: End of intervention.	Difference: **MD 0.14 lower** (CI 95% 0.29 lower — 0.01 higher)		**Moderate** [8]	Physical activity probably has little or no difference on fasting blood glucose
BMI End of intervention 7 Critical	Measured by: BMI Lower better Based on data from: 446 patients in 8 studies. [9] (Randomized controlled) Follow up: End of intervention.	Difference: **MD 0 lower** (CI 95% 0.26 lower — 0.25 higher)		**Moderate** [10]	Physical activity probably has little or no difference on BMI

1. Systematic review [233] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: Serious. Inconsistency: No serious.** The magnitude of statistical heterogeneity was moderate, with I^2:33%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. Systematic review [233] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: Serious. Inconsistency: Serious.** The magnitude of statistical heterogeneity was moderate, with I^2:68%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: Serious.** Asymmetrical funnel plot.
5. Systematic review [233] . **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: Serious. Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:85%.. **Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: Serious.** Asymmetrical funnel plot.
7. Systematic review [233] . **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: Serious. Inconsistency: No serious.** The magnitude of statistical heterogeneity was high, with I^2:42 %.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** Asymmetrical funnel plot.
9. Systematic review [233] . **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: Serious. Inconsistency: No serious.** The magnitude of statistical heterogeneity was high, with I^2:42 %.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** Asymmetrical funnel plot.

Diet

Poor quality diet is a major risk factor for first, and presumably also recurrent stroke. People who report eating a healthy diet (measured using the modified Alternate Healthy Eating index) are 40% less likely to have a first stroke than those with the lowest quality diet (O'Donnell et al 2016 *[241]*). 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 *[224]*). 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 intake lowers blood pressure (Huang et al 2020 *[242]*), but the direct effect of reducing sodium intake on recurrent stroke incidence is yet to be determined (English et al 2021 *[235]*). A meta-analysis of 123 cohort studies found that risk of first stroke was reduced with higher intakes of fruit, vegetables and fish and lower intakes of red meat, processed meats and sugar sweetened beverages (Bechtold et al 2019 *[243]*). 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 *[236]*). There is evidence that a Mediterranean-style diet may reduce stroke risk in people with pre-exisiting cardiovascular disease (Estruch et al 2018 *[244]*, English et al 2021 *[235]*, Rees et al 2019 *[240]*).

Consensus recommendation

New

DRAFT AUGUST 2021

All patients with stroke or TIA should be supported to follow a Mediterranean or similar style diet (high intake of plant-based foods such as fruit, vegetables, whole grain cereals, legumes and nuts, moderate intake of low fat dairy products, and low intake of processed and red meat and sugary foods, as well as olive oil as the main added dietary fat) to reduce the risk of recurrent stroke. (English et al 2021) *[235]*

Current recommendation has completed public consultation and has been submitted to NHMRC for consideration of approval.

Practical Info

Changing dietary patterns can be difficult and people with stroke may require ongoing expert support (from an Accredited Practising Dietitian) to achieve this. This may include discussing the evidence around the impact that a Mediterranean-style diet may have on reducing stroke risk in people with pre-existing cardiovascular disease, discussing what a Mediterranean diet consists of, as well as discussing the risks resulting from a diet high in sugar sweetened beverages, red meat and processed meats. It may also involve determining the person's cooking skills and literacy, for example, whether they are able to follow a recipe, as well as their dependence on other people to do the grocery shopping and cooking. A person's religious beliefs may also impact their ability to make dietary changes.

If a person has aphasia, this should be taken into account when communicating and when deciding on the best way to present educational and counselling information.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Trials and large cohort studies have found certain diets such as a Mediterranean style or DASH (Dietary Approaches to Stop Hypertension) style diets can modestly reduce stroke risk factors and are likely to reduce cardiovascular disease events. Little or no adverse events are reported.

Certainty of the Evidence

Moderate

Moderate. This evidence is taken from indirect comparisons of people at risk of stroke and as such has been downgraded. Much of the evidence is from large observational studies which have been upgraded due to large effect sizes.

Preference and values

Substantial variability is expected or uncertain

Changing dietary patterns can be difficult for some people due to personal and cultural values which will need to be

considered.

Resources and other considerations Factor not considered

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.

Rationale

There is evidence from primary-prevention trials that certain diets reduce the risk of stroke without harms. Such diets include Mediterranean or DASH (Dietary Approaches to Stop Hypertension) style diets. The Mediterranean diet is characterised by high intake of plant-based foods such as fruit, vegetables, whole grain cereals, legumes and nuts and low intake of processed and red meat, and sugary foods, as well as olive oil as the main added dietary fat. The DASH diet is similar but includes moderate low fat dairy and low salt intakes. Such dietary requirements should consider relevant national guidance such as the Australian Dietary Guidelines (NHMRC 2013 *[236]*) or the Eating and Activity Guidelines for New Zealand Adults (Ministry of Health 2020 *[258]*) While there is currently limited direct evidence of dietary interventions reducing recurrent stroke rates in people with first stroke, such diets are known to reduce stroke risk factors, such as blood pressure and cholesterol, known to be linked to cardiovascular events. However until further direct trial evidence is available specific to secondary stroke prevention we have provided a consensus-based recommendation.

Clinical Question/ PICO

Population: People recovery from stroke or TIA
Intervention: Diet related interventions
Comparator: control

Summary

English et al (2020)*[235]* conducted an overarching review of existing reviews of dietary interventions to prevent stroke. There was no direct trial evidence for secondary stroke prevention and the studies included relate to primary prevention in people at risk of stroke. The authors found:

- Mediterranean-style diet appears to reduce the risk of stroke by up to 40% (one RCT, n=7447; five cohort studies, n=79,287; moderate certainty evidence)
- A diet high in fruit and vegetables is likely to reduce risk of stroke by about 15% (123 cohort studies, low certainty evidence)
- DASH style diet compared to low-fat diet reduces the risk of stroke or risk factors: decreases systolic blood pressure 5.05mm Hg (95%CI -7.08 to -3.03; 67 studies, n=17,230; low certainty evidence)
- Salt reduction can lead to reductions in systolic blood pressure ~5mm Hg (one cluster RCT, n=20996; and one meta-analysis of 133 RCTs, n=12,197; moderate certainty evidence). There was a dose-response relationship, per 50 mmol reduction in 24-h urinary sodium excretion: systolic: −1·10 mm Hg (95% CI −1·54 to −0·66), and diastolic: −0·33 mm Hg (95% CI −0·63 to −0·04). However, low salt (<2645 mg/day) may increase risk based on meta-analysis of mainly observational studies.
- Folic acid supplements alone or with low-dose B12 (<0.05mg/day) in areas without folate fortification reduces the risk of stroke by 15-20% (three meta-analysis involving 12-22 studies, n>47,500 each; moderate certainty evidence)
- There was no evidence of reduced stroke risk with many interventions including vitamin D supplements, vitamin B3 (niacin) supplements, omega-3 fatty acids, higher flavan-3-ol intake, and a low-fat diet. There are no consistent results (positive or negative) from intake of other food groups such as fish, red meat and nuts based on observational studies.
- Dietary advice from health professionals may lead to short-term improvements in dietary intake (44 RCTs, n=18,175) with individualised dietary counselling by an Accredited Practising Dietitian potentially being the most effective compared to advice from medical or nursing professionals (5 RCTs, n=912).

Outcome Timeframe	**Study results and measurements**	**Comparator** control	**Intervention** Diet related interventions	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Recurrent stroke 9 Critical	1	Mediterranean diet may reduce risk of stroke by up to 40%		Moderate	A Mediterranean diet pattern may reduce risk of stroke. Dietary supplements are not effective to reduce stroke.

1. Systematic review **Supporting references:** [235],

Info Box

Practice point

- **(To be deleted -see remarks below)** Patients with stroke or TIA should be advised to manage their dietary requirements in accordance with the Australian Dietary Guidelines. (NHMRC 2013 *[236]*)
- All patients with stroke should be referred to an Accredited Practising Dietitian who can provide individualised dietary advice.

Suggested change to incorporate first practice point into background text of new draft recommendation on diet.

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 *[245]*). Being physically active is an important factor in preventing and managing stroke and other cardiovascular diseases (Warburton et al 2006 *[247]*).

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 *[224]*). 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 *[224]*). 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 *[245]*). 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 *[246]*). See also Cardiorespiratory fitness section in the Rehabilitation chapter for additional stroke specific guidelines for physical activity (Billinger et al 2014 *[248]*).

Info Box

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 *[245]*) OR
- Physical Activity Recommendations for Older Australians (65 years and older) (Commonwealth of Australia 2005 *[246]*).

Evidence To Decision

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 *[224]*). 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 *[250]*). 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 *[249]*).

Info Box

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 *[249]*).

Smoking

Smoking is a major cause of stroke (Aldoori et al 1999 *[251]*). 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 *[224]*). Indigenous Australians are still more than twice as likely as non-Indigenous Australians to be current daily smokers (AIHW 2011 *[252]*). Tobacco dependence is a chronic condition that typically requires repeated cessation treatment and ongoing care (RACGP 2019 *[253]*) 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 2019 *[253]*).

Info Box

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 2019 *[253]*)

Evidence To Decision

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.

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 *[224]*). High alcohol consumption (>2-4 standard drinks per day) increases the risk of stroke based on observational studies (Larsson et al 2016 *[256]*; Zhang et al 2014 *[257]*; Ronskley et al 2011 *[254]*). Light intake of alcohol (<2 standard drinks) may be protective against ischaemic stroke events (Larsson et al 2016 *[256]*; Zhang et al 2014 *[257]*). National guidelines recommend limiting alcohol consumption in health men and women to no more than 10 standard drinks per week and no more than four standard drinks on any one day to reduce the risk of harm (NHMRC 2020 *[255]*).

Info Box

Practice point
People with stroke or TIA should be advised to avoid excessive alcohol consumption (no more than 10 standard drinks per week and no more than 4 standard drinks on any one day) in line with the Australian Guidelines to Reduce Health Risks from Drinking Alcohol. (NHMRC 2020 *[255]*)

Evidence To Decision

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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