Stroke FOUNDATION

Clinical Guidelines for Stroke Management 2017

Chapter 3 of 8:
Acute medical and surgical management

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

Contact

Stroke Foundation
Melbourne, Victoria, Australia
guidelines@strokefoundation.org.au
+61396701000

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Disclaimer

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Summary of recommendations

Introduction

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Stroke unit care

Strong recommendation

All stroke patients should be admitted to hospital and be treated in a stroke unit with an interdisciplinary team. (Langhorne 2020 *[7]*)

Info Box

Practice points

- All stroke patients should be admitted directly to a stroke unit (preferably within three hours of stroke onset).
- For patients with suspected stroke presenting to non-stroke unit hospitals, transfer protocols should be developed and used to guide urgent transfers to the nearest stroke unit hospital.
- Where transfer is not feasible, smaller isolated hospitals should manage stroke services in a manner that adheres as closely as possible to the criteria for stroke unit care. Where possible, stroke patients should receive care in geographically discrete units.

Strong recommendation

All acute stroke services should implement standardised protocols to manage fever, glucose and swallowing difficulties in stroke patients. (Middleton et al. 2011 *[256]*)

Assessment for rehabilitation

Practice points

- Every stroke patient should have their rehabilitation needs assessed within 24–48 hours of admission to the stroke unit by members of the interdisciplinary team, using the Assessment for Rehabilitation Tool (Australian Stroke Coalition Working Group 2012 *[24]*).
- Any stroke patient with identified rehabilitation needs should be referred to a rehabilitation service.
- Rehabilitation service providers should document whether a stroke patient has rehabilitation needs and whether appropriate rehabilitation services are available to meet these needs.

Palliative care

Strong recommendation

Stroke patients and their families/carers should have access to specialist palliative care teams as needed and receive care consistent with the principles and philosophies of palliative care. (Gade et al. 2008 *[30]*)

Practice statement

Consensus-based recommendations

- For patients with severe stroke who are deteriorating, a considered assessment of prognosis or imminent death should be made.
- A pathway for stroke palliative care can be used to support stroke patients and their families/carers and improve care for people dying after stroke.

Reperfusion therapy

Thrombolysis

Strong recommendation

For patients with potentially disabling ischaemic stroke within 4.5 hours of onset who meet specific eligibility criteria, intravenous thrombolysis should be administered as early as possible after stroke onset (Wardlaw et al. 2014 *[39]*; Emberson et al. 2014 *[40]*)

Strong recommendation

For patients with potentially disabling ischaemic stroke due to large vessel occlusion who meet specific eligibility criteria, intravenous tenecteplase (0.25mg/kg, maximum of 25mg) or alteplase (0.9mg/kg, maximum of 90mg) should be administered up to 4.5 hours after the time the patient was last known to be well. (Parsons et al 2012 *[57]*, Campbell et al 2018 *[55]*)

Weak recommendation

For patients with potentially disabling ischaemic stroke without large vessel occlusion who meet specific clinical and brain imaging eligibility criteria, tenecteplase may be used as an alternative to alteplase within 4.5 hours of onset. (Huang et al 2016 *[59]*)

Strong recommendation

When using intravenous alteplase, a dose of 0.9 mg/kg, maximum of 90 mg should be administered. (Wardlaw et al. 2014 *[39]*; Emberson et al. 2014 *[40]* Anderson et al. 2016 *[42]*)

Strong recommendation

For patients with potentially disabling ischaemic stroke who meet perfusion mismatch criteria in addition to standard clinical criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) should be administered up to 9 hours after the time the patient was last known to be well, or from the midpoint of sleep for patients who wake with stroke symptoms, unless immediate endovascular thrombectomy is planned. (Ma et al 2019 *[64]*, Campbell et al 2019 *[58]*)

Weak recommendation

For patients with potentially disabling ischaemic stroke of unknown onset time who meet MRI FLAIR-diffusion mismatch criteria in addition to standard clinical criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) may be administered (Thomalla et al 2019 *[61]*).

Info Box

Practice points

Thrombolysis should be undertaken in a setting with appropriate infrastructure, facilities and network support (e.g. via telemedicine) including:

- access to an interdisciplinary acute care team with expert knowledge of stroke management, who are trained in delivery of thrombolysis and monitoring of patients receiving thrombolytic therapy
- a streamlined acute stroke assessment workflow (including ambulance pre-notification, code stroke team response and direct transport from triage to CT scan) to minimise treatment delays, and protocols available to guide medical, nursing and allied health acute phase management
- immediate access to imaging facilities and staff trained to interpret images
- routine data collected in a central register to allow monitoring, benchmarking and improvements of patient outcomes over time for those treated with reperfusion.

The patient and caregivers should be involved in the decision to give thrombolysis whenever possible and this discussion of risk and benefit documented in the medical record. However, as a time-critical emergency therapy, thrombolysis should not be delayed if the patient does not have the capacity to consent and there are no legal representatives present. Clinicians should follow local health department policies regarding consent for emergency treatment in patients who are unable to consent for themselves.

Neurointervention

Strong recommendation

For patients with ischaemic stroke caused by a large vessel occlusion in the internal carotid artery, proximal middle cerebral artery (M1 segment), or with tandem occlusion of both the cervical carotid and intracranial large arteries, endovascular thrombectomy should be undertaken when the procedure can be commenced within six hours of stroke onset. (Goyal et al. 2016 *[76]*)

Strong recommendation

For patients with ischaemic stroke caused by a large vessel occlusion in the internal carotid artery, proximal middle cerebral artery (M1 segment), or with tandem occlusion of both the cervical carotid and intracranial large arteries, endovascular thrombectomy should be undertaken when the procedure can be commenced between 6-24 hours after they were last known to be well if clinical and CT perfusion or MRI features indicate the presence of salvageable brain tissue. (Nogueira et al. 2017 [71], Albers et al. 2018 [72])

Strong recommendation In review

Eligible stroke patients should receive intravenous thrombolysis while concurrently arranging endovascular thrombectomy, with neither treatment delaying the other. (Goyal et al. 2016 *[76]*)

Strong recommendation

In selected stroke patients with occlusion of the basilar artery, endovascular thrombectomy should be undertaken. (Kumar et al. 2015 *[86]*)

Practice statement

Consensus-based recommendations

For patients with ischaemic stroke caused by occlusion in the M2 segment of the middle cerebral artery, endovascular thrombectomy may be considered based on individual patient and advanced imaging factors.

Endovascular thrombectomy should be performed by an experienced neurointerventionist with recognised training in the procedure (Conjoint Committee for Recognition of Training in Interventional Neuroradiology CCINR.org.au).

Dysphagia

Weak recommendation Updated evidence, no change in recommendation

People with acute stroke should have their swallowing screened, using a validated screening tool, by a trained healthcare professional. (Poorjavad et al 2014 *[113]*; Benfield et al 2020 *[134]*)

Practice statement Updated evidence, no change in recommendation

Consensus-based recommendation

People with acute stroke should have their swallowing screened within four hours of arrival at hospital and before being given any oral food, fluid or medication. (Bray et al. 2016 *[124]*; Ouyang et al 2020 *[137]*)

Weak recommendation Updated evidence, no change in recommendation

All stroke patients who have failed swallow screening or who deteriorate should have a comprehensive assessment of swallowing performed by a speech pathologist. (Kertscher et al. 2014 *[116]*; O'Horo et al. 2015 *[118]*)

Strong recommendation In review

For stroke survivors with swallowing difficulties, behavioural approaches such as swallowing exercises, environmental modifications, safe swallowing advice, and appropriate dietary modifications should be used early. (Geeganage et al. 2012 *[108]*)

Weak recommendation against In review

For stroke survivors with dysphagia, non-invasive brain stimulation should only be provided within a research framework. (Pisegna et al. 2016 *[110]*)

Weak recommendation against In review

For patients with stroke, acupuncture should not be used for treatment of dysphagia in routine practice other than as part of a research study. (Long et al. 2012 *[107]*)

Weak recommendation against In review

For stroke survivors with dysphagia, surface neuromuscular electrical stimulation should only be delivered by clinicians experienced in this intervention, and be applied according to published parameters in a research framework. (Chen et al. 2016 *[102]*)

Weak recommendation against In review

For stroke survivors with dysphagia, pharyngeal electrical stimulation is not routinely recommended. (Bath et al. 2016 *[104]*; Scutt et al. 2015 *[105]*)

Practice statement

Consensus-based recommendations

- Until a safe swallowing method is established for oral intake, patients with dysphagia should have their nutrition and hydration assessed and managed with early consideration of alternative non-oral routes.
- Patients with dysphagia on texture-modified diets and/or fluids should have their intake and tolerance to the modified diet monitored regularly due to the increased risk of malnutrition and dehydration.
- Patients with dysphagia should be offered regular therapy that includes skill and strength training in direct therapy (with food/fluids) and indirect motor therapy which capitalises on the principles of neural plasticity to improve swallowing skills.
- Patients with persistent weight loss, dehydration and/or recurrent chest infections should be urgently reviewed.
- All staff and carers involved in feeding patients should receive appropriate training in feeding and swallowing techniques.
- All staff should be appropriately trained in the maintenance of oral hygiene, including daily brushing of teeth and/or dentures and care of gums.

Please also refer to the topic Early Nutrition in Managing Complications.

Acute antithrombotic therapy

Strong recommendation

Patients with ischaemic stroke who are not receiving reperfusion therapy should receive antiplatelet therapy as soon as brain imaging has excluded haemorrhage. (Sandercock et al. 2014 *[164]*)

Strong recommendation against

Acute antiplatelet therapy should not be given within 24 hours of thrombolysis administration with the exception of patients who require stent implantation as part of acute stroke therapy. (Zinkstok et al. 2012 *[168]*)

Strong recommendation against

Routine use of anticoagulation in patients without cardioembolism (e.g. atrial fibrillation) following TIA/stroke is not recommended. (Sandercock et al. 2015 *[161]*; Whiteley et al. 2013 *[167]*)

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 *[171]*)

Weak recommendation New

Aspirin plus ticagrelor commenced within 24 hours may be used in the short term (first 30 days) in patients with minor ischaemic stroke or high-risk TIA to prevent stroke recurrence. (Johnston et al 2020 *[174]*)

Acute blood pressure lowering therapy

Weak recommendation against

Intensive blood pressure lowering in the acute phase of care to a target SBP of < 140 mmHg is not recommended for any patient with stroke. (Bath and Krishnan 2014 *[180]*)

Weak recommendation

In patients with intracerebral haemorrhage, blood pressure may be acutely reduced to a target systolic blood pressure of around 140 mmHg (but not substantially below). (Tsivgoulis et al. 2014 *[183]*; Qureshi et al. 2016 *[181]*)

Weak recommendation

Pre-existing antihypertensive medication may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 *[180]*)

Practice statement

Consensus-based recommendations

- All acute stroke patients 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.

Surgery for ischaemic stroke

Strong recommendation Updated evidence, no change in recommendation

Selected patients aged 60 years and under with malignant middle cerebral artery territory infarction should undergo urgent neurosurgical assessment for consideration of decompressive hemicraniectomy. When undertaken, hemicraniectomy should ideally be performed within 48 hours of stroke onset. (Cruz-Flores et al. 2012 *[194]*; Reinink et al. 2021 *[199]*)

Weak recommendation Updated evidence, no change in recommendation

Decompressive hemicraniectomy may be considered in highly selected stroke patients over the age of 60 years, after careful consideration of the pre-morbid functional status and patient preferences. (Reinink et al. 2021 *[199]*)

Practice statement

Consensus-based recommendation
For selected patients with large cerebellar infarction threatening brainstem and 4th ventricular compression, decompressive surgery should be offered.

Management of cerebral oedema

Weak recommendation against

Corticosteroids are not recommended for management of stroke patients with brain oedema and raised intracranial pressure. (Sandercock et al. 2011 *[195]*)

Practice statement

Consensus-based recommendation
In stroke patients with brain oedema and raised intracranial pressure, osmotherapy and hyperventilation can be trialled while a neurosurgical consultation is undertaken.

Intracerebral haemorrhage (ICH) management

Medical interventions

Weak recommendation

- For stroke patients with warfarin-related intracerebral haemorrhage, prothrombin complex concentrate should be urgently administered in preference to standard fresh frozen plasma to reverse coagulopathy. (Steiner et al. 2016 *[204]*)
- Intravenous vitamin K (5–10 mg) should be used in addition to prothrombin complex to reverse warfarin but is insufficient as a sole treatment. (Steiner et al. 2016 *[204]*)

Weak recommendation

Stroke patients with intracerebral haemorrhage related to direct oral anticoagulants should urgently receive a specific reversal agent where available. (Pollack et al. 2016 *[207]*; Connolly 2016 *[208]*)

Strong recommendation against

For stroke patients with intracerebral haemorrhage previously receiving antiplatelet therapy, platelet transfusion should not be administered. (Baharoglu et al. 2016 *[205]*)

Weak recommendation

For stroke patients with intracerebral haemorrhage, blood pressure may be acutely reduced to a target systolic blood pressure of around 140 mmHg (but not substantially below) (see Acute blood pressure lowering therapy).

Surgical interventions

Weak recommendation against In review

For stroke patients with supratentorial intracerebral haemorrhage (lobar, basal ganglia and/or thalamic locations), routine surgical evacuation is not recommended outside the context of research. (Mendelow et al. 2013 *[211]*; Gregson et al. 2012 *[214]*)

Weak recommendation against

For stroke patients with intraventricular haemorrhage, the use of intraventricular thrombolysis via external ventricular drain catheter is not recommended outside the context of research. (Gregson et al. 2012 *[214]*; Naff et al. 2011 *[215]*)

Practice statement

Consensus-based recommendations

- For selected patients with large (> 3 cm) cerebellar haemorrhage, decompressive surgery should be offered. For other infratentorial haemorrhages (< 3 cm cerebellar, brainstem) the value of surgical intervention is unclear.
- Ventricular drainage as treatment for hydrocephalus is reasonable, especially in patients with decreased level of consciousness.
- In previously independent patients with large supratentorial haemorrhage and deteriorating conscious state, haematoma evacuation may be a life-saving measure but consideration of the likely level of long term disability is required.

Oxygen therapy

Weak recommendation against Updated

For acute stroke and Transient Ischaemic Attack (TIA) patients who have SpO_2 >92% on room air, the routine use of supplemental oxygen is not recommended. (Chu et al 2018 *[220]*; Ding et al 2018 *[219]*)

Remark: We had added further details on oxygen thresholds and provided additional updated information in the Key information, Rationale and Practical info. No change to overall grade of recommendation.

Weak recommendation against

For acute ischaemic stroke patients, hyperbaric oxygen therapy is not recommended. (Bennett et al. 2014 *[218]*)

Practice statement Updated

Consensus-based recommendation

If supplemental oxygen is required (SpO_2 <93% on room air) a target oxygen saturation of 94-96% is reasonable, or 88-92% if the patient is at risk of hypercapnic respiratory failure. (Beasley et al 2015 *[223]*)

Remark: We have made a change to the threshold to consider oxygen therapy from <95% to <93% on room air. We have also added a target level if oxygen therapy is provided.

Neuroprotection

Practice statement

Consensus-based recommendation

For stroke patients, putative neuroprotective agents, including hypothermic cooling, are not recommended outside the context of research.

Practice statement

Consensus-based recommendation

Patients with acute ischaemic stroke who were receiving statins prior to admission can continue statin treatment.

Glycaemic therapy

Strong recommendation

All stroke patients should have their blood glucose level monitored for the first 72 hours following admission, and appropriate glycaemic therapy instituted to treat hyperglycaemia (glucose levels greater than 10 mmol/L), regardless of their diabetic status. (Middleton et al. 2011 *[256]*)

Strong recommendation against

For stroke patients, an intensive approach to the maintenance of tight glycaemic control (between 4.0–7.5 mmol/L) is not recommended. (Bellolio et al. 2014 *[249]*; Ntaios et al. 2014 *[247]*; Johnston et al. 2019 *[250]*)

Pyrexia management

Strong recommendation

All stroke patients should have their temperature monitored at least four times a day for 72 hours. (Middleton et al. 2011 *[256]*)

Weak recommendation

Stroke patients with fever ≥ 37.5 °C may be treated with paracetamol as an antipyretic therapy. (Chen et al. 2018 *[264]*; Middleton et al. 2011 *[256]*)

Acute stroke telehealth services

Strong recommendation New

DRAFT RECOMMENDATION FOR PUBLIC CONSULTATION JUNE 2021
In hospitals without onsite 24/7 stroke medical specialist availability, telestroke systems should be used to assist in patient assessment and decision making regarding acute thrombolytic therapy and possible transfer for endovascular therapy. This system should include the ability for stroke medical specialists to access remote brain imaging scans and preferably include the use of videoconferencing facilities or, if not possible, ensure the diagnosis and management discussions between local clinicians/family/patient occurs via a telephone consultation. (Lazarus et al 2020 *[265]*; Bladin et al 2020 *[268]*)

Head position

Weak recommendation New

DRAFT RECOMMENDATION FOR PUBLIC CONSULTATION JUNE 2021
Patients with acute stroke, while in bed and not receiving nasogastric feeding, may be managed in any position during the first 24 hours after hospital admission.

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

Australian Government
National Health and Medical Research Council

These guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council

(NHMRC) on 25 July 2017, with subsequent amendments approved on 22 November 2017, 9 July 2018 (updated recommendations for Neurointervention), 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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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

3.1 Does care on a stroke unit improve outcomes for people with stroke?

3.2 Do strategies to assist palliation and death improve outcomes for people with stroke and their family?

3.3 Does the administration of thrombolysis improve outcomes after acute ischemic stroke?

3.4 Does the use of neurointerventional treatments improve outcomes in people with stroke?

3.5 What is the optimal time to screen for dysphagia?

3.6 Does comprehensive swallow assessment improve outcomes for people who have failed a swallow screen?

3.7 Which interventions improve outcomes in stroke patients with dysphagia?

3.8 Does the use of antithrombotic therapy within first 48 hours improve outcomes in acute stroke?

3.9 Does the use of acute blood pressure lowering therapy improve outcomes for people with stroke?

3.10 Does the use of surgical interventions improve the outcomes for people with acute ischemic stroke?

3.11 What non-surgical interventions improve outcomes in acute stroke patients with cerebral oedema / raised intracranial pressure?

3.12 Does the administration of medical interventions improve outcomes after acute intracerebral haemorrhagic stroke?

3.13 Do surgical interventions improve outcomes after acute intracerebral haemorrhagic stroke?

3.14 Does oxygen therapy improve outcomes in stroke patients who are not hypoxic?

3.15 Does glycaemic therapy improve outcomes in stroke patients with hyperglycaemia?

3.16 Does the use of neuroprotective agents improve outcomes for people with acute stroke?

3.17 What interventions improve outcomes in stroke survivors with pyrexia?

3.18 Does the use of telehealth improve outcomes for patients with acute (or suspected) stroke?

Acute medical and surgical management - overview

This chapter covers medical and surgical management in the acute phase of care. Importantly though, several other critical components of very early assessment (including screening) and management should be routinely provided in addition to those discussed in this chapter. These include nutrition and hydration, incontinence, deep venous thrombosis or pulmonary embolism and early mobilisation.

A patient's rehabilitation needs and goals should be assessed by staff trained in rehabilitation within 24–48 hours of admission to the stroke unit using the Assessment for Rehabilitation Tool, and a tailored rehabilitation program commenced. (*See relevant sections in Rehabilitation for guidance on the timing of specific interventions).*

Stroke unit care

The organisation of hospital services to provide stroke unit care is the single most important recommendation for improving stroke management. While numbers of stroke units and stroke unit beds have increased between 2010 and 2019, the percentage of patients receiving stroke unit care has platued (67-69%) over the last 6 years (Stroke Foundation 2019 *[15]*). Therefore stroke unit care should be the highest priority for clinicians and administrators to consider.

Models of stroke unit care described in the literature include:

- acute stroke unit – acute unit in a discrete ward (usually discharged within seven days),
- comprehensive stroke unit – combined acute and rehabilitation unit in a discrete ward,
- stroke rehabilitation unit – a discrete rehabilitation unit for stroke patients who are transferred from acute care 1–2 weeks post stroke, and
- mixed rehabilitation ward – rehabilitation provided on a ward managing a general caseload.

The evidence for the benefits of stroke unit care is clearest for units that can provide several weeks of rehabilitation on a comprehensive stroke unit or stroke rehabilitation unit (Langhorne et al 2020 *[7]*). Services that can provide combined or highly integrated acute and rehabilitation care appear to deliver the best outcomes.

In Australia, most stroke units have a primary focus on acute care and early aspects of rehabilitation, with varying degrees of intensity and follow-up. There are 91 stroke units managing acute stroke patients (a small number of these also managing rehabilitation) but only 13 stroke rehabilitation units (units reporting co-location of stroke beds) as reported in the National Stroke Audits in 2019 *[28]* and 2020*[15]* .

The stroke units that have been shown to deliver highly effective stroke care share a number of characteristics, including:

- location in one ward;
- comprehensive assessments;
- a coordinated multidisciplinary team;
- early mobilisation and avoidance of bed-rest;
- staff with a special interest in the management of stroke, and access to ongoing professional education and training;
- clear communication, with regular team meetings to discuss management (including discharge planning) and other meetings as needed (e.g. family conferences), and
- active encouragement of stroke survivors and their carers/families to be involved in the rehabilitation process.

Several observational studies found that, excluding the effects of rt-PA treatment, very early (less than three hours after stroke onset) admission to a stroke unit for ischaemic stroke patients resulted in significantly better recovery at three months (National Institutes of Health Stroke Scale [NIHSS] 34.6% vs 15.2%; modified Rankin Score [mRS] 32.9% vs 16.8%) without any significant difference in mortality (Silvestrelli et al. 2006 *[16]*; Naganuma et al. 2009 *[18]*; Leon-Jimenez et al. 2014 *[17]*). Evidence derived from other studies for pre-hospital and thrombolysis services also show improved processes of care (door-to-brain imaging) and access to proven interventions (rt-PA, stroke unit care) with direct access to stroke unit hospitals.

All hospital services should clearly review existing stroke services in light of the recommendations below. For hospitals without existing stroke units, the Stroke Foundation National Stroke Services Framework *[14]* provides details of the minimum standards for acute stroke unit care: the recommended infrastructure, processes, workforce and monitoring which can be used to plan for stroke service improvement. For hospitals with existing stroke units, consideration should be given to reviewing the percentage of stroke patients actually admitted to the stroke unit to determine if there is adequate capacity (i.e. bed numbers). Clear protocols for bed allocation are needed for all stroke unit hospitals.

Strong recommendation

All stroke patients should be admitted to hospital and be treated in a stroke unit with an interdisciplinary team. (Langhorne 2020 *[7]*)

Practical Info

Further details about the definition of a stroke unit can be found in the National Stroke Services Framework *[14]* available from the Stroke Foundation website. Importantly, services must have patients cared for by the same staff on the one ward.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

There is substantial evidence of benefit from organised inpatient stroke unit care of stroke patients: 2 fewer deaths, 6 fewer being dependent, and 6 more living at home, with every 100 stroke patients (Langhorne 2020 *[7]*). The benefit applies to all types of stroke and the full range of stroke severity and patient age. Care must be delivered in the one area/ward as there is little benefit for mobile stroke teams. There is no evidence of harm from admitting stroke patients to a stroke unit (Langhorne 2020 *[7]*).

Certainty of the Evidence — Moderate

The overall quality of evidence was reported as moderate for most outcomes (Langhorne 2020 *[7]*). However, this was primarily due to potential performance bias (patient and staff aware of treatment) which is very difficult to control. Sensitivity analysis of only high quality trials revealed effects remained robust and long term outcomes favoured stroke unit care, with participants often forgetting details of hospital care, thus limiting bias. It was the view of the expert working group that it is unlikely these issues significantly change the high certainty of effects.

Preference and values — No substantial variability expected

There appears to be no significant impact of patient preference and values on provision of organised inpatient stroke unit care.

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

<u>Resources considerations</u>

There is evidence from several studies in an Australian settings that stroke units are cost-effective compared to other ward care. In an observational study conducted in Australia (Zhai et al. 2017 *[21]*), the cost effectiveness of stroke units compared to conventional ward care was assessed using a historical control design (n=103 in the control period; n=186 in the intervention period). Only hospitalisation costs were included in this analysis (cost reference year not reported). Compared to conventional ward care, treatment in a stroke unit resulted in shorter length of stay (4.6 days in the intervention period and 9.7 days in control period), a trends towards improved morbidity and mortality at 90 days after stroke, and lower cost of admission ($AU 6061 in the intervention period and $AU 6382 in the control period). Two other economic evaluations of stroke unit care have been previously conducted in an Australian setting using population-based stroke data from 1997–1999. In the first 28 weeks after stroke, stroke unit care was found to be cost-effective when compared to care on a general ward, costing an additional AU$16,372 per severe complication avoided (cost reference year 1998) (Moodie et al. 2006 *[11]*). Over a lifetime, stroke unit care was found to cost an additional AU$1,288 per disability adjusted life year avoided when compared to care provided on a general ward (cost reference year 1997) (Mihalopoulos et al. 2005 *[169]*).

In a systematic review of three studies conducted in Europe, no significant differences in costs between stroke units and general wards were found (Brady et al. 2005 *[19]*). There is also some more recent evidence from New Zealand and the United Kingdom that stroke unit care is either cost-saving or cost-effective per QALY gained over a lifetime compared to standard care (Hunter et al. 2013 *[12]*; Te Ao et al. 2012 *[13]*). For patients provided thrombolysis, management in a stroke unit care may be as effective as management in an intensive care unit and cost saving (Alexandrov et al. 2016 *[22]*).

<u>Implementation considerations</u>

The Australian National Acute Stroke Services Framework clearly defines the services, infrastructure and staff found in a stroke unit (Stroke Foundation 2019 *[14]*). There are clinical indicators collected in the National Stroke Audit to determine both the number of patients who receive care on a stroke unit during their acute admission and the number of patients who spend at least 90% of their acute admission on a stroke unit. Both of these clinical indicators are included in the Acute Stroke Clinical Care Standard. There are also organisational indicators collected on whether hospitals provide specialist stroke unit care and whether patients with stroke are most likely to be admitted to an acute stroke unit first. Further organisational indicators are collected on the presence of co-located stroke beds and dedicated multidisciplinary team members who have a special interest in stroke.

Rationale

Stroke patients who receive organised inpatient care in a stroke unit are more likely to be alive, independent and living at home one year after the stroke, based on the 2020 Cochrane review which included 29 trials and 5902 patients (Langhorne 2020 *[7]*). Stroke unit care must comprise at least four minimum criteria as outlined in the National Stroke Services Framework. That is, care delivered

on the one ward by an interdisciplinary team who meet at least once a week to plan patient care and who also have professional development specific to stroke.

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Organised stroke unit care
Comparator: Alternative services (less organised care)

Summary

A Cochrane review conducted by the Stroke Unit Trialists' Collaboration (2020) *[7]* compared organised stroke unit care to alternative services. The review included 29 RCTs with 5902 participants. Organised stroke unit care was defined as focused care for stroke patients by a multidisciplinary team specialising in stroke management. This included:

- Stroke wards where care was given in a discrete ward caring exclusively for stroke patients.
- Mixed rehabilitation wards with multidisciplinary teams and specialist nursing staff in a ward that does not care exclusively for stroke patients.
- Mobile stroke teams that provide care in a variety of settings

Overall, organised stroke unit care significantly reduced overall poor outcome (OR 0.77, 95% CI 0.69 to 0.87; moderate quality evidence), mortality (OR 0.76, 95% CI 0.66 to 0.88; moderate quality evidence), and significantly reduced the odds of death or institutionalisation (OR OR 0.76, 95% CI 0.67 to 0.85; moderate quality evidence) and death or dependency (OR 0.75, 95% CI 0.66 to 0.85; moderate quality evidence) with stroke unit care compared to conventional care. Absolute risk reduction found two more people survived, 6 more living at home or living independently per 100 patients.

Network meta-analysis comparing different kinds of stroke units (general ward as comparator) reported the odds of a poor outcome were: stroke ward (OR 0.74, 95% CI 0.62 to 0.89, moderate-quality evidence); mobile stroke team (OR 0.88, 95% CI 0.58 to 1.34, low-quality evidence); mixed rehabilitation ward (OR 0.70, 95% CI 0.52 to 0.95, low-quality evidence). This is based on 20 trials (4127 participants) comparing organised (stroke unit) care with a general ward, six trials (982 participants) compared different forms of organised (stroke unit) care, and three trials (793 participants) incorporated more than one comparison.

Overall quality for main results was conservatively downgraded in this update to 'moderate' primarily due to lack of blinding of patients and staff (performance bias). The authors acknowledged that blinding was very difficult with such interventions and undertook sensitivity analysis which confirmed effects were robust. Authors also acknowledged at long term outcome measurement most patients had forgotten details of their hospital stay. It is our view that further large trials of stroke unit care are unlikely and that overall evidence is robust and could be considered 'high'.

Outcome Timeframe	**Study results and measurements**	**Comparator** Alternative services	**Intervention** Organised stroke unit care	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Dependency or institutional care by the end of scheduled follow-up median 12 month follow up 9 Critical	Relative risk 0.77 (CI 95% 0.69 — 0.87) Based on data from 5,336 patients in 26 studies. (Randomized controlled) Follow up: median 12 months.	577 per 1000	517 per 1000 Difference: **60 fewer** per 1000 (CI 95% 80 fewer — 30 fewer)	**Moderate** Downgraded to due potential performance bias. Sensitivity analysis of high quality studies confirmed effects. [1]	Organised stroke unit care decreases dependency or institutional care by the end of scheduled follow-up
Death or dependency by the end of scheduled follow-up up to 12 months	Odds Ratio 0.75 (CI 95% 0.66 — 0.85) Based on data from 4,854 patients in 24 studies. (Randomized controlled) Follow up: Median of 12 months.	609 per 1000	549 per 1000 Difference: **60 fewer** per 1000 (CI 95% 90 fewer — 42 fewer)	**Moderate** Downgraded to due potential performance bias. Sensitivity analysis of high quality studies confirmed effects. [2]	The people receiving organised inpatient (stroke unit) care were more likely to survive and regain independence than those receiving less organised care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Alternative services	**Intervention** Organised stroke unit care	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical					
Death by the end of scheduled follow-up Up to 12 months 7 Critical	Odds Ratio 0.76 (CI 95% 0.66 — 0.88) Based on data from 5,902 patients in 29 studies. (Randomized controlled) Follow up: median 12 months.	219 per 1000	199 per 1000 Difference: **20 fewer** per 1000 (CI 95% 40 fewer — 10 fewer)	**Moderate** Downgraded to due potential performance bias. Sensitivity analysis of high quality studies confirmed effects. [3]	The people receiving organised inpatient (stroke unit) care were more likely to survive than those receiving less organised care.
Death or institutional care by the end of scheduled follow-up Up to 12 months 8 Critical	Odds Ratio 0.76 (CI 95% 0.67 — 0.85) Based on data from 4,887 patients in 25 studies. (Randomized controlled) Follow up: median 12 months.	405 per 1000	345 per 1000 Difference: **60 fewer** per 1000 (CI 95% 90 fewer — 30 fewer)	**Moderate** Downgraded to due potential performance bias. Sensitivity analysis of high quality studies confirmed effects.	The people receiving organised inpatient (stroke unit) care were more likely to survive and return home than those receiving less organised care.
Length of stay in a hospital or institution or both Until discharge 7 Critical	Based on data from: 4,162 patients in 19 studies. (Randomized controlled)		Difference: **SMD 0.16 lower** (CI 95% 0.33 lower — 0.01 higher)	**Low** The calculation of a summary result for length of stay was subject to major methodological limitations. [4]	Organised stroke unit care may decrease length of stay by mean of 4 days

1. **Risk of Bias: No 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: No serious. Imprecision: No serious. Publication bias: No serious.**
2. **Risk of Bias: No serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. The sensitivity analysis based on those trials that used an unequivocally blinded assessment suggested that such bias has not seriously influenced the results., Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: No serious.** . **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
4. **Risk of Bias: No serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** due to LOS calculated in different ways(acute hospital vs total hospital, two trials recorded median rather than mean and in two trials SD had to be inferred from p value or from results of similar trials). The magnitude of statistical heterogeneity was high, with I^:86-88 %.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Clinical Question/ PICO

Population: Adults with stroke
Intervention: stroke unit ward
Comparator: General medical wards

Summary

A Cochrane review conducted by the Stroke Unit Trialists' Collaboration (2020) *[7]* compared organised stroke unit care to alternative services. The review included 29 RCTs with 5902 participants. Overall, organised stroke unit care significantly reduced overall poor outcome (OR 0.77, 95% CI 0.69 to 0.87; moderate quality evidence), mortality compared to conventional care (OR 0.76, 95% CI 0.66 to 0.88; moderate quality evidence), and significantly reduced the odds of death or institutionalisation (OR OR 0.76, 95% CI 0.67 to 0.85; moderate quality evidence) and death or dependency (OR 0.75, 95% CI 0.66 to 0.85; moderate quality evidence) with stroke unit care compared to conventional care. Absolute risk reduction found two more people survived, 6 more living at home or living independently per 100 patients.

Direct pairwise comparison of stroke ward versus general ward: 15 trials (3523 participants) found a reduction in the odds of a poor outcome at the end of follow-up (OR 0.78, 95% CI 0.68 to 0.91; moderate-quality evidence).
Direct comparison of mobile stroke team versus general ward: two trials (438 participants) found little difference in the odds of a poor outcome at the end of follow-up (OR 0.80, 95% CI 0.52 to 1.22; low-quality evidence).
Direct comparison of mixed rehabilitation ward versus general ward: six trials (630 participants) found a reduction in the odds of a poor outcome at the end of follow-up (OR 0.65, 95% CI 0.47 to 0.90; moderate-quality evidence).

Network meta-analysis comparing different kinds of stroke units (general ward as comparator) reported the odds of a poor outcome were: stroke ward (OR 0.74, 95% CI 0.62 to 0.89, moderate-quality evidence); mobile stroke team (OR 0.88, 95% CI 0.58 to 1.34, low-quality evidence); mixed rehabilitation ward (OR 0.70, 95% CI 0.52 to 0.95, low-quality evidence). This is based on 20 trials (4127 participants) comparing organised (stroke unit) care with a general ward, six trials (982 participants) compared different forms of organised (stroke unit) care, and three trials (793 participants) incorporated more than one comparison.

Overall quality for main results was conservatively downgraded in this update to 'moderate' primarily due to lack of blinding of patients and staff (performance bias). The authors acknowledged that blinding was very difficult with such interventions and undertook sensitivity analysis which confirmed effects were robust. Authors also acknowledged at long term outcome measurement most patients had forgotten details of their hospital stay. It is our view that further large trials of stroke unit care are unlikely and that overall evidence is robust and could be considered 'high' for stroke unit care but lower quality for comparison for mobile stroke team and mixed rehabilitation wards.

Outcome Timeframe	**Study results and measurements**	**Comparator** General medical wards	**Intervention** stroke unit ward	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Poor outcome by end of scheduled follow-up [1] 12 month 8 Critical	Odds Ratio 0.78 (CI 95% 0.68 — 0.91) Based on data from 3,321 patients in 14 studies. (Randomized controlled) Follow up: median 12 months.	549 per 1000	499 per 1000 Difference: **50 fewer** per 1000 (CI 95% 90 fewer — 20 fewer)	**Moderate** Downgraded to due potential performance bias. Sensitivity analysis of high quality studies confirmed effects. [2]	Stroke unit ward decreases poor outcome by end of scheduled follow-up
Death by the end of scheduled follow-up Median follow-up of 12 months 9 Critical	Odds Ratio 0.75 (CI 95% 0.63 — 0.9) Based on data from 3,523 patients in 15 studies. (Randomized controlled) Follow up: Median follow-up of 12 months.	242 per 1000	202 per 1000 Difference: **40 fewer** per 1000 (CI 95% 70 fewer — 20 fewer)	**Moderate** Downgraded to due potential performance bias. Sensitivity analysis of high quality studies confirmed effects. [3]	Stroke unit ward reduces risk of death compared to care on general medical ward
Death or institutional care by the end of scheduled follow-up Median follow-up of 12 months	Odds Ratio 0.75 (CI 95% 0.63 — 0.9) Based on data from 2,924 patients in 13 studies. (Randomized controlled) Follow up: Median follow-up of 12 months.	383 per 1000	323 per 1000 Difference: **60 fewer** per 1000 (CI 95% 100 fewer — 30 fewer)	**Moderate** Downgraded to due potential performance bias. Sensitivity analysis of high quality studies confirmed	Stroke unit ward decreases death or institutional care by the end of scheduled follow-up

Outcome Timeframe	**Study results and measurements**	**Comparator** General medical wards	**Intervention** stroke unit ward	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical				effects. [4]	
Death or dependency by the end of scheduled follow-up Median follow-up 12 months 9 Critical	Odds Ratio 0.75 (CI 95% 0.64 — 0.88) Based on data from 2,839 patients in 12 studies. (Randomized controlled) Follow up: Median follow-up of 12 months.	602 per 1000	532 per 1000 Difference: 70 fewer per 1000 (CI 95% 100 fewer — 30 fewer)	**Moderate** Downgraded to due potential performance bias. Sensitivity analysis of high quality studies confirmed effects. [5]	The people receiving inpatient (stroke unit) care were more likely to survive and regain independence than those receiving care in general medical wards.
Length of stay (days) in a hospital or institution Median follow-up 12 months 7 Critical	Based on data from: 2,547 patients in 10 studies. (Randomized controlled) Follow up: Median follow-up of 12 months.	Difference: SMD 0.13 lower (CI 95% 0.29 lower — 0.04 higher)		**Low** Interpretation of length of stay data was complicated by substantial heterogeneity. [6]	Stroke care ward may lead to slightly shorter (mean 2.2 days) than care on general medical wards

1. mRS 3-6 or requiring institutional care
2. **Risk of Bias: No 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: No serious. Imprecision: No serious. Publication bias: No serious.**
3. **Risk of Bias: No serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
4. **Risk of Bias: No serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
5. **Risk of Bias: No serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
6. **Risk of Bias: No serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:70 %.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Info Box

Practice points

- All stroke patients should be admitted directly to a stroke unit (preferably within three hours of stroke onset).
- For patients with suspected stroke presenting to non-stroke unit hospitals, transfer protocols should be developed and used to guide urgent transfers to the nearest stroke unit hospital.
- Where transfer is not feasible, smaller isolated hospitals should manage stroke services in a manner that adheres as closely as possible to the criteria for stroke unit care. Where possible, stroke patients should receive care in geographically discrete units.

Practical Info

All patients should be informed about options for transfer and the benefits of transport to a specialist stroke service.

Evidence To Decision

Resources and other considerations

Implementation consideration
There is a clinical indicator collected in the National Stroke Audit to determine the median time from arrival at hospital to admission to a stroke unit for patients with stroke.

Rationale

Several observational studies found that, excluding the effects of rt-PA treatment, very early (less than three hours after stroke onset) admission to a stroke unit for ischaemic stroke patients resulted in significantly better recovery at three months (National Institutes of Health Stroke Scale [NIHSS] 34.6% vs 15.2%; modified Rankin Score [mRS] 32.9% vs 16.8%) without any significant difference in mortality (Silvestrelli et al. 2006 *[16]*; Naganuma et al. 2009 *[18]*; Leon-Jimenez et al. 2014 *[17]*).

Strong recommendation

All acute stroke services should implement standardised protocols to manage fever, glucose and swallowing difficulties in stroke patients. (Middleton et al. 2011 *[256]*)

Practical Info

In the Quality in Acute Stroke Care (QASC) study, monitoring and prompt treatment of hyperglycaemia, fever and swallowing dysfunction were critical in improving healthcare process and patient outcomes. For details on the management of these complications, refer to the sections Glycaemic therapy, Pyrexia management, and Dysphagia.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

A multidisciplinary, nurse-initiated treatment protocol for the management of fever, hyperglycaemia, and swallowing dysfunction (Middleton et al. 2011 *[256]*) demonstrated a significant reduction of death and dependency at 90 days (157 less per 1000, number needed to treat 6), and improvement of physical health (3.4 higher on SF-36 physical health score). Functional independence measured with Barthel Index also indicated a non-significant trend of improvement.

Certainty of the Evidence — Moderate

The quality of evidence is moderate as only one study, albeit a large multi-centre randomised controlled trial with high methodological quality.

Preference and values — No substantial variability expected

It is expected that patients would want to receive this protocol shown to improve their outcomes.

Resources and other considerations — Factor not considered

Rationale

The Quality in Acute Stroke Care (QASC) study provided evidence that an acute protocol aiming to ensure monitoring and prompt treatment of common complications fever, hyperglycaemia and swallowing reduced death and dependency in patients in stroke units (Middleton et al. 2011 *[256]*). Furthermore, it is likely that patients would want to receive this best-standard care. Therefore it should be provided to all stroke patients.

Clinical Question/ PICO

Population: Continuous versus intermittent physiological monitoring for acute stroke
Intervention: Continuous monitoring
Comparator: Intermittent monitoring of physiological variables

Summary

Ciccone et al. (2013) *[10]* conducted a Cochrane review assessing whether continuous monitoring of physiological variables affected patients' prognosis of mortality or disability. Three studies were included (N = 354), including two randomised controlled trials and one quasi-RCT where patients were allocated to continuous or intermittent monitoring based on the availability of beds. Continuous monitoring was associated with decreased death and disability at 3 months (OR 0.27, 95% CI 0.13 to 0.56), as well as a non-significant reduction in all-cause mortality. However, the decrease in death and disability was non-significant when excluding the quasi-RCT with high risk of bias. Cardiac complications were also detected significantly more often, but comparisons of other outcomes such as dependency, vascular death, and neurological complications showed no significant differences.

Outcome Timeframe	**Study results and measurements**	**Comparator** Intermittent monitoring of physiological variables	**Intervention** Continuous monitoring	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death or dependency by the end of scheduled follow up Discharge to 3 months 9 Critical	Odds Ratio 0.27 (CI 95% 0.13 — 0.56) Based on data from 354 patients in 3 studies. [1] (Randomized controlled) Follow up: Discharge to 3 months.	469 per 1000	193 per 1000 Difference: **276 fewer** per 1000 (CI 95% 366 fewer — 138 fewer)	**Low** The evidence was low because the trial which contributed most to the primary outcome (Cavallini 2003) was not truly randomised as participants were allocated to a conventional stroke unit or to a stroke unit with continuous monitoring purely on the basis of bed availability, there was no long-term follow up and it is not certain that the assessment of outcomes was blinded. If this study is removed from the meta-analysis the result is no longer statistically significant (OR 0.32, 95% CI 0.06 to 1.63), with consistent heterogeneity between the two remaining studies (I2 = 67%, 95% CI 93% to 44%). [2]	Continuous monitoring significantly reduced death and disability at three months or at discharge but these results depended on one study at high risk of bias.
Cardiac complications	Odds Ratio 8.65 (CI 95% 2.52 — 29.66)	17	130	**Low** The quality of the	Continuous monitoring was associated with a

Outcome Timeframe	**Study results and measurements**	**Comparator** Intermittent monitoring of physiological variables	**Intervention** Continuous monitoring	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Discharge to three months 7 Critical	Based on data from 354 patients in 3 studies. [3] (Randomized controlled) Follow up: Discharge to three months.	per 1000 Difference: **113 more** per 1000 (CI 95% 25 more — 322 more)	per 1000	evidence was low. There was slight heterogeneity of the studies, a small number of studies, small samples sizes and a high risk of bias for the trial that contributed most in terms of the number of participants enrolled. [4]	significant increase in the detection of cardiac complications (arrhythmias, heart failure, myocardial infarction)
Fever Discharge to three months 7 Critical	Odds Ratio 2.17 (CI 95% 1.27 — 3.7) Based on data from 354 patients in 3 studies. [5] (Randomized controlled) Follow up: Discharge to three months.	**158** per 1000 Difference: **131 more** per 1000 (CI 95% 34 more — 252 more)	**289** per 1000	**Low** The quality of the evidence was low. There was slight heterogeneity of the studies, a small number of studies, small samples sizes and a high risk of bias for the trial that contributed most in terms of the number of participants enrolled. [6]	Continuous monitoring was associated with a significant increase in the detection of fever.
Length of stay (days) Discharge to three months 7 Critical	Based on data from: 354 patients in 3 studies. [7] (Randomized controlled) Follow up: Discharge to three months.	Difference: **MD 5.24 lower** (CI 95% 10.51 lower — 0.03 higher)		**Very low** There are a small number of studies and small samples sizes. There was substantial heterogeneity across trials for this outcome (I^2 = 83%, 95% CI 94% to 49%; P = 0.003) and if the VERITAS 2007 study was removed from the analysis the reduction in hospital stay with continuous monitoring was statistically significant (mean difference (MD) -8.15 days, 95% CI -9.85 to -6.44) without significant inconsistency (I2 = 0%, P = 0.54). [8]	Continuous monitoring was associated with a non-significant reduction in the number of days of hospital stay.

1. Systematic review [10] with included studies: Sulter 2003, VERITAS 2007, Cavallini 2003. **Baseline/comparator:** Control arm of reference used for intervention.

2. **Risk of Bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. Systematic review [10] with included studies: Sulter 2003, VERITAS 2007, Cavallini 2003. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: Very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**
5. Systematic review [10] with included studies: Cavallini 2003, Sulter 2003, VERITAS 2007. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: Very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**
7. Systematic review [10] with included studies: Cavallini 2003, VERITAS 2007, Sulter 2003. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: Very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:83 %.. **Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Acute nursing intervention
Comparator: Control

Summary

The Quality in Acute Stroke Care (QASC) study conducted by Middleton et al. (2011) *[256]* was a single-blind cluster randomised trial, assessing the benefits of evidence-based treatment protocols in acute stroke units. The Fever, Sugar, Swallowing (FeSS) intervention involved temperature monitoring, monitoring of blood glucose and dysphagia assessment and was aimed at promoting prompt nursing assessment and bedside treatment. The results showed a significant reduction in death or dependency at 90 days (modified Rankin Scale scores >= 2), with an adjusted absolute risk reduction of 15.7%. The intervention group also showed higher rates of functional independence, both when independence was classified as a Barthel Index score >= 60 or >= 95, although the difference was non-significant. Other outcomes suggested improved processes of care in the intervention stroke units, with significantly reduced temperatures and blood glucose, and higher proportions of swallowing screening. Patients with severe strokes may have been under-represented due to the exclusion of patients receiving palliation only, but in other respects the study was high quality and provides a high degree of certainty about the observed results.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Acute nursing intervention	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death or dependency [1] 90 days after admission 9 Critical	n/a Based on data from 1,007 patients in 1 studies. [2] (Randomized controlled) Follow up: 90 days.	577 per 1000	420 per 1000 Difference: **157 fewer** per 1000 (CI 95% 58 fewer — 254 fewer)	**Moderate** Due to serious imprecision [3]	The FeSS protocol for acute stroke care probably decreases death or dependency
Functional independence	n/a	600	695	**Moderate** Due to serious	The FeSS protocol for acute stroke care

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Acute nursing intervention	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
(Barthel Index >= 95) 8 Critical	Based on data from 955 patients in 1 studies. [4] (Randomized controlled) Follow up: 90 days.	per 1000	per 1000 Difference: **95 more** per 1000 (CI 95% 5 fewer — 195 more)	imprecision [5]	probably has little or no difference on functional independence (Barthel Index >= 95)
Functional Independence (Barthel Index >= 60) 8 Critical	n/a Based on data from 955 patients in 1 studies. [6] (Randomized controlled) Follow up: 90 days.	898 per 1000	923 per 1000 Difference: **25 more** per 1000 (CI 95% 36 fewer — 86 more)	**Moderate** Due to serious imprecision [7]	The FeSS protocol for acute stroke care has little or no difference on functional independence (Barthel Index >= 60)
Physical health [8] 90 days after admission 7 Critical	Measured by: SF-36 Physical health score High better Based on data from: 1,009 patients in 1 studies. [9] (Randomized controlled) Follow up: 90 days.	Difference: **MD 3.4 higher** (CI 95% 1.2 higher — 5.5 higher)		**Moderate** Due to serious imprecision [10]	The FeSS protocol for acute stroke care improves physical health
Mental health 90 days after admission 7 Critical	Measured by: SF-36 Mental health score High better Based on data from: 1,009 patients in 1 studies. [11] (Randomized controlled) Follow up: 90 days.	Difference: **MD 0.5 higher** (CI 95% 1.9 lower — 2.8 higher)		**Moderate** Due to serious imprecision [12]	The FeSS protocol for acute stroke care has little or no difference on mental health

1. Dependency categorised as modified Rankin Scale scores >= 2. The RCT reported absolute risk reductions rather than a relative effect estimate such as an odds ratio or relative risk so only absolute estimates are reported here
2. Primary study[256]. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Inconsistency: No serious. Indirectness: No serious.** Excluded palliative patients so may have under-represented severe stroke patients.. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
4. Primary study[256]. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Inconsistency: No serious. Indirectness: No serious.** Excluded palliative patients so may have under-represented severe stroke patients.. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
6. Primary study[256]. **Baseline/comparator:** Control arm of reference used for intervention.
7. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
8. The mean difference reported in the RCT was covariate adjusted so the raw means do not match this reported difference. Means have been left blank and only the difference reported.
9. Primary study[256]. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: No serious. Indirectness: No serious.** Excluded palliative patients so may have under-represented severe stroke patients.. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
11. Systematic reviewwith included studies: [256]. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: No serious. Indirectness: No serious.** Excluded palliative patients so may have under-represented severe stroke patients.. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**

Assessment for rehabilitation

There is evidence that people with mild stroke may have impairments that are overlooked by healthcare professionals unless specific assessments are conducted (Edwards et al. 2006 *[23]*). Similarly there is evidence that rehabilitation needs of patients with severe stroke are inconsistently documented (Lynch et al. 2015 *[25]*), and that people with severe stroke are not routinely referred to rehabilitation service providers for consideration of access to ongoing rehabilitation (Lynch et al. 2016 *[27]*). Therefore, it is important that a formal assessment for rehabilitation is performed for all people after stroke.

The Assessment for Rehabilitation Tool (ART) was developed in 2011 by the Australian Stroke Coalition Rehabilitation Working Group to enhance equity of access to rehabilitation following stroke (Australian Stroke Coalition Rehabilitation Working Group 2012 *[24]*). The ART was developed in consultation with people with stroke and healthcare professionals following a review of the best available research evidence and a survey of current practice, and was piloted prior to its release in 2012.

Use of the ART is one of the essential principles of the *National Rehabilitation Stroke Services Framework* (Stroke Foundation 2013 *[29]*) and has been shown to assist healthcare professionals working in Australian acute stroke units to identify rehabilitation needs of people with stroke that are frequently overlooked, such as continence and mood (Lynch et al. 2016 *[26]*, Stroke Foundation 2019 *[28]*).

Practice points

- Every stroke patient should have their rehabilitation needs assessed within 24–48 hours of admission to the stroke unit by members of the interdisciplinary team, using the Assessment for Rehabilitation Tool (Australian Stroke Coalition Working Group 2012 *[24]*).
- Any stroke patient with identified rehabilitation needs should be referred to a rehabilitation service.
- Rehabilitation service providers should document whether a stroke patient has rehabilitation needs and whether appropriate rehabilitation services are available to meet these needs.

Practical Info

The Assessment for Rehabilitation Tool *[24]* has three sections. The *Domains* section is used to identify the specific rehabilitation needs of people with stroke, the *Participation* section allows documentation of previous roles (consistent with the World Health Organisation's International Classification of Functioning, Disability and Health Framework) and the *Environment* section is used to document background information relevant for rehabilitation.

All people with stroke who do not meet the exception criteria should be referred to rehabilitation services (home-based, community-based or in an inpatient rehabilitation facility) to determine whether the rehabilitation service can meet the person's rehabilitation requirements, and to determine whether the patient can access ongoing rehabilitation.

The Australian Stroke Coalition Rehabilitation Working Group has developed four exceptions to rehabilitation based on consensus opinion. These are

1. Person with stroke has returned to pre-morbid function, i.e. made a full recovery in all aspects including physical, emotional, psychological and cognitive function.
2. Palliation: death is imminent; person with stroke should be referred to the palliative care team.
3. Coma/non-responsive (not drowsy).
4. Refused: person with stroke does not wish to participate in rehabilitation.

While there are no grounds for restricting access to rehabilitation to any stroke survivor with identified rehabilitation needs, there may well be a mismatch between demand for rehabilitation and availability of services.

Evidence To Decision

Resources and other considerations

Implementation consideration

There is a clinical indicator collected in the National Stroke Audit to determine if an assessment for rehabilitation was performed.

Rationale

There is no evidence that particular cohorts of people with stroke will not benefit from rehabilitation. Rather, the latest Cochrane review of the evidence for inpatient care for people with stroke stated that "there are no firm grounds for restricting access

according to a person's age, sex, stroke severity or pathological stroke type" [Stroke Unit Trialists Collaboration 2013 *[7]*, p18]. The Australian Stroke Coalition Rehabilitation Working Group has developed four exceptions to rehabilitation to guide decision-making (see practical information section).

Palliative care

9% of acute stroke patients die in hospital during acute care (Stroke Foundation 2019 *[28]*) and approximately 20% die as a result of the stroke in the first 30 days (Thrift et al. 2000 *[38]*).

Practical end-of-life issues, such as the use of a medical power of attorney and advance care directives, should be discussed. Organ donation may be sensitively raised if appropriate. Issues of bereavement may become part of the responsibility of the stroke team.

Detailed Palliative care service guidelines can be found on the Palliative Care Australia website.

Strong recommendation

Stroke patients and their families/carers should have access to specialist palliative care teams as needed and receive care consistent with the principles and philosophies of palliative care. (Gade et al. 2008 *[30]*)

Practical Info

Referral to palliative care should be routine for patients in whom survival is thought to be unlikely.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

Gade et al. (2008) *[30]* (N=512) showed that interdisciplinary palliative care could improve advanced directives (number needed to treat to benefit 7.5), decrease ICU admissions, improve patient satisfaction and communication with providers, and increase length of hospice stay. No harms were reported.

Certainty of the Evidence — Moderate

The evidence is considered moderate due to confidence intervals not being reported, which made the range of possible benefit hard to determine.

Preference and values — No substantial variability expected

The qualitative studies by Payne et al. (2010) *[33]*; Burton and Payne (2012) *[32]* and de Boer et al. (2015) *[34]* discuss the need for palliative care services not to focus exclusively on end-of-life care but also to support quality of life for patients who have had a stroke and are likely to have a poor outcome and/or die in the acute phase of care.

The studies suggested that the significant advances made to implement evidence of rapid neurological assessment, specialist management and organised stroke services will mean that there will an increasing need for patients to have access to specialist palliative care services when needed and for all staff to be appropriately trained in palliative/supportive care.

Although these studies were undertaken mainly in the UK they would have direct applicability to the stroke unit care model in Australia and the needs of patients and their families/carers in relation to palliative care.

Whilst the evidence of patient's views on palliative care is understandably limited it is clear that from a patient's perspective the management of physical symptoms and psychological distress when the outcome of their stroke is likely to lead to major disability/death is appropriate and needed.

Blacquiere et al. (2013) *[35]*, a Canadian study, quantified the satisfaction with palliative care of families of patients who had died from stroke. Overall their satisfaction was high (9.04 out of 10) with most satisfaction about decision-making but least about emotional needs being met. There was less satisfaction about the control of individual symptoms and provision of adequate information. The most contentious area was the cessation of artificial hydration and feeding.

Although none of the studies directly assess whether families wanted palliative care for the patient following a stroke there is support for the provision of this care when needed. These limited studies identified an expressed desire from families for the patient to be pain-free and not suffering emotional distress. It is also clear that the satisfaction ratings support the view that the families valued the palliative care they received although they thought it could be improved.

It is not likely that the values and preferences in the Australian context would differ significantly.

Resources and other considerations No important issues with the recommended alternative

Resources considerations

Gade et al. (2008) *[30]* reported significantly lower total health costs for patients randomised to inpatient palliative care services compared to usual care. Mean total costs were US$14,486 in the palliative care group and US$21,252 in the usual care group (cost reference year 2002/2003), with the difference driven by lower hospital readmission costs (US$6,421 per patient for the palliative care group and US$13,275 for usual care). Patients in the palliative care group also had significantly fewer intensive care unit stays when readmitted. However, only a small subset of patients in this study were hospitalised for stroke (6%).

Implementation considerations

There is an organisational indicator collected in the National Stroke Audit on whether participating services have access to palliative care services for patients with stroke. There are also clinical indicators collected on the total number of patients with stroke who underwent palliative care and the median time between a patient's admission to hospital and the decision to palliate.

Rationale

Gade et al. (2008) *[30]* demonstrated that multidisciplinary palliative care teams reduced hospital admissions and increased decision-making (number of advanced care directives). They also improved communication and patient satisfaction slightly. A number of studies (both qualitative and quantitative) reported that the management of physical symptoms and psychological distress when the outcome of stroke is likely to lead to major disability/death is appropriate and needed. It was also reported that there is a need to not focus exclusively on end-of-life care but also to support quality of life for patients who have had a stroke and are likely to have a poor outcome and/or die in the acute phase of care.

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Interdisciplinary palliative care
Comparator: Usual care

Summary

Gade et al. (2008) *[30]* carried out a multicentre randomised controlled trial (N = 517) to assess the impact of an interdisciplinary palliative care service (IPCS) compared to usual hospital care. The IPCS care teams included palliative care nurses and physicians, social workers and chaplains. Primary outcomes were "symptom control, levels of emotional and spiritual support, patient satisfaction, and total health services costs at 6 months post-index hospitalisation". Patients receiving IPCS care reported higher satisfaction on the Care Experience scale and Doctors, Nurses/Other Care Providers Communication scale. Total costs were also lower in the IPCS group, with a mean 6-month saving of $4,855 (USD) per patient. IPCS patients were also more likely to have completed advanced directives by the time of hospital discharge, and had lower numbers of ICU admissions. There were no differences in survival or symptom control between the groups.

Creutzfield et al. (2012) *[31]* conducted a narrative literature review investigating the palliative care needs of stroke survivors. The review included evidence for central poststroke pain, hemiplegic shoulder pain, painful spasticity, fatigue, incontinence, post-stroke seizures, sexual dysfunction, sleep-disordered breathing, depression and emotionalism. The authors also reviewed the role of caregivers and ways to support them. The literature search was conducted using PubMed; searching from 1995 and limited to clinical practice guidelines and RCTs. Outcomes of interest included:

Pain: specifically central post-stroke pain (CPSP) and hemiplegic shoulder pain (HSP). One study (N = 15) found the tricyclic antidepressant (TCA) amitriptyline to be effective in CPSP with other TCAs and selective noradrenergic receptor inhibitors (SNRIs) showing effectiveness for neuropathic pain. The anticonvulsant lamotrigine was moderately effective in 30 patients with CPSP. For HSP the authors found that a shoulder sling during ambulation may support the arm to reduce pain and prevent upper extremity trauma. Promising interventions requiring further study include IM Botox-A, intra-articular steroid

injections and neuromuscular electrical stimulation.

Psychological outcomes reviewed included post-stroke depression (PSD), anxiety and emotionalism. The efficacy of medications to prevent PSD is unclear however pharmacologic treatment of PSD was found to lead to a reduction in various measures of depression but it was unclear what effect they have on functional outcomes. Adverse events were common and included central nervous system events (confusion, sedation, tremor) and GI effects (constipation, diarrhoea). Controlled trials on PSD were limited to TCAs and SSRIs and they found that while TCAs are effective in reducing depression, their cholinergic side effects limit their clinical usefulness, especially in older, frail patients with vascular disease. The data for SSRIs was mixed however the safety profile was more favourable making them the drug of choice. One study suggested that the SSRI citalopram may be more effective in "anxious depressed" (agitated, irritable) patients, whereas the noradrenergic drug reboxetine may be more effective in "retarded depressed" (mentally and physically slowed down) patients. While psychological, "talking" interventions (mostly behavioural interventions: identifying symptoms and causes of depression, and identifying and planning pleasant activities) seem promising, their benefit is not yet convincing, and their use should be tailored individually. Anxiety may accompany depression so for this reason antidepressant medications (e.g. citalopram) may be effective for generalised anxiety or panic pattern symptoms in this setting. If anxiety is severe and if the lifespan is limited, however, benzodiazepines are the drugs of choice. No drugs were recommended for emotionalism at this time.

Social outcomes reviewed included:
Care giving and receiving. Women, younger caregivers, those with poor physical health and those caring for patients with severe cognitive, behavioural and emotional changes are at highest risk of caregiver burn-out. Support programs should focus on increasing self-efficacy, active coping strategies and social support. If necessary, referrals should be made to appropriate services that meet identified social needs and promote access to care, transportation, rehabilitation, medications, counselling, community resources and equipment. Common fears specific to stroke caregivers are caused by the uncertainty of prognosis with the fear of another stroke, and the feeling of abandonment, especially when their loved one is unable to communicate. Caregiver's needs include information provision, managing emotions, social support, health maintenance and practical problem-solving. Training caregivers in their new role has been shown to reduce perceived and actual burden while improving psychosocial outcomes in both caregivers and patients. Over 90% of caregivers also reported that their experience as a stroke caregiver had increased their appreciation of life. The authors recommend consultation with a local social worker familiar with resources in the patient's community to ensure that all opportunities are explored.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Palliative care	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Advance directives [1] At discharge	n/a Based on data from 512 patients in 1 studies. (Randomized controlled) Follow up: At discharge.	778 per 1000	911 per 1000 Difference: 133 more per 1000	**Moderate** The difference was significant (chi-squared test) but confidence intervals were not reported. Due to serious imprecision [2]	Interdisciplinary palliative care probably increases completion of advance directives
ICU admissions	n/a Based on data from 448 patients in 1 studies. (Randomized controlled)	96 per 1000	52 per 1000	**Moderate** The difference was significant according to a chi-squared test, but confidence intervals were not reported. Due to serious imprecision [3]	Interdisciplinary palliative care probably decreases ICU admissions
Patient satisfaction - care environment	Measured by: MCOHPQ Place of Care environment scale Scale: 0 — 10 High better	6.4 (Mean)	6.8 (Mean)	**Moderate** The difference was significant but no confidence	Interdisciplinary palliative care probably improves patient satisfaction with the care environment

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Palliative care	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
2 weeks after discharge	Based on data from: 295 patients in 1 studies. (Randomized controlled) Follow up: Within 2 weeks of discharge.	Difference: MD 0.4 higher CI 95%		intervals were reported. Due to serious imprecision [4]	slightly
Patient satisfaction - communication with providers 2 weeks after discharge	Measured by: Doctors, Nurses / Other Care Providers - Communication scale Scale: 0 — 10 High better Based on data from: 341 patients in 1 studies. (Randomized controlled) Follow up: Within 2 weeks of discharge.	7.4 (Mean)	8 (Mean) Difference: MD 0.6 higher CI 95%	**Moderate** The difference was significant but no confidence intervals were reported. Due to serious imprecision [5]	Interdisciplinary palliative care probably improves patient satisfaction regarding communication with providers slightly
Hospice length of stay	Measured by: Days in hospice Based on data from: 512 patients in 1 studies. (Randomized controlled)	12 days (Median)	24 days (Median) Difference: 12 higher CI 95%	**Moderate** The difference was significant but no confidence intervals were reported. Due to serious imprecision [6]	Interdisciplinary palliative care probably increases hospice length of stay

1. Number of patients with a complete advance directive at time of discharge
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, confidence intervals not reported so range of possible benefit hard to determine . **Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, confidence intervals not reported so range of possible benefit hard to determine . **Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, confidence intervals not reported so range of possible benefit hard to determine . **Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, confidence intervals not reported so range of possible benefit hard to determine . **Publication bias: No serious.**
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, confidence intervals not reported so range of possible benefit hard to determine . **Publication bias: No serious.**

Practice statement

Consensus-based recommendations

- For patients with severe stroke who are deteriorating, a considered assessment of prognosis or imminent death should be made.
- A pathway for stroke palliative care can be used to support stroke patients and their families/carers and improve care for people dying after stroke.

Practical Info

Hospitals that receive patients experiencing acute stroke should develop a protocol for patients with sever stroke who are deteriorating, whereby a considered assessment of prognosis or imminent death should be made.

Each hospital that receives patients experiencing acute stroke should develop a stroke palliative care pathway, protocols and referral agreements to be routinely activated for patients with a considered assessment of prognosis of imminent death.

When talking about a patient, do not assume the patient's state or consciousness. Talk in front of them as though they can hear.

Rationale

Mortality after stroke is not insignificant. A previous systematic review (7 trials) showed that carers of stroke patients have different needs to those involved in specialist palliative care in cancer. They require more support, particularly as they are likely to be older and in poor health, and caring for their family members in difficult circumstances, often unsupported (Stevens et al. 2007 *[36]*).

An observational study was identified that developed and implemented a care pathway for palliative care in acute stroke. The study reported improved processes of care based on national standards, compared to care provided prior to the pathway (Jack et al. 2004 *[37]*).

Reperfusion therapy

Thrombolysis and endovascular thrombectomy (intra-arterial clot retrieval) are discussed separately below.

Thrombolysis

Most strokes are due to blockage of an artery in the brain by a blood clot. Prompt treatment with clot-dissolving (thrombolytic) drugs can restore blood flow before major brain damage has occurred and assist people to make a good recovery from their stroke (Wardlaw et al. 2014 *[39]*). Thrombolytic drugs can also, however, cause serious bleeding in the brain, which can be fatal (Wardlaw et al. 2014 *[39]*). Thrombolytic therapy has now been evaluated in many randomised trials in acute ischaemic stroke. In October 2003 the thrombolytic drug alteplase was licensed by the Australian Therapeutic Goods Administration for use in acute ischaemic stroke.

Access to thrombolysis remains lower than achievable levels in Australia. In the National Stroke Audit in 2019, the overall thrombolysis rate was 10%, despite 82% of hospitals reporting provision of thrombolysis (Stroke Foundation 2019 *[28]*). 26% of patients arriving within 4.5 hours of stroke onset received thrombolysis (Stroke Foundation 2019 *[28]*). Only 32% of appropriate patients that received thrombolysis did so within 60 minutes of hospital arrival.

The failure to fully implement stroke thrombolysis is an international problem, but numerous studies have demonstrated that treatment of up to 20% of all ischaemic stroke patients is achievable. In Australia, new models of care need to be developed and assessed, tailored to local circumstances. Local and network interventions will need to be developed and evaluated. Such interventions may need to include telemedicine resources and training for regional and rural centres, systems-level coordination and changes, and appropriate numbers of trained acute stroke personnel with obvious implications for ongoing training and support. Given the potential risks of thrombolysis, adverse outcomes can occur with inappropriate use, and routine audit and ongoing quality improvement will be essential to identify problem areas and local solutions.

Strong recommendation

For patients with potentially disabling ischaemic stroke within 4.5 hours of onset who meet specific eligibility criteria, intravenous thrombolysis should be administered as early as possible after stroke onset (Wardlaw et al. 2014 *[39]*; Emberson et al. 2014 *[40]*)

Practical Info

Intravenous thrombolysis eligibility should be determined by an assessment of the balance of risk versus benefit in the individual patient. "Potentially disabling ischaemic stroke" as included in the guideline recommendation does not require any particular threshold score to be achieved on the National Institutes of Health Stroke Scale. The NINDS tPA trial included patients with "measurable neurological deficit". For example, an isolated hemianopia (NIHSS 2) would qualify as potentially disabling, and isolated dysphasia or significant hand weakness with minimal arm drift may also warrant treatment. Some guidelines have recommended against treatment of "severe" stroke. Patients with severe stroke have a worse prognosis than milder stroke patients. However, the magnitude of treatment benefit (as measured by the odds ratio of excellent functional outcome) in individual patient data meta-analysis was consistent across the spectrum of stroke severity (Emberson et al. 2014 *[40]*) and patients may still wish to have this treatment so discussions regarding benefits and harms with patient and family should still occur. Rapidly improving clinical severity has sometimes been regarded as an exclusion from thrombolysis. However, these patients have a substantial risk of subsequent deterioration and treatment should be considered if there is still a potentially disabling deficit or if imaging indicates a persisting vessel occlusion (Coutts et al. 2012 *[52]*).

Benefit from thrombolysis is strongly time-dependent and so treatment should be commenced as early as possible after stroke onset. Commencing treatment beyond 4.5 hours in patients selected purely on the basis of non-contrast CT imaging has not been shown to be of net benefit. However, alteplase has been shown to be beneficial beyond 4.5h of the time the patient was last known to be well in patients selected using perfusion imaging or diffusion-FLAIR MRI (see separate recommendation).

If possible, thrombolytic treatment should proceed after communication with the patient and their family regarding the rationale behind thrombolysis, its potential risks and benefits. Communication should be clear and simple but should not introduce delay to thrombolytic treatment given the strong effect of treatment time.

Contraindications to thrombolysis generally relate to either systemic or intracerebral bleeding risk or potential alternative diagnosis of a stroke mimic. Many proposed criteria were adopted directly from trial exclusion criteria, and studies of "off-label"

thrombolysis have suggested that some of these may not be well justified. Limitations on age have been imposed in some trials, but an individual patient data meta-analysis of all alteplase trials has clearly demonstrated a treatment benefit are independent of age (p=0.74). (Bluhmki et al. 2020 *[69]*) For those >80 years there was higher proportion of good outcome (mRS 0-1; 19.1% vs 13.1%; p=0.01), an increased risk of sICH (3.7% vs 0.4%, p=0.0002) but no increase in overall 90-day mortality (p=0.8). However, those >80 years compared to <80years do have higher 90-day mortality (29.9% vs 10.2%) due in part to higher co-morbidities and more severe strokes. The patient's pre-morbid level of function rather than chronological age should be considered when deciding whether to treat.

Conditions such as seizures, hypoglycaemia and hyperglycaemia may present as stroke mimics and have been regarded as exclusions from some trials. Brain imaging can potentially overcome these diagnostic pitfalls by proving a diagnosis of ischaemic stroke. Seizure should not prevent thrombolysis if there is a vessel occlusion or perfusion lesion diagnostic of stroke and there has been no significant trauma as a result of the seizure. Hypoglycaemia should be corrected and, if symptoms remain and there is imaging evidence of stroke, the patient can receive thrombolysis. Hyperglycaemia is a negative prognostic factor but, in the presence of confirmed diagnosis of stroke, should not prevent thrombolysis and the hyperglycaemia should be treated in parallel.

Contraindications:

- Acute intracranial haemorrhage.
- Extensive frank hypodensity on CT scan (greater than 1/3 of middle cerebral artery territory or equivalent).
  This should prompt reassessment of the stroke onset time. Subtle ischaemic changes (loss of grey-white differentiation) are not a contraindication but reflect irreversible injury.
- Active non-compressible systemic bleeding.
- Systemic coagulopathy *(NB thrombolysis should not be delayed by coagulation testing unless there is clinical suspicion of coagulopathy)*.
  – platelet count < 100,000 mm^3 (based on expert consensus)
  – INR > 1.7, including warfarin use (based on limited observational data)
  – unfractionated heparin within 48 hours with an elevated APTT
  – low molecular weight heparin within 24 hours (excluding prophylactic doses [Cooray et al. 2019 *[72]*]) with abnormal anti-factor Xa activity
  – direct oral anticoagulant use (e.g. apixaban, dabigatran, rivaroxaban, edoxaban) within 48 hours with abnormal coagulation parameters as appropriate to the particular medication, unless a specific reversal agent is available (see below).
- Infective endocarditis (increased risk of symptomatic intracerebral haemorrhage)
- Thoracic aortic dissection (increased risk of death)

Relative contraindications (careful consideration of risk and benefit required):

- Severe uncontrolled high blood pressure: the standard recommendation based on expert consensus is to lower elevated blood pressure to < 185/110 mmHg prior to thrombolysis and maintain this level. If blood pressure cannot be lowered then thrombolysis should not be commenced.
- Previous intracerebral haemorrhage (not including cerebral microbleeds on MRI).
- Cranial or spinal surgery or major head trauma within 3 months (expert consensus).
- Other major surgery or trauma within 14 days (expert consensus) – consider discussion with the surgeon involved.
- Recent gastrointestinal or genitourinary tract bleeding within 21 days (expert consensus).
- Central nervous system intra-axial neoplasm (i.e. meningioma is not a contraindication).
- Ischaemic stroke within 3 months (consider the size of the previous infarct and severity of current stroke).

Other notes:

Prior ischaemic stroke within 3 months - thrombolysis may be reasonable under some circumstances, weighing the extent of previous infarction and time elapsed as markers of haemorrhagic transformation risk versus the risk of disability due to the current stroke and the suitability of alternative treatment options including endovascular thrombectomy. Allowing for potential selection bias due to non-randomised physician decision making, safety (sICH, mortality) and efficacy (early improvement, functional outcomes at 90 days) did not differ between patients with or without recent ischaemic stroke based on observational data from 6 studies (n=53,631 of whom 912 had prior stroke within 3 months). (Tsivgoulis et al. 2019 *[71]*)

Cervical artery (extra-cranial) dissection – available data suggest alteplase is safe in these patients.

Pregnancy – there is no known fetal toxicity related to alteplase but experience is limited. Uterine bleeding and fetal death is a potential risk. This needs to be balanced against the risk of the stroke and potential alternative endovascular treatment.

Menstrual bleeding is not regarded as a contraindication to thrombolysis but should be monitored in the first 24 hours.

Unruptured aneurysms have not been demonstrated to pose an increased risk for thrombolysis. Experience with unruptured arteriovenous malformations and ruptured aneurysms that have been secured is very limited.

Lumbar puncture within 7 days is not regarded as an absolute contraindication although there are limited data on this scenario.

Direct oral anticoagulants and thrombolysis:

There are currently limited data on the safety of intravenous thrombolysis in patients taking direct oral anticoagulants (DOACs). If the patient is known to have not taken their anticoagulant within 48 hours and they have normal renal function then thrombolysis should be no greater risk than in unanticoagulated patients. When anticoagulation has been taken within 48 hours, or this is unknown, the options are 1) empiric reversal of the anticoagulant with a specific reversal agent (e.g. idarucizumab for dabigatran) and then thrombolysis, 2) coagulation testing using the assay appropriate to the particular medication (calibrated factor Xa assay for apixaban or rivaroxaban, dilute thrombin time for dabigatran) with subsequent thrombolysis if the level is deemed sufficiently low to justify the risk, or 3) immediate endovascular thrombectomy without thrombolysis if this is rapidly available and there is a suitable large vessel occlusion. The likely relative delay to obtain blood test results versus commencing endovascular thrombectomy should be considered.

"Safe" levels of direct anticoagulants have not been established. Most consensus recommendations are based on trough levels observed in the pivotal trials, which is probably more conservative than the INR > 1.7 criterion used for warfarin. Examples of suggested drug levels that may allow thrombolysis when a specific reversal agent is not available are: dabigatran < 40 ng/mL, apixaban < 10 ng/mL and rivaroxaban < 100 ng/mL, but these may evolve and careful individual risk benefit consideration is advised. One review (6 studies, n=52823: 366 with prior DOACs, 2133 on warfarin, and 50324 with no prior anticoagulation) found no increased risk of symptomatic intracerebral heamorrhage in patients using DOACs who were nonetheless given thrombolysis compared to warfarin (INR <1.7) or without anticoagulation therarpy. (Shahjouei et al. 2019 *[70]*) Pre-treatment with idarucizumab did not change the risk of harm based on 123 cases. (Shahjouei et al. 2019 *[70]*) However, there were no data on the length of time since the last dose of DOAC or the plasma level of DOAC at the time of thrombolysis and these data are susceptible to selection bias.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

Alteplase significantly improved the overall odds of a good stroke outcome at 90 days when administered within 4.5 hours of stroke onset: 114 more patients had favourable outcome per 1000 patients treated within 3 hours, and 51 more per 1000 patients treated between 3 and 4.5 hours) (Emberson et al. 2014 *[40]*). Earlier treatment was associated with greater benefits. There was no significant benefit when alteplase was delivered after 4.5 h using standard clinical and non-contrast CT eligibility criteria. These functional outcome benefits included the potentially detrimental effect of symptomatic intracerebral haemorrhage. Alteplase increased the risk of symptomatic intracerebral haemorrhage (31 per 1000 using the SITS definition of symptomatic haemorrhage). There was an increased risk of fatal intracranial haemorrhage during the first week in alteplase treated patients (25 per 1000 for 0–3 hr (2.5% excess) and 20 per 1000 for 3–4.5 hr (2% excess) (Emberson et al. 2014 *[40]*). However, at 90 days there was no significant difference in mortality.

Certainty of the Evidence — High

The overall quality of evidence is high, based on meta-analyses of large randomised controlled trials with low risk of bias.

Preference and values — No substantial variability expected

For most patients the benefits in reduced disability would be preferred to the small risk of symptomatic haemorrhage. Evidence indicates that >75% of patients would consent to stroke thrombolysis and would also want to receive thrombolysis if they were unable to consent themselves. This was very similar to the proportion of patients who would want CPR if they had a cardiac arrest (Chiong et al. 2014 *[54]*).

Resources and other considerations No important issues with the recommended alternative

Resources considerations

A decision analytic model using information on patients with ischaemic stroke treated with alteplase at a single Australian hospital was used to assess the cost-effectiveness of alteplase over 12 months after stroke (Tan Tanny et al. 2013 *[47]*). Treatment with alteplase within 4.5 hours was found to be cost-effective compared to no alteplase treatment (produced health gains for an acceptable additional cost to the alternative) at an additional cost of AU$2,377 per life-year saved and AU$1,478 per QALY gained (cost reference year not reported) (Tan Tanny et al. 2013 *[47]*). There is also evidence from economic modelling using stroke incidence data that alteplase commenced within 3 hours is more effective and less costly compared to no alteplase treatment. (Mihalopoulos et al. 2005 *[169]*)

There is evidence from studies conducted outside of Australia that treatment with alteplase within 4.5 hours of stroke onset is either cost-effective or dominant over placebo in the long-term (Pan et al. 2014 *[48]*; Boudreau et al. 2014 *[49]*; Tung et al. 2011 *[50]*; Boudreau et al. 2013 *[51]*).

In a systematic review of cost-effectiveness data, Demaerschalk et al. (2010) *[46]* found that alteplase increased hospitalisation costs, but resulted in long-term cost savings associated with decreased nursing home and rehabilitation costs. However, this was based on data published in 1998 and economic evaluations utilising newer research findings are required.

Implementation considerations

There is a clinical indicator collected in the National Stroke Audit to determine the total number of patients with ischaemic stroke who receive thrombolysis. There are also clinical indicators collected on the total number of patients who received thrombolysis if they were admitted to hospital within 4.5 hours of their symptom onset, and also for those patients who did receive thrombolysis, if this was administered within 60 minutes of the patient's arrival. A further clinical indicator is collected to determine the median time (and interquartile range) from stroke symptom onset to the time of delivery of thrombolysis. An additional clinical indicator is also collected to determine the median time from admission to the administering of thrombolysis for patients with ischaemic stroke.

Rationale

High-quality evidence suggests that the benefits of intravenous alteplase outweigh its harms if given within 4.5 hours in patients satisfying specific criteria (Wardlaw et al. 2014 *[39]*; Emberson et al. 2014 *[40]*). Benefits have not been established beyond 4.5 hours in patients selected based on non-contrast CT and clinical criteria. However, patients selected using perfusion imaging do benefit beyond 4.5 hours (see separate recommendation).

Clinical Question/ PICO

Population: Adults with acute stroke treated within 6 hours without perfusion imaging selection
Intervention: Intravenous alteplase
Comparator: Control

Summary

A Cochrane review by Wardlaw et al. (2014) *[39]* included 27 RCTs of thrombolytic agents for treatment of ischaemic stroke using eligibility criteria based on clinical characteristics and non-contrast CT brain. In most trials, treatment began up to 6 hours after stroke. Death or dependency by the end of follow-up was significantly reduced in the 10 trials using intravenous alteplase when the entire 0–6 hour treatment window (which is not current clinical practice) was considered (OR 0.84, 95% CI 0.77 to 0.93), although there was significant heterogeneity. A stronger effect was seen when analysing intravenous alteplase given with 3 hours of stroke (OR 0.65, 95% CI 0.54 to 0.80) with no significant heterogeneity. However, intravenous alteplase was also associated with a significant increase in 7 to 10-day mortality of around 2.6%, driven largely by increased risk of fatal intracranial haemorrhage (OR 4.18, 95% CI 2.99 to 5.84) which occurred in approximately 1.9% of patients. There was strong evidence for a net benefit of rt-PA treatment for death and dependency, particularly for rt-PA administered within 3 hours.

The benefits also appear to continue into the long term, although data are more limited. The IST-3 collaborative group (2013) *[41]* reported 18-month follow-up outcomes from an RCT (N = 2348) administering intravenous alteplase within 6 hours. Alteplase treatment was associated with an increased number of patients alive and independent at 18 months (Oxford Handicap Scale score 0–2, OR 1.28, 95% CI 1.03 to 1.57). The difference in patients alive and with an excellent

outcome was not significant (OHS score 0–1, OR 1.23, 95% 0.98 to 1.55). In ordinal analysis, there was a significant overall shift towards improved functional outcome (OR 1.30, 95% CI 1.10–1.55; p=0.002). There was no difference in death by 18 months (34.9% alteplase vs 35.1% control, p=0.85). At 3 years of follow-up, there was again no overall difference in survival (46.8% alteplase vs 50.5% control, p=0.11).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Intravenous alteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death or dependency at the end of follow-up [1] End of follow-up 9 Critical	Odds Ratio 0.84 (CI 95% 0.77 — 0.93) Based on data from 6,886 patients in 10 studies. [2] (Randomized controlled) Follow up: ranges from 1 week to >1 year.	583 per 1000	540 per 1000 Difference: **43 fewer** per 1000 (CI 95% 65 fewer — 18 fewer)	**Moderate** Due to serious inconsistency [3]	Intravenous alteplase reduces death or dependency at the end of follow-up
Death 7 to 10 days 9 Critical	Odds Ratio 1.44 (CI 95% 1.18 — 1.76) Based on data from 5,535 patients in 8 studies. [4] (Randomized controlled) Follow up: 7 to 10 days.	64 per 1000	90 per 1000 Difference: **26 more** per 1000 (CI 95% 11 more — 43 more)	**High**	Intravenous alteplase increases death early after stroke
Death at the end of follow-up End of follow-up	Odds Ratio 1.06 (CI 95% 0.94 — 1.2) Based on data from 7,012 patients in 12 studies. [5] (Randomized controlled) Follow up: ranges from 1 week to >1 year.	185 per 1000	194 per 1000 Difference: **9 more** per 1000 (CI 95% 9 fewer — 29 more)	**High** [6]	There is little or no difference in death at the end of follow-up
Fatal intracranial haemorrhage 7-10 days 9 Critical	Odds Ratio 4.18 (CI 95% 2.99 — 5.84) Based on data from 6,683 patients in 8 studies. [7] (Randomized controlled) Follow up: 7 to 10 days.	6 per 1000	25 per 1000 Difference: **19 more** per 1000 (CI 95% 12 more — 28 more)	**High**	Intravenous alteplase increases fatal intracranial haemorrhage early after stroke
Symptomatic intracranial haemorrhage [8] 7-10 days 8 Critical	Odds Ratio 3.72 (CI 95% 2.98 — 4.64) Based on data from 7,011 patients in 12 studies. [9] (Randomized controlled) Follow up: 7 to 10 days.	18 per 1000	64 per 1000 Difference: **46 more** per 1000 (CI 95% 34 more — 60 more)	**High**	Intravenous alteplase increases symptomatic intracranial haemorrhage early after stroke

1. Dependency defined as Modified Rankin Scale 3-6
2. Systematic review [39] with included studies: NINDS 1995, IST3 2012, Wang 2003, ATLANTIS A 2000, ECASS 1995, ECASS 3 2008, ECASS II 1998, ATLANTIS B 1999, Mori 1992, EPITHET 2008. **Baseline/comparator:** Control arm of reference used for intervention.

3. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:63%.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
4. Systematic review [39] with included studies: ECASS II 1998, Mori 1992, EPITHET 2008, IST3 2012, ECASS 1995, Wang 2003, Haley 1993, ECASS 3 2008. **Baseline/comparator:** Control arm of reference used for intervention.
5. Systematic review [39] with included studies: Haley 1993, IST3 2012, ECASS 3 2008, Mori 1992, Wang 2003, ATLANTIS B 1999, ATLANTIS A 2000, NINDS 1995, ECASS II 1998, EPITHET 2008, ECASS 1995, JTSG 1993. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** 95%CI crosses 1 but it's unlikely to change clinical decision. **Publication bias: No serious.**
7. Systematic review [39] with included studies: ECASS 3 2008, NINDS 1995, Haley 1993, ECASS II 1998, ECASS 1995, IST3 2012, ATLANTIS B 1999, ATLANTIS A 2000. **Baseline/comparator:** Control arm of reference used for intervention.
8. Includes fatal symptomatic ICH
9. Systematic review [39] with included studies: Haley 1993, NINDS 1995, ATLANTIS A 2000, ECASS 1995, IST3 2012, ATLANTIS B 1999, JTSG 1993, ECASS 3 2008, Mori 1992, Wang 2003, EPITHET 2008, ECASS II 1998. **Baseline/comparator:** Control arm of reference used for intervention.

Clinical Question/ PICO

Population: Adults with acute stroke treated within 3 hours without perfusion imaging selection
Intervention: Intravenous alteplase
Comparator: Control

Summary

An individual patient data meta-analysis conducted by Emberson et al. (2014) *[40]* included subgroup analyses for patients treated ≤ 3 hours after stroke, > 3 and ≤ 4.5 hours, and > 4.5 hours using eligibility criteria based on clinical characteristics and non-contrast CT brain. It showed that treatment within 3 hours was associated with the greatest improvement in excellent outcomes (mRS of 0 or 1) at 90 days (114 per 1000). Alteplase was associated with increased risk of intracranial haemorrhage within 7 days, which led to death in approximately 2% of patients. Subsequent higher rates of death in the control group meant there was no difference in mortality at 3 months. By 3–6 months the average absolute increase in disability-free survival was 10% for patients treated within 3.0 h, which includes the impact of symptomatic haemorrhage.

A Cochrane review by Wardlaw et al. (2014) *[39]* included 27 RCTs of thrombolytic agents for the treatment of ischaemic stroke. In most trials, treatment began up to 6 hours after stroke. Death or dependency by the end of follow-up was significantly reduced in the 10 trials using intravenous alteplase (OR 0.84, 95% CI 0.77 to 0.93), although there was significant heterogeneity. A stronger effect was seen when analysing intravenous alteplase given with 3 hours of stroke (OR 0.65, 95% CI 0.54 to 0.80) with no significant heterogeneity.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Intravenous alteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Excellent outcome (modified Rankin Scale 0-1) [1] 3-6 months 8 Critical	Odds Ratio 1.75 (CI 95% 1.35 — 2.27) Based on data from 1,549 patients in 9 studies. (Randomized controlled) Follow up: 3 to 6 months.	231 per 1000	345 per 1000 Difference: **114 more** per 1000 (CI 95% 58 more — 174 more)	**High** [2]	Intravenous alteplase within 3 hours increases favourable outcome

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Intravenous alteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death 90 days 9 Critical	Hazard Ratio 1 (CI 95% 0.81 — 1.24) Based on data from 1,549 patients in 9 studies. (Randomized controlled)			**High** 3	Intravenous alteplase within 3 hours has little or no difference on death
Fatal intracranial haemorrhage 7 days 9 Critical	Odds Ratio 10.86 (CI 95% 2.54 — 46.41) Based on data from 1,549 patients in 9 studies. (Randomized controlled)	3 per 1000	32 per 1000 Difference: **29 more** per 1000 (CI 95% 5 more — 120 more)	**High** 4	Intravenous alteplase within 3 hours increases fatal intracranial haemorrhage

1. Modified Rankin Scale score of 0 or 1 - return to all usual pre-stroke activities
2. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
4. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Clinical Question/ PICO

Population: Adults with acute stroke treated at 3-4.5 hours without perfusion imaging selection
Intervention: Intravenous alteplase
Comparator: Control

Summary

An individual patient data meta-analysis conducted by Emberson et al. (2014) *[40]* included subgroup analyses for patients treated <= 3 hours after stroke, > 3 and <= 4.5 hours, and > 4.5 hours using eligibility criteria based on clinical characteristics and non-contrast CT brain. It showed that treatment with 4.5 hours was associated with the improvement on good stroke outcomes (mRS of 0 or 1) at 90 days (51 per 1000). Alteplase was associated with increased risk of intracranial haemorrhage within 7 days (23 per 1000). Overall, by 3–6 months the average absolute increase in disability-free survival was 5% for patients treated between 3.0 and 4.5 hours which includes the effect of intracerebral haemorrhage.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Intravenous alteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death 90 days 9 Critical	Hazard Ratio 1.14 (CI 95% 0.95 — 1.36) Based on data from 2,812 patients in 9 studies. (Randomized controlled)			**High** 1	Intravenous alteplase between 3 and 4.5 hours has little or no difference on death

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Intravenous alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Excellent outcome (modified Rankin Scale 0-1) [2] 3-6 months 8 Critical	Odds Ratio 1.26 (CI 95% 1.05 — 1.51) Based on data from 2,812 patients in 9 studies. (Randomized controlled)	301 per 1000	352 per 1000 Difference: **51 more** per 1000 (CI 95% 10 more — 93 more)	**High** 3	Intravenous alteplase between 3 and 4.5 hours increases favourable outcome
Fatal intracranial haemorrhage 7 days 9 Critical	Odds Ratio 5.63 (CI 95% 2.49 — 12.76) Based on data from 2,812 patients in 9 studies. (Randomized controlled)	5 per 1000	28 per 1000 Difference: **23 more** per 1000 (CI 95% 7 more — 55 more)	**High** 4	Intravenous alteplase between 3 and 4.5 hours increases fatal intracranial haemorrhage

1. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
2. modified Rankin Scale score of 0 or 1 - return to all usual pre-stroke activities
3. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
4. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Clinical Question/ PICO

Population: Adults with acute stroke treated at 4.5-6 hours without perfusion imaging selection
Intervention: Intravenous alteplase
Comparator: Control

Summary

An individual patient data meta-analysis conducted by Emberson et al. (2014) *[40]* included subgroup analyses for patients treated <= 3 hours after stroke, > 3 and <= 4.5 hours, and 4.5 - 6 hours using eligibility criteria based on clinical characteristics and non-contrast CT brain. It showed that treatment between 4.5–6 hours was associated with a small improvement on good stroke outcomes (mRS of 0 or 1) at 90 days (30 per 1000), but also increased risk of fatal intracranial haemorrhage within 7 days (21 per 1000). In this case, it is unclear that the benefits outweigh the potential harms.

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Intravenous alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Death 90 days	Hazard Ratio 1.22 (CI 95% 0.99 — 1.5) Based on data from 2,395 patients in 9	CI 95%		**High** 1	Intravenous alteplase after 4.5 hours slightly increases death

Outcome Timeframe	Study results and measurements	Comparator Control	Intervention Intravenous alteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
9 Critical	studies. (Randomized controlled) Follow up: 90 days.				
Excellent outcome (modified Rankin Scale 0-1) [2] 3-6 months 8 Critical	Odds Ratio 1.15 (CI 95% 0.95 — 1.4) Based on data from 2,395 patients in 9 studies. (Randomized controlled)	306 per 1000	336 per 1000 Difference: **30 more** per 1000 (CI 95% 11 fewer — 76 more)	**High** 3	Intravenous alteplase after 4.5 hours slightly increases favourable outcome
Fatal intracranial haemorrhage 7 days 9 Critical	Odds Ratio 8.16 (CI 95% 2.88 — 23.11) Based on data from 2,395 patients in 9 studies. (Randomized controlled)	3 per 1000	24 per 1000 Difference: **21 more** per 1000 (CI 95% 6 more — 62 more)	**High** 4	Intravenous alteplase after 4.5 hours increases fatal intracranial haemorrhage

1. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
2. modified Rankin Scale score of 0 or 1 - return to all usual pre-stroke activities
3. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
4. **Inconsistency: No serious.** no heterogeneity analysis was done. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Strong recommendation

For patients with potentially disabling ischaemic stroke due to large vessel occlusion who meet specific eligibility criteria, intravenous tenecteplase (0.25mg/kg, maximum of 25mg) or alteplase (0.9mg/kg, maximum of 90mg) should be administered up to 4.5 hours after the time the patient was last known to be well. (Parsons et al 2012 *[57]*, Campbell et al 2018 *[55]*)

Practical Info

Eligibility criteria using tenecteplase are the same as those listed for alteplase. Tenecteplase is administered as a single bolus over 5 seconds. The recommended dose used in ischaemic stroke is 0.25mg/kg (maximum 25mg) which is substantially lower than that used for ST-elevation myocardial infarction (approximately 0.5mg/kg) and this must be clearly stated in protocols as **use of tenecteplase for stroke is off-label** and all packaging and product information refers to the cardiac dose. The use of tenecteplase doses higher than 0.25mg/kg is currently investigational.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Tenecteplase significantly improved the overall odds of a good stroke outcome at 90 days versus alteplase when administered within 4.5 hours of stroke onset to patients with a large vessel occlusion in two randomised controlled trials.

The Australian tenecteplase trial (Parsons et al 2012 *[57]*) studied patients with large vessel occlusion prior to the introduction of endovascular thrombectomy. Tenecteplase-treated patients had improved reperfusion, early neurological recovery and functional outcomes at 3 months, particularly in the 0.25mg/kg dose tier. The EXTEND-IA TNK trial (Campbell et al 2018 *[55]*) studied similar patients who were planned to undergo endovascular thrombectomy and used a 0.25mg/kg tenecteplase dose. Tenecteplase-treated patients had increased reperfusion prior to thrombectomy and improved functional outcomes at 3 months, The risk of symptomatic intracerebral haemorrhage was similar with tenecteplase versus alteplase (1% in each group in the EXTEND-IA TNK trial). In the EXTEND-IA TNK part 2 trial (Campbell et al 2020 *[68]*) demonstrated no advantage of increasing the tenecteplase dose from 0.25mg/kg to the 0.4mg/kg dose.

Certainty of the Evidence Moderate

The overall quality of evidence is moderate to high, based on the two main randomised controlled trials with low risk of bias. Overall quality was high but certainty was downgraded due to relatively small number of participants. The evidence is consistent across all five trials involving tenecteplase.

Preference and values No substantial variability expected

For most patients the benefits in reduced disability would be preferred to the small risk of symptomatic haemorrhage. Tenecteplase increased the chance of benefit with same (small) risk of bleeding so would be preferred in most cases.

Resources and other considerations No important issues with the recommended alternative

Resources considerations

Tenecteplase in less expensive than alteplase in Australia and New Zealand. In EXTEND-IA TNK tenecteplase reduced the requirement for endovascular thrombectomy and reduced long term disability, both of which also reduce treatment cost.

Implementation considerations

There is a clinical indicator collected in the National Stroke Audit to determine the total number of patients with ischaemic stroke who receive thrombolysis. There are also clinical indicators collected on the total number of patients who received thrombolysis if they were admitted to hospital within 4.5 hours of their symptom onset, and also for those patients who did receive thrombolysis, if this was administered within 60 minutes of the patient's arrival. A further clinical indicator is collected to determine the median time (and interquartile range) from stroke symptom onset to the time of delivery of thrombolysis. An additional clinical indicator is also collected to determine the median time from admission to the administering of thrombolysis for patients with ischaemic stroke.

Rationale

The evidence for alteplase is now well established (see previous recommendation). In patients with large vessel occlusion who did not receive thrombectomy, a pooled individual patient data meta-analysis of the Australian and ATTEST randomised trials (Bivard et al 2017*[67]*) demonstrated improved reperfusion and functional outcomes with tenecteplase. The EXTEND-IA TNK trial (Campbell et al 2018 *[55]*) demonstrated improved reperfusion and functional outcome in large vessel occlusion ischaemic stroke patients who were also treated with thrombectomy. Taken together, the evidence from these randomised trials, specifically in patients with stroke due to large vessel occlusion, indicates that intravenous tenecteplase is likely superior, and certainly non-inferior, to alteplase, with or without the addition of endovascular thrombectomy. This was reinforced in a systematic review of five trials with tenecteplase which demonstrated non-inferiority across all trials (Burgos 2019 *[66]*). Another review found the most favourable dose was 0.25mg/kg (Kheiri et al 2018)*[56]*. Similarly, the EXTEND-IA TNK part 2 trial (Campbell et al 2020 *[68]*) demonstrated no advantage of increasing the tenecteplase dose from 0.25mg/kg to the 0.4mg/kg dose that was used in the NOR-TEST trial. There was no significant difference in safety (accounting for an imbalance in procedure-related wire perforations). Given that thrombolytic dose for stroke is usually based on estimated weight, this provides reassurance that there is a window of safety when using 0.25mg/kg tenecteplase if weight is inadvertently overestimated.

Due to the relatively small number of patients in the trials we have not formally recommended tenecteplase be given in preference to alteplase in these patients. However, the greater convenience and reduced cost of tenecteplase versus alteplase is also an important consideration.

Clinical Question/ PICO

Population: Adults with acute stroke due to large vessel occlusion treated at 0-4.5 hours without perfusion imaging selection

Intervention: Intravenous tenecteplase

Comparator: Intravenous alteplase

Summary

A review by Katsanos et al (2021)*[281]* investigated intravenous thrombolysis with tenecteplase with four studies and 433 patients. Patients with large vessel occlusions (LVO) receiving tenecteplase had higher modified Rankin Scale scores (OR 2.06, 95% CI 1.15 to 3.69; 2 studies, n= 277), successful recanalisation (OR 3.05, 95% CI 1.73 to 5.40; 3 studies, n= 315) and functional improvement (cOR 1.84, 95% CI 1.18 to 2.87; 3 studies, n= 315) at 3 months compared with LVO patients receiving alteplase. No difference was found for symptomatic intracranial haemorrhage (OR 0.66, 95% CI 0.19 to 2.23; 3 studies, n= 395), any intracranial haemorrhage (OR 0.87, 95% CI 0.35 to 2.17; 3 studies, n= 395), rates of disability (OR 1.49, 95% CI 0.95 to 2.32; 3 studies, n= 433) and rate of mortality (OR 0.93, 95% CI 0.31 to 2.80; 3 studies, n= 395) at 3 months between the groups.

The previous evidence is based on data from 3 randomised controlled trials, two of which preceded the use of endovascular thrombectomy. The pooled individual patient data from Parsons et al 2012*[57]* and ATTEST*[60]* therefore provides direct evidence of the efficacy of tenecteplase versus alteplase on reperfusion and functional outcomes without confounding by endovascular thrombectomy. EXTEND-IA TNK*[55]* reflects the current clinical practice for most Australian and New Zealand hospitals of thrombolysis followed by endovascular thrombectomy for patients with large vessel occlusion and provided the reperfusion and functional outcome data for patients proceeding to endovascular thrombectomy. There were statistcally significant improvements in early reperfusion and in 90 day functional outcome. However, the relatively small number of patients in the trials led to a moderate quality rating. EXTEND-IA TNK part 2 trial (Campbell et al 2020 *[68]*) demonstrated no advantage of increasing the tenecteplase dose from 0.25mg/kg to the 0.4mg/kg dose that was used in the NOR-TEST trial. There was no significant difference in safety (accounting for an imbalance in procedure-related wire perforations).

Outcome Timeframe	**Study results and measurements**	**Comparator** Intravenous alteplase	**Intervention** Intravenous tenecteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Successful recanalisation [1] Before EVT 7 Critical	Odds Ratio 3.05 (CI 95% 1.73 — 5.4) Based on data from 315 patients in 3 studies. [2] (Randomized controlled)	227 per 1000	472 per 1000 Difference: 245 more per 1000 (CI 95% 110 more — 386 more)	Moderate	Intravenous tenecteplase probably improves successful recanalisation
Improved functional outcome [3] 3 months 9 Critical	Odds Ratio 1.84 (CI 95% 1.18 — 2.87) Based on data from 315 patients in 3 studies. (Randomized controlled)	CI 95%		Moderate	Intravenous tenecteplase probably improves improved functional outcome
Death 3 months 8 Critical	Odds Ratio 0.93 (CI 95% 0.31 — 2.8) Based on data from 395 patients in 3 studies. (Randomized controlled)	130 per 1000	122 per 1000 Difference: 8 fewer per 1000 (CI 95% 86 fewer — 165 more)	Low CI fails to exclude important benefit or important harms.	Intravenous tenecteplase has little or no effect on death

Outcome Timeframe	Study results and measurements	Comparator Intravenous alteplase	Intervention Intravenous tenecteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
Symptomatic intracerebral haemorrhage [4] 48 hours 8 Critical	Odds Ratio 0.66 (CI 95% 0.19 — 2.23) Based on data from 395 patients in 3 studies. (Randomized controlled)	31 per 1000	21 per 1000 Difference: **10 fewer** per 1000 (CI 95% 25 fewer — 36 more)	**Low** CI fails to exclude important benefit or important harms.	Intravenous tenecteplase has little or no effect on symptomatic intracerebral haemorrhage versus alteplase
Any intracerebral haemorrhage [5] 48 hours 8 Critical	Odds Ratio 0.87 (CI 95% 0.35 — 2.17) Based on data from 395 patients in 3 studies. (Randomized controlled)	115 per 1000	102 per 1000 Difference: **13 fewer** per 1000 (CI 95% 71 fewer — 105 more)	**Low** CI fails to exclude important benefit or important harms.	Intravenous tenecteplase has little or no effect on any intracerebral haemorrhage versus alteplase
Disability 72 hours 8 Critical	Odds Ratio 1.09 (CI 95% 0.37 — 3.16) Based on data from 395 patients in 3 studies. (Randomized controlled)	510 per 1000	532 per 1000 Difference: **22 more** per 1000 (CI 95% 232 fewer — 257 more)	**Very low** CI fails to exclude important benefit or important harms, significant heterogeneity between studies [6]	Intravenous tenecteplase has little or no effect on disability

1. Opening of the occluded blood vessel in the brain
2. Systematic review [281] . **Baseline/comparator:** Control arm of reference used for intervention.
3. Improvement by >=1 point on the modified Rankin Scale
4. Bleeding into the brain causing neurological worsening within 48 hours of treatment (SITS definition - parenchymal haematoma type 2 associated with >=4 point increase in National Institutes of Health Stroke Scale Score)
5. Bleeding into the brain causing neurological worsening within 48 hours of treatment (SITS definition - parenchymal haematoma type 2 associated with >=4 point increase in National Institutes of Health Stroke Scale Score)
6. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2:... %.. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Clinical Question/ PICO

Population: Adults with acute stroke treated within 4.5 hours
Intervention: Intravenous tenecteplase
Comparator: Intravenous alteplase

Summary

The evidence is drawn from an individual patient data meta-analysis of 3 randomised trials (Huang et al 2016 *[59]*). The subgroup treated with 0.25mg/kg tenecteplase was extracted as this dose was superior to 0.1mg/kg and there were insufficient data using 0.4mg/kg. Point estimates favoured tenecteplase versus alteplase but there were no statistically significant differences. Subsequent to this meta-analysis the NOR-TEST trial (n=1100) showed similar outcomes with 0.40mg/kg tenecteplase versus alteplase but in a very mild stroke population (median NIHSS 4) and this was not a formal non-inferiority trial (Logallo et al 2017 *[60]*). Recently non-inferiority involving five trials (n=1585 patients). Across the trials TNK dosing was 0.1 mg/kg in 6.8%, 0.25 mg/kg in 24.6%, and 0.4 mg/kg in 68.6%. Good clinical outcome (modified Rankin Scale score, 0-1) at 3 months was similar between TNK 57.9% versus ALT 55.4% and feel within the prespecified noninferiority margin. Similar results were found for modified Rankin Scale score, 0-2, modified

Rankin Scale shift analysis, and safety outcomes (Burgos and Saver 2019*[66]*).

Ongoing phase 3 trials are comparing tenecteplase and alteplase in patients without large vessel occlusion.

Outcome Timeframe	**Study results and measurements**	**Comparator** Intravenous alteplase	**Intervention** Intravenous tenecteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Excellent outcome (modified Rankin Scale 0-1) [1] 3 months 8 Critical	Odds Ratio 1.8 (CI 95% 0.9 — 3.4) Based on data from 216 patients in 3 studies. (Randomized controlled) Follow up: 216.	306 per 1000	442 per 1000 Difference: **136 more** per 1000 (CI 95% 22 fewer — 294 more)	**Moderate** Due to serious imprecision [2]	Intravenous tenecteplase probably improves excellent outcome (modified rankin scale 0-1) slightly
Functional Independence (modified Rankin Scale 0-2) [3] 3 months 8 Critical	Odds Ratio 2 (CI 95% 0.6 — 6.3) Based on data from 216 patients in 3 studies. (Randomized controlled) Follow up: 216.	407 per 1000	579 per 1000 Difference: **172 more** per 1000 (CI 95% 115 fewer — 405 more)	**Moderate** Due to serious imprecision [4]	Intravenous tenecteplase probably improves functional independence (modified rankin scale 0-2) slightly
Death [5] 3 months 8 Critical	Odds Ratio 0.9 (CI 95% 0.4 — 2) Based on data from 216 patients in 3 studies. (Randomized controlled) Follow up: 216.	157 per 1000	144 per 1000 Difference: **13 fewer** per 1000 (CI 95% 88 fewer — 114 more)	**Moderate** Due to serious imprecision [6]	Intravenous tenecteplase probably has little or no effect on death
Symptomatic intracerebral haemorrhage 24 hours 8 Critical	Relative risk 0.6 (CI 95% 0.2 — 2.1) Based on data from 216 patients in 3 studies. (Randomized controlled) Follow up: 216.	65 per 1000	39 per 1000 Difference: **26 fewer** per 1000 (CI 95% 52 fewer — 72 more)	**Moderate** Due to serious imprecision [7]	Intravenous tenecteplase probably has little or no effect on symptomatic intracerebral haemorrhage versus alteplase

1. Modified Rankin Scale 0-1 indicates return to all regular pre-stroke activities at 3 months post-stroke, some stroke symptoms may remain.
2. **Risk of Bias: No serious.** Lack of blinding of participants but assessors were blinded. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
3. Functional Independence (modified Rankin Scale 0-2) at 3 months post-stroke
4. **Risk of Bias: No serious.** Lack of blinding of participants but assessors were blinded. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. Death at 3 months
6. **Risk of Bias: No serious.** Lack of blinding of participants but assessors were blinded. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. **Risk of Bias: No serious.** Lack of blinding of participants but assessors blinded. **Inconsistency: No serious. Indirectness:**

No serious. Imprecision: Serious. Wide confidence intervals. **Publication bias: No serious.**

Weak recommendation

For patients with potentially disabling ischaemic stroke without large vessel occlusion who meet specific clinical and brain imaging eligibility criteria, tenecteplase may be used as an alternative to alteplase within 4.5 hours of onset. (Huang et al 2016 *[59]*)

Practical Info

Eligibility criteria using tenecteplase are the same as those listed for alteplase. Tenecteplase is administered as a single bolus over 5 seconds. The recommended dose used in ischaemic stroke is 0.25mg/kg (maximum 25mg) which is substantially lower than that used for ST-elevation myocardial infarction (approximately 0.5mg/kg) and this must be clearly stated in protocols as **use of tenecteplase for stroke is off-label** and all packaging and product information refers to the cardiac dose. The use of tenecteplase doses higher than 0.25mg/kg is currently investigational.

In hospitals that do not stock alteplase, tenecteplase is a reasonable alternative. Patients should be enrolled in randomised trials wherever possible.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Evidence from an individual patient meta-analysis of 3 trials suggested that tenecteplase is at least as effective as alteplase in ischaemic stroke patients without large vessel occlusion and the risk of symptomatic intracerebral haemorrhage is no higher (Huang et al 2016 *[59]*). A subsequent study-level meta-analysis including 5 trials also found similar benefits and harms to alteplase (Kheiri et al 2018 *[56]*). However, there are ongoing phase 3 trials addressing this issue and formal non-inferiority has not been demonstrated at this stage.

Certainty of the Evidence

Moderate

The trials are heterogeneous in stroke severity and the dose of tenecteplase used and the total number of patients is moderate. Further trials may alter the balance of evidence.

Preference and values

No substantial variability expected

There was deemed to be little difference in the patient preferences and values of tenecteplase over alteplase.

Resources and other considerations

No important issues with the recommended alternative

Tenecteplase is less expensive and easier to administer than alteplase.

Rationale

The evidence suggests that tenecteplase is at least as effective as alteplase in ischaemic stroke patients without large vessel occlusion and the risk of symptomatic intracerebral haemorrhage is no higher (Huang et al 2016 *[59]*, Kheiri et al 2018 *[56]*). Non-inferiority has been demonstrated based on analysis of five trials (N=1585) (Burgos 2019 *[66]*). However, there are ongoing phase 3 trials addressing this issue and the strength of recommendation is therefore weak as further trials may shift the balance of evidence.

Clinical Question/ PICO

Population: Adults with acute stroke treated within 4.5 hours
Intervention: Intravenous tenecteplase
Comparator: Intravenous alteplase

Summary

The evidence is drawn from an individual patient data meta-analysis of 3 randomised trials (Huang et al 2016 *[59]*). The subgroup treated with 0.25mg/kg tenecteplase was extracted as this dose was superior to 0.1mg/kg and there were insufficient data using 0.4mg/kg. Point estimates favoured tenecteplase versus alteplase but there were no statistically significant differences. Subsequent to this meta-analysis the NOR-TEST trial (n=1100) showed similar outcomes with 0.40mg/kg tenecteplase versus alteplase but in a very mild stroke population (median NIHSS 4) and this was not a formal non-inferiority trial (Logallo et al 2017 *[60]*). Recently non-inferiority involving five trials (n=1585 patients). Across the trials TNK dosing was 0.1 mg/kg in 6.8%, 0.25 mg/kg in 24.6%, and 0.4 mg/kg in 68.6%. Good clinical outcome (modified Rankin Scale score, 0-1) at 3 months was similar between TNK 57.9% versus ALT 55.4% and feel within the prespecified noninferiority margin. Similar results were found for modified Rankin Scale score, 0-2, modified Rankin Scale shift analysis, and safety outcomes (Burgos and Saver 2019*[66]*).

Ongoing phase 3 trials are comparing tenecteplase and alteplase in patients without large vessel occlusion.

Outcome Timeframe	**Study results and measurements**	**Comparator** Intravenous alteplase	**Intervention** Intravenous tenecteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Excellent outcome (modified Rankin Scale 0-1) [1] 3 months 8 Critical	Odds Ratio 1.8 (CI 95% 0.9 — 3.4) Based on data from 216 patients in 3 studies. (Randomized controlled) Follow up: 216.	306 per 1000	442 per 1000 Difference: **136 more** per 1000 (CI 95% 22 fewer — 294 more)	**Moderate** Due to serious imprecision [2]	Intravenous tenecteplase probably improves excellent outcome (modified rankin scale 0-1) slightly
Functional Independence (modified Rankin Scale 0-2) [3] 3 months 8 Critical	Odds Ratio 2 (CI 95% 0.6 — 6.3) Based on data from 216 patients in 3 studies. (Randomized controlled) Follow up: 216.	407 per 1000	579 per 1000 Difference: **172 more** per 1000 (CI 95% 115 fewer — 405 more)	**Moderate** Due to serious imprecision [4]	Intravenous tenecteplase probably improves functional independence (modified rankin scale 0-2) slightly
Death [5] 3 months 8 Critical	Odds Ratio 0.9 (CI 95% 0.4 — 2) Based on data from 216 patients in 3 studies. (Randomized controlled) Follow up: 216.	157 per 1000	144 per 1000 Difference: **13 fewer** per 1000 (CI 95% 88 fewer — 114 more)	**Moderate** Due to serious imprecision [6]	Intravenous tenecteplase probably has little or no effect on death
Symptomatic intracerebral haemorrhage 24 hours	Relative risk 0.6 (CI 95% 0.2 — 2.1) Based on data from 216 patients in 3 studies. (Randomized controlled)	65 per 1000	39 per 1000 Difference: **26 fewer** per 1000	**Moderate** Due to serious imprecision [7]	Intravenous tenecteplase probably has little or no effect on symptomatic intracerebral haemorrhage versus

Outcome Timeframe	Study results and measurements	Comparator Intravenous alteplase	Intervention Intravenous tenecteplase	Certainty of the Evidence (Quality of evidence)	Plain text summary
8 Critical	Follow up: 216.	(CI 95% 52 fewer — 72 more)			alteplase

1. Modified Rankin Scale 0-1 indicates return to all regular pre-stroke activities at 3 months post-stroke, some stroke symptoms may remain.
2. **Risk of Bias: No serious.** Lack of blinding of participants but assessors were blinded. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
3. Functional Independence (modified Rankin Scale 0-2) at 3 months post-stroke
4. **Risk of Bias: No serious.** Lack of blinding of participants but assessors were blinded. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. Death at 3 months
6. **Risk of Bias: No serious.** Lack of blinding of participants but assessors were blinded. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. **Risk of Bias: No serious.** Lack of blinding of participants but assessors blinded. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

Strong recommendation

When using intravenous alteplase, a dose of 0.9 mg/kg, maximum of 90 mg should be administered. (Wardlaw et al. 2014 *[39]*; Emberson et al. 2014 *[40]* Anderson et al. 2016 *[42]*)

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

In one large randomised controlled trial with mostly Asian patients (N=3206), low-dose (0.6 mg/kg) intravenous alteplase reduced the risk of intracerebral haemorrhage (11 fewer per 1000 patients), but patients tended to have increased death or disability (22 more per 1000) and the trial did not meet non-inferiority criteria compared to 0.9 mg/kg *[42]*.

Certainty of the Evidence — High

The overall quality of evidence for the 0.9mg/kg dose of alteplase is high, based on meta-analyses of large randomised controlled trials with low risk of bias and the direct comparison versus 0.6mg/kg in the ENCHANTED trial that did not demonstrate non-inferiority.

Preference and values — No substantial variability expected

For most patients the benefits in reduced disability would be preferred to the small risk of symptomatic haemorrhage. Evidence indicates that >75% of patients would consent to stroke thrombolysis and would also want to receive thrombolysis if they were unable to consent themselves. This was very similar to the proportion of patients who would want CPR if they had a cardiac arrest (Chiong et al. 2014 *[54]*).

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

Resources considerations

A decision analytic model using information on patients with ischaemic stroke treated with alteplase at a single Australian hospital was used to assess the cost-effectiveness of alteplase over 12 months after stroke (Tan Tanny et al. 2013 *[47]*). Treatment with alteplase within 4.5 hours was found to be cost-effective compared to no alteplase treatment (produced health gains for an acceptable additional cost to the alternative) at an additional cost of AU$2,377 per life-year saved and AU$1,478 per QALY gained (cost reference year not reported) (Tan Tanny et al. 2013 *[47]*). There is also evidence from economic modelling using stroke incidence data that alteplase commenced within 3 hours is more effective and less costly compared to no alteplase treatment. (Mihalopoulos et al. 2005 *[169]*)

There is evidence from studies conducted outside of Australia that treatment with alteplase within 4.5 hours of stroke onset is either cost-effective or dominant over placebo in the long-term (Pan et al. 2014 *[48]*; Boudreau et al. 2014 *[49]*; Tung et al. 2011 *[50]*; Boudreau et al. 2013 *[51]*).

In a systematic review of cost-effectiveness data, Demaerschalk et al. (2010) *[46]* found that alteplase increased hospitalisation costs, but resulted in long-term cost savings associated with decreased nursing home and rehabilitation costs. However, this was based on data published in 1998 and economic evaluations utilising newer research findings are required.

Implementation considerations

There is a clinical indicator collected in the National Stroke Audit to determine the total number of patients with ischaemic stroke who receive thrombolysis. There are also clinical indicators collected on the total number of patients who received thrombolysis if they were admitted to hospital within 4.5 hours of their symptom onset, and also for those patients who did receive thrombolysis, if this was administered within 60 minutes of the patient's arrival. A further clinical indicator is collected to determine the median time (and interquartile range) from stroke symptom onset to the time of delivery of thrombolysis. An additional clinical indicator is also collected to determine the median time from admission to the administering of thrombolysis for patients with ischaemic stroke.

Rationale

High-quality evidence suggests that the benefits of intravenous alteplase at a dose of 0.9mg/kg outweigh its harms if given within 4.5 hours in patients satisfying specific criteria (Wardlaw et al. 2014 *[39]*; Emberson et al. 2014 *[40]*). Benefits have not been established beyond 4.5 hours in patients selected based on non-contrast CT and clinical criteria. However, patients selected using perfusion imaging do benefit beyond 4.5 hours (see separate recommendation).

Lower dose alteplase (0.6 mg/kg) did not meet non-inferiority criteria and therefore standard (0.9 mg/kg) dose is recommended (Wardlaw et al. 2014 *[39]*; Anderson et al. 2016 *[42]*).

Clinical Question/ PICO

Population: Adults with acute stroke
Intervention: Low-dose intravenous alteplase
Comparator: Standard-dose intravenous alteplase

Summary

Anderson et al. (2016) *[42]* compared low-dose (0.6 mg per kilogram body weight) intravenous alteplase to standard dose (0.9 mg per kilogram) in an open-label randomised trial (N = 3310). While previous evidence on intravenous alteplase has suggested that a dose of 0.9 mg per kilogram body weight provided benefits in the form of increased survival without disability, the treatment has also been associated with increased intracerebral haemorrhage, particularly in the short term. This risk of intracerebral haemorrhage may be higher in Asian populations. In this trial, low-dose alteplase did not meet non-inferiority criteria compared to standard dose treatment when comparing the primary outcome of modified Rankin scale scores 2–6 (OR 1.09, 95% CI 0.95 to 1.25), where the boundary for non-inferiority was prespecified at 1.14. However, there were significantly fewer symptomatic intracerebral haemorrhages in patients treated with low-dose alteplase (1% for the low-dose group vs 2.1% for the standard dose). The trial included predominantly Asian patients which could limit generalisability, but in subgroup analyses, no significant differences were seen between Asian and non-Asian patients. Median stroke severity (NIHSS 8) was milder than in the major preceding thrombolysis trials.

Previous comparisons of dosages, included in a 2013 Cochrane review by Wardlaw et al. *[43]*, provided limited evidence on overall mortality or death and dependency. Only a few small trials reporting these outcomes were included in the review, with results from 5 studies (N = 496) showing a lower number of total deaths in patients given higher-dose alteplase (OR 0.74, 95% 0.37 to 1.52) but no significant differences. Four included trials also showed significantly increased fatal intracranial haemorrhage but the total number of events was low, with 3 out of 4 included trials observing no fatal ICH.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard-dose intravenous alteplase	**Intervention** Low-dose intravenous alteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Improved functional outcome [1] 90 days 8 Critical	Odds Ratio 1 (CI 95% 0.89 — 1.13) Based on data from 3,206 patients in 1 studies. (Randomized controlled) Follow up: 90 days.			**Low** Due to serious imprecision, Due to serious indirectness [2]	Low-dose intravenous alteplase may have little or no effect on functional outcome
Symptomatic ICH [3] 90 days 8 Critical	Odds Ratio 0.48 (CI 95% 0.27 — 0.86) Based on data from 3,297 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	21 per 1000	10 per 1000 Difference: **11 fewer** per 1000 (CI 95% 15 fewer — 3 fewer)	**Low** Due to serious imprecision, Due to serious indirectness [4]	Low-dose intravenous alteplase may decrease symptomatic ICH
Death or disability [5] 90 days 9 Critical	Odds Ratio 1.09 (CI 95% 0.95 — 1.25) Based on data from 3,206 patients in 1 studies. (Randomized controlled)	511 per 1000	533 per 1000 Difference: **22 more** per 1000 (CI 95% 13 fewer — 55 more)	**Low** Due to serious imprecision, Due to serious indirectness [6]	Low-dose intravenous alteplase may slightly increase death or disability
Death 90 days 9 Critical	Odds Ratio 0.8 (CI 95% 0.63 — 1.01) Based on data from 3,297 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	103 per 1000	84 per 1000 Difference: **19 fewer** per 1000 (CI 95% 36 fewer — 1 more)	**Low** Due to serious imprecision, Due to serious indirectness [7]	Low-dose intravenous alteplase may slightly decrease death

1. Ordinal analysis of improvement on modified Rankin Scale
2. **Inconsistency: No serious. Indirectness: Serious.** Mostly Asian population. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
3. SITS-MOST criteria: A large local or remote parenchymal pattern and neurologic deterioration from baseline (increase of more than 4 points in NIHSS score) or death within 36 hours
4. **Inconsistency: No serious. Indirectness: Serious.** Mostly Asian population. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
5. Disability classified as Modified Rankin Scale 2-6
6. **Inconsistency: No serious. Indirectness: Serious.** Mostly Asian population. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
7. **Inconsistency: No serious. Indirectness: Serious.** Mostly Asian population. **Imprecision: Serious.** Only data from one

study. **Publication bias: No serious.**

Strong recommendation

For patients with potentially disabling ischaemic stroke who meet perfusion mismatch criteria in addition to standard clinical criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) should be administered up to 9 hours after the time the patient was last known to be well, or from the midpoint of sleep for patients who wake with stroke symptoms, unless immediate endovascular thrombectomy is planned. (Ma et al 2019 *[64]*, Campbell et al 2019 *[58]*)

Practical Info

Intravenous thrombolysis eligibility in patients beyond 4.5 hours requires evidence of perfusion mismatch, in addition to all the standard eligibility criteria described in the 0-4.5 hour thrombolysis recommendations.

Perfusion mismatch can be assessed using CT perfusion or MR perfusion-diffusion mismatch. Validated thresholds for hypoperfusion (Tmax>6 seconds or delay time > 3 seconds) should be used when defining perfusion mismatch. Similarly the irreversibly injured ischaemic core should be defined using a validated threshold (e.g. CT perfusion: relative cerebral blood flow <30% of normal brain tissue; Diffusion MRI: apparent diffusion co-efficient <620μm^2/s). CT perfusion is more widely and rapidly available in the Australian and New Zealand context. Treatment decisions based purely on visual assessment of perfusion maps is discouraged - this approach based on MRI was used in the ECASS4-EXTEND trial which was neutral overall. Only 55% of patients met automated mismatch criteria, mostly due to small perfusion lesions that did not reach the Tmax>6second hypoperfusion threshold. There was a statistically significant functional improvement (ordinal shift analysis) in the subgroup with automated mismatch. Patients not meeting automated mismatch criteria showed no evidence of benefit and trends to increased risks which, although tests of statistical interaction were non-significant, does not support treatment in the absence of automated mismatch.

Careful inspection of the non-contrast CT brain is particularly crucial in the later time window. In addition to excluding pre-existing subtle haemorrhagic transformation, the extent and severity of hypodensity on the non-contrast CT likely corresponds to the risk of post-treatment haemorrhagic transformation. The site of occlusion can shift distally, particularly in the later time window, and this can lead to non-contrast CT hypodensity outside the current perfusion lesion which may invalidate a perceived mismatch and pose a risk of haemorrhagic transformation.

Where possible clear communication and gaining consent should be undertaken with the patient and/or their family. Explanation in simple language should involve how thrombolysis works and why it is being recommended including the risks and benefits. Brain imaging findings should also be discussed. The decision aids with MAGICapp can be used in the discussion.

The extended time window thrombolysis trials did not include patients treated with endovascular thrombectomy which is now part of standard care for patients with large vessel occlusion and perfusion mismatch up to 24 hours. Large vessel occlusion was present in ~70% of patients in the extended time window thrombolysis trial patients. There was no evidence of treatment effect heterogeneity between the patients with and without large vessel occlusion in the meta-analysis of EXTEND, ECASS4 and EPITHET. If endovascular thrombectomy is not immediately available on-site then patients meeting these criteria should receive thrombolysis and proceed to endovascular thrombectomy as rapidly as possible. If endovascular thrombectomy is immediately available, the existing trial data are not informative about the benefits and risks of combined therapy and this is the focus of ongoing clinical trials.

The implementation of this recommendation requires access to CT perfusion and specialist stroke expertise which is currently variable outside metropolitan hospitals. Stroke telemedicine and image transfer for central processing are strategies successfully used in Victoria to overcome geographical and expertise barriers.

Evidence To Decision

Benefits and harms	Substantial net benefits of the recommended alternative

Alteplase significantly improved the overall odds of a good stroke outcome at 90 days when administered 4.5 to 9 hours after stroke onset or in patients with stroke symptoms on awakening (wake-up stroke). 160 more patients per 1000 patients treated returned to all their usual activities (mRS 0-1). Alteplase also significantly increased the odds of ≥1 point improvement in modified Rankin scale in ordinal analysis that accounts for shifts in disability across the full range of the modified Rankin Scale. Although the onset time in wake-up stroke is unknown, there is indirect evidence that many strokes occur close to the time of waking. In the pivotal trials, the stroke onset time for wake-up stroke patients was defined as the midpoint of going to sleep and waking with stroke and patients and patients were enrolled if they were within 9 hours of that midpoint.

Notably door to needle time in the trials was ~2 hours due to the lack of systems to rapidly screen patients presenting >4.5 hours in the period preceding evidence for endovascular thrombectomy up to 24h post stroke onset. The magnitude of benefit may therefore be greater with faster treatment in routine clinical practice.

Previous trials showed no significant benefit when alteplase was delivered after 4.5 h using standard clinical and non-contrast CT eligibility criteria and patients in the recent trials who did not meet automated perfusion mismatch criteria had no signal of benefit.

Alteplase increased the risk of symptomatic intracerebral haemorrhage (by 42 per 1000 using the SITS definition of symptomatic haemorrhage). There was an increased risk of fatal intracranial haemorrhage in alteplase treated patients (20 per 1000). However, at 90 days there was no significant difference in mortality or the composite of death and requirement for nursing home care.

Certainty of the Evidence High

The overall quality of evidence is high, based on meta-analyses of three randomised controlled trials with low risk of bias. There are relatively small numbers for safety outcomes (mortality, sICH) and therefore the certainty of evidence for these outcomes should be considered moderate.

Preference and values No substantial variability expected

For most patients the benefits in reduced disability would be preferred to the small risk of symptomatic haemorrhage. Evidence indicates that >75% of patients would consent to stroke thrombolysis and would also want to receive thrombolysis if they were unable to consent themselves. This was very similar to the proportion of patients who would want CPR if they had a cardiac arrest (Chiong et al. 2014 *[54]*).

Resources and other considerations No important issues with the recommended alternative

<u>Resources considerations</u>

To date there have not been formal economic evaluations of perfusion-selected thrombolysis beyond 4.5 hours. However, the magnitude of benefit is at least as great as thrombolysis 0-3 hours and the costs are no different so the cost effectiveness of alteplase demonstrated in the early time window should also apply to the perfusion mismatch selected patients beyond 4.5 hours. The requirement for perfusion imaging to identify eligible patients for thrombolysis and thrombectomy in the extended time window is a relevant consideration for some centres outside major metropolitan areas where this imaging is not currently performed. Most current CT scanner hardware is capable of acquiring CT perfusion and automated software processing is available, potentially through central servers where volume at smaller hospitals does not justify on-site installation. Radiographers who have been trained to acquire CT angiography will be able to also acquire CT perfusion with minimal additional training.

<u>Implementation considerations</u>

There is a clinical indicator collected in the National Stroke Audit to determine the total number of patients with ischaemic stroke who receive thrombolysis. There are also clinical indicators collected on the total number of patients who received thrombolysis if they were admitted to hospital within 4.5 hours of their symptom onset, and also for those patients who did receive thrombolysis, if this was administered within 60 minutes of the patient's arrival. A further clinical indicator is

collected to determine the median time (and interquartile range) from stroke symptom onset to the time of delivery of thrombolysis. An additional clinical indicator is also collected to determine the median time from admission to the administering of thrombolysis for patients with ischaemic stroke.

Rationale

High-quality evidence suggests that the benefits of intravenous alteplase outweigh its harms if given to selected patients satisfying specific perfusion mismatch and clinical criteria. The available trials did not include patients also treated with endovascular thrombectomy which is now standard care in this time window for patients with large vessel occlusion and perfusion mismatch (see Neurointervention section). Whether intravenous thrombolysis provides additional benefit to endovascular thrombectomy in this time window is unknown and the subject of ongoing trials. Thrombolysis is recommended in patients with large vessel occlusion who do not have immediate, on-site access to endovascular thrombectomy e.g. during transfer to an endovascular-capable hospital.

There was no evidence of treatment effect heterogeneity within the 4.5-6 vs 6-9h or Wake-up strata in the meta-analysis. Analogous data in patients treated with thrombectomy in an extended time window using the same imaging selection also showed no effect of time when imaging was favourable (Albers et al 2018 *[92]*).

Clinical Question/ PICO

Population: Adults with acute stroke treated 4.5-9 hours or after wake-up onset using perfusion imaging selection
Intervention: Intravenous alteplase
Comparator: Control

Summary

The data are drawn from an individual patient data meta-analysis of 3 randomised, placebo-control trials and the subgroup meeting automated perfusion mismatch criteria were extracted (Campbell et al. 2019*[58]*). Excellent functional outcome occurred in 36% alteplase-treated patients versus 26% placebo-treated patients, p=0.01. Symptomatic intracerebral haemorrhage was increased with alteplase (5% versus 1%, p=0.07). However, this did not negate an overall functional benefit in ordinal (shift) analysis which accounts for transitions across the disability spectrum (common odds ratio 1·68 (95%CI 1·11–2·53), p=0.01). Patients not meeting automated mismatch criteria showed no evidence of benefit and trends to increased risks which, although tests of statistical interaction were non-significant, does not support treatment in the absence of automated mismatch.

A review by Campbell et al (2020)*[280]* investigated whether the benefit of intravenous alteplase across 4.5- to 9- hours and wake-up stroke time windows with two studies and 295 patients. Reperfusion was assessable in 51% (68 of 133, 2 studies) of the alteplase group and in 28% (38 of 137, 2 studies) of the placebo reperfusion group (p< 0.001). Reperfusion improved functional outcome (common OR 7.7, 95% CI 4.6 to 12.8) and at every timepoint of interest. Symptomatic haemorrhage occurred in 5.9% (3 of 51) in the 4.5- to 6-hours group, 7.1% (2 of 28) in the 6- to 9-hours group, and 5.5% (4 of 73) in the wake-up stroke in patients treated with alteplase.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Intravenous alteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Excellent outcome (modified Rankin Scale 0-1) [1] 3 months	Odds Ratio 2.06 (CI 95% 1.17 — 3.62) Based on data from 304 patients in 3 studies. [2] (Randomized controlled) Follow up: 303.	260 per 1000	420 per 1000	**High** [3]	Intravenous alteplase improves excellent outcome (modified rankin scale 0-1) for patients with evidence of salvageable brain tissue using perfusion imaging.
		Difference: **160 more** per 1000 (CI 95% 31 more — 300 more)			

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Intravenous alteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
8 Critical					
Functional Independence (modified Rankin Scale 0-2) [4] 3 months 8 Critical	Odds Ratio 2.22 (CI 95% 1.25 — 3.94) Based on data from 304 patients in 3 studies. [5] (Randomized controlled) Follow up: 303.	397 per 1000	594 per 1000 Difference: **197 more** per 1000 (CI 95% 54 more — 325 more)	**High** [6]	Intravenous alteplase improves functional independence (modified rankin scale 0-2)
Improved functional outcome [7] 3 months 8 Critical	Odds Ratio 1.68 (CI 95% 1.11 — 2.53) Based on data from 304 patients in 3 studies. [8] (Randomized controlled) Follow up: 303.	CI 95%		**High** [9]	Intravenous alteplase improves functional outcome
Death 3 months 8 Critical	Odds Ratio 1.28 (CI 95% 0.6 — 2.73) Based on data from 304 patients in 304 studies. [10] (Randomized controlled) Follow up: 304.	105 per 1000	131 per 1000 Difference: **26 more** per 1000 (CI 95% 39 fewer — 138 more)	**Moderate** Due to serious imprecision [11]	Intravenous alteplase has little or no effect on death
Symptomatic intracerebral haemorrhage [12] 24 hours 8 Critical	Odds Ratio 7.29 (CI 95% 0.88 — 60.18) Based on data from 304 patients in 3 studies. [13] (Randomized controlled) Follow up: 304.	7 per 1000	49 per 1000 Difference: **42 more** per 1000 (CI 95% 1 fewer — 291 more)	**Moderate** Due to serious imprecision [14]	Intravenous alteplase increases symptomatic intracerebral haemorrhage

1. Modified Rankin Scale 0-1 indicates return to all regular pre-stroke activities at 3 months post-stroke, some stroke symptoms may remain.
2. Systematic review. Data for subset of patients with automated perfusion mismatch.. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [58],
3. **Risk of Bias: No serious.** double blind placebo controlled RCT. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Wide confidence intervals, Relatively low number of patients. **Publication bias: No serious.** ECASS-4 trial was stopped early due to slow recruitment (119 of planned 264 patients included). Commercial Funding for one included trial (ECASS-4). .
4. Functional Independence (modified Rankin Scale 0-2) at 3 months post-stroke
5. Systematic review. Data from subset of patients with automated perfusion mismatch. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [58],
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Wide confidence intervals, Low number of patients. **Publication bias: No serious.** ECASS-4 trial was stopped early due to slow recruitment (119 of planned 264 patients included). Commercial Funding for one included trial (ECASS-4)..
7. Functional improvement by >=1 point on the modified Rankin Scale (ordinal shift analysis)

8. Systematic review. Data from subset of patients with automated perfusion mismatch. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [58],
9. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Wide confidence intervals, Low number of patients. **Publication bias: No serious.** ECASS-4 trial was stopped early due to slow recruitment (119 of planned 264 patients included). Commercial Funding for one included trial (ECASS-4). .
10. Systematic review. Data from subset of patients with automated perfusion mismatch. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [58],
11. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**
12. Bleeding into the brain causing neurological worsening within 24 hours of treatment (SITS definition - parenchymal haematoma type 2 associated with >=4 point increase in National Institutes of Health Stroke Scale Score)
13. Systematic review. Data from subset of patients with automated perfusion mismatch. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [58],
14. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Low number of patients. **Publication bias: No serious.** ECASS-4 trial was stopped early due to slow recruitment (119 of planned 264 patients included). Commercial Funding for one included trial (ECASS-4). .

Weak recommendation

For patients with potentially disabling ischaemic stroke of unknown onset time who meet MRI FLAIR-diffusion mismatch criteria in addition to standard clinical criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) may be administered (Thomalla et al 2019 *[61]*).

Practical Info

The FLAIR-diffusion mismatch selection approach requires rapid access to MRI. This is not possible at many hospitals and challenging even at major tertiary centres. Some stroke patients cannot have MRI due to agitation, instability or metallic implants (which may be difficulty to fully characterise in the emergency setting).

The "absence" of FLAIR hyperintensity is a subjective assessment - with careful windowing most patients have some degree of FLAIR hyperintensity within the diffusion lesion. WAKE-UP investigators operationalised this as "no parenchymal hyperintensity with standard window settings". Initial studies of the sensitivity and specificity of FLAIR-diffusion mismatch for detection of patients with stroke onset <4.5h indicated that ~60% of patients who were within 4.5h met the FLAIR negative criteria (a negative predictive value of 54%, Thomalla et al Lancet Neurol 2011).

The alternative option for patient selection beyond 4.5h of the last known well time is CT perfusion. Most current CT scanners can acquire CT perfusion which makes this approach more accessible and generalisable. There is some overlap in the patients eligible using these two selection approaches but whether FLAIR-diffusion mismatch patients without perfusion mismatch benefit from thrombolysis and vice versa has not be definitely established.

One population of perfusion-mismatch negative patients of interest is lacunar stroke. A substudy of WAKE-UP examined patients with MRI-proven lacunar stroke (Barow et al 2019). The benefit of thrombolysis in lacunar stroke has been debated and accurate diagnosis of lacunar stroke in previous thrombolysis trials has been difficult due to the lack of MRI data. This study was able to show a very similar benefit of alteplase in the lacunar subgroup compared to non-lacunar patients in WAKE-UP, providing reassurance that lacunar stroke patients do indeed benefit from thrombolysis.

The THAW randomised trial used FLAIR-diffusion mismatch selection with 0.6mg/kg alteplase in Japan. THAWS was stopped early and did not show a signal of benefit (Koga et al 2019 *[62]*). Use of standard dose (0.9mg/kg) alteplase is advised.

Evidence To Decision

Benefits and harms	Substantial net benefits of the recommended alternative

FLAIR-diffusion mismatch using MRI (a diffusion lesion that is not yet hyperintense on FLAIR imaging) indicates likely time of onset <4.5 hours. This imaging profile identified patients with unknown onset time who benefited from alteplase in the WAKE-UP randomised trial (Thomalla et al 2018 *[61]*). Excellent outcome occurred in 53.3% alteplase-treated patients versus 41.8% control patients (benefit for 115 per 1000). The risk of symptomatic intracerebral haemorrhage in WAKE-UP was 2.0% with alteplase and mortality was not significantly different (4.1% alteplase vs 1.2% placebo, p=0.07). The THAWS randomised trial using the same imaging selection approach with 0.6mg/kg alteplase in Japan was stopped early and recently presented in abstract form. THAWS did not show a signal of benefit (Koga et al 2019 *[62]*).

Certainty of the Evidence Moderate

Certainty of evidence is moderate as evidence is based on a single well conducted randomised controlled trial which was terminated early and some outcomes were imprecise.

Preference and values Substantial variability is expected or uncertain

There are alternative imaging selection strategies (perfusion mismatch with CT or MRI) that also identify patients who benefit from alteplase, despite having unknown onset or being >4.5h since onset. FLAIR-Diffusion mismatch and perfusion mismatch have intersecting but different populations of patients eligible. Urgent MRI is not possible in many hospitals and is not suitable for all patients.

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

Urgent access to MRI is not possible in many hospitals and limited even in large tertiary centres. MRI is not suitable for all patients due to metallic implants, agitation, medical instability or claustrophobia.

Rationale

The evidence for using MRI FLAIR-diffusion mismatch (a diffusion lesion that is not yet hyperintense on FLAIR imaging that indicates likely time of onset <4.5 hours) comes from a single well-conducted randomised controlled trial (Thomalla et al 2018 [59]). WAKE-up enrolled a relatively mild stroke patients with median NIHSS 6 and large vessel occlusion was only present in ~22%. Excellent outcome occurred in 53.3% alteplase-treated patients versus 41.8% control patients (benefit for 115 per 1000). The risk of symptomatic intracerebral haemorrhage in WAKE-UP was 2.0% with alteplase and mortality was not significantly different (4.1% alteplase vs 1.2% placebo, p=0.07). The THAWS randomised trial using the same imaging selection approach with 0.6mg/kg alteplase in Japan was stopped early and was recently presented in abstract form (*[62]*). THAWS did not show a signal of benefit. The practicality of urgent MRI-based patient selection in Australia and New Zealand is limited to major tertiary centres.

Clinical Question/ PICO

Population: Adults with acute stroke of uncertain onset time treated on the basis of MRI diffusion-FLAIR mismatch

Intervention: Intravenous Alteplase

Comparator: Control

Summary

The WAKE-UP randomised trial forms the evidence for this PICO. Excellent outcome occurred in 53.3% alteplase-treated patients versus 41.8% control patients (benefit for 115 per 1000). The risk of symptomatic intracerebral haemorrhage in WAKE-UP was 2.0% with alteplase and mortality was not significantly different (4.1% alteplase vs 1.2% placebo, p=0.07). The THAW randomised trial using the same imaging selection approach with 0.6mg/kg alteplase in Japan was stopped early and did not show a signal of benefit.

A review by Thomalla et al (2020)*[279]* explored intravenous alteplase for stroke with unknown time of onset with various advanced brain imaging and included four studies (including the WAKE-UP and THAW studies) and 843

participants. Favourable outcomes at 90 days occurred in 47% (199 of 420) patients with alteplase and 39% (160 of 409) patients in standard care or placebo (aOR 1.49, 95% CI 1.10 to 2.03; 4 studies, n=829). Alteplase was associated with better functional outcome (adjusted common OR 1.38, 95% CI 1.05 to 1.80; 4 studies, n= 829) and independent outcome (aOR 1.50, 95% CI 1.06 to 2.12; 4 studies, n= 829). The prevalence of symptomatic intracranial haemorrhage was higher in the alteplase group than among controls (3% [n=11] vs <1% [n=2], adjusted OR 5.58, 95% CI 1.22 to 25.50; 4 studies, n= 829).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Intravenous Alteplase	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Excellent Outcome (modified Rankin Scale 0-1) [1] 3 months 8 Critical	Odds Ratio 1.61 (CI 95% 1.09 — 2.36) Based on data from 503 patients in 1 studies. (Randomized controlled) Follow up: 490.	418 per 1000	536 per 1000 Difference: **118 more** per 1000 (CI 95% 21 more — 211 more)	**High** [2]	Intravenous alteplase improves excellent outcome (modified rankin scale 0-1)
Improved Functional Outcome (modified Rankin Scale) [3] 3 months 8 Critical	Odds Ratio 1.62 (CI 95% 1.17 — 2.23) Based on data from 503 patients in 1 studies. (Randomized controlled) Follow up: 490.	CI 95%		**High** [4]	Intravenous alteplase improves functional outcome (modified rankin scale)
Death [5] 3 months 8 Critical	Odds Ratio 3.38 (CI 95% 0.92 — 12.52) Based on data from 503 patients in 1 studies. (Randomized controlled) Follow up: 495.	12 per 1000	39 per 1000 Difference: **27 more** per 1000 (CI 95% 1 fewer — 120 more)	**Moderate** Due to serious imprecision [6]	Intravenous alteplase probably has little or no effect on death
Symptomatic intracerebral haemorrhage 24 hours 8 Critical	Odds Ratio 4.95 (CI 95% 0.57 — 42.87) Based on data from 503 patients in 1 studies. (Randomized controlled) Follow up: 495.	4 per 1000	19 per 1000 Difference: **15 more** per 1000 (CI 95% 2 fewer — 143 more)	**Moderate** Due to serious imprecision [7]	Intravenous alteplase probably increases symptomatic intracerebral haemorrhage

1. Modified Rankin Scale 0-1 indicates return to all regular pre-stroke activities at 3 months post-stroke, some stroke symptoms may remain.
2. **Risk of Bias: No serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Only data from one study. **Publication bias: No serious.**
3. Improvement by >=1 point on the modified Rankin Scale at 3 months
4. **Risk of Bias: No serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits.

Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Only data from one study. **Publication bias: No serious.**
5. Death at 3 months
6. **Risk of Bias: No serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
7. **Risk of Bias: No serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Only data from one study. **Publication bias: No serious.**

Info Box

Practice points
Thrombolysis should be undertaken in a setting with appropriate infrastructure, facilities and network support (e.g. via telemedicine) including:

- access to an interdisciplinary acute care team with expert knowledge of stroke management, who are trained in delivery of thrombolysis and monitoring of patients receiving thrombolytic therapy
- a streamlined acute stroke assessment workflow (including ambulance pre-notification, code stroke team response and direct transport from triage to CT scan) to minimise treatment delays, and protocols available to guide medical, nursing and allied health acute phase management
- immediate access to imaging facilities and staff trained to interpret images
- routine data collected in a central register to allow monitoring, benchmarking and improvements of patient outcomes over time for those treated with reperfusion.

The patient and caregivers should be involved in the decision to give thrombolysis whenever possible and this discussion of risk and benefit documented in the medical record. However, as a time-critical emergency therapy, thrombolysis should not be delayed if the patient does not have the capacity to consent and there are no legal representatives present. Clinicians should follow local health department policies regarding consent for emergency treatment in patients who are unable to consent for themselves.

Evidence To Decision

Resources and other considerations

Implementation considerations
There are organisational indicators collected in the National Stroke Audit to determine whether participating hospitals offer tPA for clinically appropriate patients with stroke and, if the hospital does offer this intervention, whether it is available 24 hours a day, 7 days a week.

Neurointervention

Although intravenous recombinant tissue plasminogen activator (rt-PA) improves survival and functional outcomes when administered as early as possible after onset of ischaemic stroke, its use is limited by the narrow therapeutic time window, important contraindications, and limited efficacy in patients with proximal large arterial occlusions (Badhiwala et al. 2015 *[74]*). This has led to substantial interest in endovascular therapies for acute ischaemic stroke in recent years.

Endovascular thrombectomy (also called mechanical thrombectomy or endovascular clot retrieval) is a minimally invasive procedure performed via angiogram. In most cases the femoral artery is accessed via the groin and a small tube (catheter) passed up into the brain to the site of the blocked blood vessel. Various techniques are then available to the neurointerventionist to remove the clot. Stent retrievers (a metal net that can be deployed in the clot and then removed under suction) were the devices most commonly used in the positive randomised trials.

Australia played a key role in landmark endovascular thrombectomy research. However, in the recent National Stroke Audit only 19 hospitals in Australia reported the availability of this therapy, and 13 were able to provide a truly continuous 24/7 service (Stroke Foundation 2019 *[28]*). The critical time-dependence of clinical outcomes following thrombectomy means that systems of care to deliver suitable patients to the appropriate centre for treatment are crucial. The most appropriate solution needs to be tailored to the local environment. As a complex procedure requiring a specialised neurointerventional workforce and infrastructure, outcomes are likely to be improved by centralisation in high-volume centres. Telemedicine to allow assessment of rural patients is an important option. Careful planning with ambulance services to ensure time-critical transfers are expedited is central to the success of hub and spoke models. Ongoing trials are evaluating whether clinical triage scores can identify large vessel occlusion patients in the field and allow bypass directly to an endovascular centre. Mobile stroke units with on-board CT scanners that can identify large vessel occlusion are also in use in various parts of the world.

When fully implemented, endovascular thrombectomy may be applicable for up to 10% of all ischaemic stroke patients and these represent the group most likely to sustain death and disability if rapid restoration of blood flow is not achieved.

As noted in the guidelines introduction, overall, the guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 25 July 2017, (with a subsequent minor amendment approved on 22 November 2017 and further admendments relating to endovascular thrombectomy within 6-24 hours after time last seen well (within this section) was approved on 9 July 2018) 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 5 years.

Strong recommendation

For patients with ischaemic stroke caused by a large vessel occlusion in the internal carotid artery, proximal middle cerebral artery (M1 segment), or with tandem occlusion of both the cervical carotid and intracranial large arteries, endovascular thrombectomy should be undertaken when the procedure can be commenced within six hours of stroke onset. (Goyal et al. 2016 *[76]*)

Practical Info

New trials versus old trials – patient selection, device effectiveness and the importance of fast treatment

The success of the trials published in 2015 contrasts with three neutral trials published in 2013, and there are important lessons to learn from the differences between these two generations of trials. The positive trials all selected patients who had a proven large vessel occlusion on non-invasive angiography (mostly CT angiography) and hence this should be regarded as standard imaging for all patients who are potential thrombectomy candidates. The positive trials used more effective devices but also treated faster than the neutral trials. The crucial dependence of clinical outcomes on fast reperfusion has been emphasised in the HERMES time-to-treatment meta-analysis (Saver et al. 2016 *[83]*), which showed that for every 9-minute delay to achieve reperfusion, 1 in every 100 treated patients had a worse disability outcome (higher score by 1 or more levels on the modified Rankin Scale). That effect was magnified once the patient was in hospital, and for every 4-minute delay to achieve reperfusion after ED arrival, 1 in every 100 treated patients had a worse disability outcome. This difference may relate to imprecisions in estimating time of stroke onset that do not apply to hospital arrival time. However, it does emphasise that, even in those patients who met imaging selection criteria on arrival, there is clinically important stroke progression in the time between imaging and reperfusion and this delay must be minimised to optimise patient outcomes.

Which patients are likely to benefit?

Endovascular thrombectomy trials have shown striking consistency in treatment effect across important clinical and radiological subgroups, indicating that most patients with ischaemic stroke due to a large vessel occlusion will benefit when the procedure is commenced within 6 hours (and benefit extended to 7 hours 18 min in the HERMES meta-analysis) (Saver et al. 2016 *[83]*). Few patients in the initial randomised trials were treated beyond 6 hours. The subsequent DAWN and DEFUSE 3 randomised trials used advanced imaging selection with the aim of identifying patients who could benefit from later treatment (potentially up to 24 hours after stroke onset).

The HERMES pooled individual patient data meta-analysis (Goyal et al. 2016 *[76]*) showed that **treatment benefit over standard**

care was consistent across the full spectrum of age. Elderly patients were included with no age limit in three of the randomised trials, provided they had independent pre-morbid function (mRS 0–2). There was a substantial mortality benefit in patients aged over 80, with no increase in severe disability. In clinical practice, judgement is required for patients with a degree of pre-morbid disability. Patients who are living at home but have some services which make them "mRS 3" may well benefit from treatment.

There was also **benefit across the spectrum of clinical severity**. There were relatively few very mild patients included with NIHSS < 6 and so confidence in this group is reduced. However, other sources of information indicate that patients with a large vessel occlusion who initially have mild symptoms can often deteriorate later, which may be beyond the window for reperfusion therapies (Coutts et al. 2012 *[52]*), and so careful individualised judgement is required in these patients.

The **target vessel occlusions** are particularly those involving the **internal carotid artery (ICA) and proximal middle cerebral artery (MCA "M1"** – for this purpose defined as occlusion prior to the genu in the sylvian fissure). Patients with "tandem" stenosis or occlusion of the extracranial carotid artery and an intracranial ICA/M1 occlusion also showed definite benefit, despite the increased technical challenges and potential requirement for carotid angioplasty or stenting in these patients. Treatment benefit in more **distal "M2" middle cerebral artery occlusions** has also been reported based on individual patient meta-analysis from the HERMES dataset (Menon et al 2019 *[100]*). Treatment was strongest in patients with proximal M2 occlusion and in dominant M2 segment occlusion. No sICH were found out of the 130 patients receiving thrombectomy whereas there was 5 sICH in the control group. Similarly, observational studies have indicated equivalent safety and benefits of M2 thrombectomy (Alexander et al 2020 *[101]*). The anatomy and clinical impact of M2 occlusions can vary but treatment can be considered on an individual basis. **Basilar artery occlusion** patients were excluded from the recent trials due to a mixture of lack of equipoise and concerns about increased heterogeneity that would occur if they were included. The AUST trial (Macleod et al. 2005 *[85]*) randomised 16 patients and showed a trend favouring treatment that was supported by meta-analysis of observational data demonstrating that recanalisation was associated with improved outcome (Kumar et al. 2015 *[86]*). A clear difference between thrombolysis and thrombectomy was not demonstrated in the BASICS registry, although this preceded the availability of current generation devices (Schonewille et al. 2009 *[84]*). There are ongoing randomised trials (BASICS, BEST) but the observational data clearly demonstrate a large magnitude benefit of recanalisation, acceptable safety profile and a dire natural history. This forms the basis of a strong recommendation despite the absence of randomised trials. The time window for treatment of basilar artery occlusions is not well-established. Stroke onset in basilar artery occlusion can be stuttering with initial vertigo, diplopia or dysarthria that later progresses to paralysis and/or coma. This may confound the usual definition of time of onset as "last known normal time" and onset of severe symptoms/coma may be more appropriate. The BASICS registry found that good outcomes were rare when coma had been present for more than 9 hours.

Available evidence suggests that **advanced imaging** (e.g. CT perfusion) is helpful diagnostically and prognostically. However, even patients with a large area of irreversible injury may benefit from thrombectomy within 6 hours of stroke onset. This also holds for patients with moderately extensive non-contrast CT changes (eg ASPECTS > 5). Benefit of treatment in patients with ASPECTS 0–4 is uncertain and individualised judgement is required.

Procedural aspects

There are multiple stent retrievers available and no head-to-head comparisons have been made, although available data from the MR CLEAN trial suggested that the two most common devices Solitaire FR and TREVO produced similar results (Dippel et al. 2016 *[82]*). An alternative approach is suction (or aspiration) via a large bore catheter as studied in the THERAPY trial. This trial was stopped very early due to loss of equipoise in the trial population when the other trials reported positive results. Results were therefore inconclusive but suggested trends to benefit using this approach.

In observational studies, performing the procedure under general anaesthetic (GA) has repeatedly been associated with worse outcome than performing thrombectomy with the patient awake (Brinjikji et al. 2017 *[94]*, Campbell et al. 2018 *[97]*). Despite similar stroke severity in GA and no GA groups, these data may be confounded by sicker patients requiring general anaesthesia. However, there is concern regarding hypotension, which is very frequent during induction of general anaesthesia, and treatment delays. Three single centre randomised trials showed no difference, or even slight benefit, of GA versus conscious sedation using the same anaesthetic agents (Schönenberger et al. 2016 *[89]*, Lowhagen et al. 2017 *[90]*, Simonsen et al. 2018 *[95]*). These trials achieved exceptionally fast GA induction (median 9 minutes delay when intubating the patients) and had strict protocols for maintaining blood pressure and other physiological parameters. If general anaesthesia is required due to patient agitation or challenging anatomy, close attention to maintaining normotension (systolic BP > 140 mmHg) is strongly advised. The majority of anterior circulation procedures can be performed awake with rates of general anaesthesia <10% in some randomised trials.

Systems of care

Individual patient data meta-analysis of the 5 HERMES randomised trials showed the critical impact of time to reperfusion on patient outcome. For every 9 minute increase in onset to reperfusion time, 1 in 100 patients suffered greater disability (>=1 point higher mRS at 3 months). (Saver et al. 2016 *[83]*)

Given this critical time-dependence, workflow both before and after hospital arrival needs to be optimised. Protocols that formalise referral networks, patient transfer processes and the communication of key information such as imaging between treating hospitals are essential. Telemedicine has been a key facilitator of access to endovascular thrombectomy for rural patients. Units should monitor and benchmark metrics such as "door-to-puncture" and "imaging-to-puncture" times in order to troubleshoot processes and undertake continuous improvement.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

There is clear and high quality evidence of improved functional outcome (229 more patients had functional independence per 1000 stroke patients treated) and lower mortality (44 fewer patients died with every 1000 stroke patients treated), with no evidence of increased risk of symptomatic intracerebral haemorrhage (Goyal et al. 2016 *[76]*).

Certainty of the Evidence — High

Five independent randomised trials from different health care settings produced highly consistent results and have been combined in an individual patient data meta-analysis (Goyal et al. 2016 *[76]*). Subsequently, a further large trial (THRACE) has shown similar results and two trials that were stopped very early with low numbers (PISTE and THERAPY) demonstrated similar trends (Mocco et al. 2016 *[87]*; Muir et al. 2016 *[88]*).

Preference and values — No substantial variability expected

Patients would want to receive this intervention shown to improve functional outcomes.

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

<u>Resources considerations</u>

There is evidence from North American and European evaluations that mechanical thrombectomy combined with alteplase was more effective and cost-saving (Aronsson et al. 2015 *[79]*; Lobotesis et al. 2016 *[81]*) or cost-effective (Ganesalingam et al. 2016 *[80]*) when compared to alteplase alone. These findings were consistent despite regional differences in costs and how mechanical thrombectomy was performed.

Economic evaluations of mechanical thrombectomy have not yet been published in peer-reviewed journals for an Australian setting. However, findings from economic modeling that was performed for a submission to the Medical Services Advisory Committee (MSAC) of the Australian Government by Medtronic are consistent with the findings from the peer-reviewed literature. In the sensitivity analyses conducted for the MSAC work on the base case model using the lifetime horizon, cost-effectiveness remained acceptable (< $50,000 per QALY gained) even with changes in utility values, procedure costs, costs associated with acute/mid-term or long-term management and rates of recurrent stroke.

Rationale

Endovascular thrombectomy is effective in a broad range of patients without evidence of an effect of age, sex or clinical severity on treatment benefit (Goyal et al. 2016 *[76]*). The majority of the patients enrolled in the randomised trials had treatment commenced within 6 hours although, in individual patient data meta-analysis, the benefit of thrombectomy extended to at least 7.3 hours (Saver et al. 2016 *[83]*).

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Endovascular mechanical thrombectomy

Comparator: Standard medical care

Summary

Goyal et al. (2016) *[76]* conducted an individual patient meta-analysis that pooled results from five recent trials of endovascular thrombectomy. The included trials were different to previously published trials in that they all used CT or magnetic resonance imaging to target large vessel occlusions, emphasised fast treatment, and used second-generation neurothrombectomy devices with better recanalization rates and lower complications. The primary outcome was scores on the modified Rankin scale, analysed using ordinal logistic regression to estimate the odds that intervention would improve mRS scores by 1 or more points. Intervention was shown to increase the odds of improvement significantly (common odds ratio 2.49, 95% CI 1.76 to 3.53). The number needed to treat for one patient to have a reduction of their mRS score of 1 point or more was 2.6. The dichotomous outcome of mRS 0–2 vs 3–6 also showed a significant increase in functional independence (adjusted OR 2.71, 95% CI 2.07 to 3.55). There were no significant effects on 90-day mortality or symptomatic intracranial haemorrhage. The trials were generally of high quality, with blinded outcome assessment, and effects were consistent across trials.

A previous meta-analysis by Badhiwala et al. (2015) *[74]* included the same 5 trials as the Goyal et al. analysis but also included 3 earlier trials. The pooled results showed a significant increase in the odds of a reduction of mRS score (OR 1.56, 95% CI 1.14 to 2.13), and in the odds of functional independence (OR 1.71, 95% CI 1.18 to 2.49), although in both cases the effect appeared to be weaker than the comparable analysis in the Goyal et al. meta-analysis.

The stronger effects in the Goyal et al. analysis may result from the newer trials employing improved patient selection and achieving faster, more effective reperfusion as discussed above. There was a significant interaction between functional outcome and year of publication in the Badhiwala et al. analysis.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention**	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Improved functional outcome [1] 3 months 8 Critical	Odds Ratio 2.49 (CI 95% 1.76 — 3.53) Based on data from 1,287 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	Difference: **385 more** CI 95%		**High** Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomized controlled trials with consistent effects. [2]	Endovascular mechanical thrombectomy improves functional outcome
Functional independence [3] 3 months 8 Critical	Odds Ratio 2.71 (CI 95% 2.07 — 3.55) Based on data from 1,278 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	**265** per 1000	**494** per 1000 Difference: **229 more** per 1000 (CI 95% 296 more — 162 more)	**High** Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomized controlled trials with consistent effects. [4]	Endovascular mechanical thrombectomy improves functional independence
Mortality 3 months	Odds Ratio 0.73 (CI 95% 0.47 — 1.13) Based on data from 1,279 patients in 5	**189** per 1000	**145** per 1000	**High** Overall mortality did not differ with endovascular	Endovascular mechanical thrombectomy has little or no effect on mortality overall with a significant

Outcome Timeframe	Study results and measurements	Comparator	Intervention	Certainty of the Evidence (Quality of evidence)	Plain text summary
9 Critical	studies. (Randomized controlled) Follow up: 3 months.	Difference: **44 fewer** per 1000 (CI 95% 19 more — 90 fewer)		mechanical thrombectomy. However the subgroup aged >80 years did have a significant reduction in mortality. [5]	reduction in patients aged > 80 years
Symptomatic intracranial haemorrhage [6] within 36 hours of treatment 8 Critical	Odds Ratio 1.07 (CI 95% 0.62 — 1.84) Based on data from 1,287 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	43 per 1000	46 per 1000 Difference: **3 more** per 1000 (CI 95% 33 more — 16 fewer)	**High** No difference in the rate of symptomatic haemorrhage [7]	Endovascular mechanical thrombectomy has little or no effect on symptomatic intracranial haemorrhage

1. improvement by at least 1 level of the modified Rankin score
2. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
3. modified Rankin Scale 0-2
4. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
5. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
6. Hemorrhagic transformation of the infarct leading to significant clinical deterioration as defined per trials
7. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..

Strong recommendation

For patients with ischaemic stroke caused by a large vessel occlusion in the internal carotid artery, proximal middle cerebral artery (M1 segment), or with tandem occlusion of both the cervical carotid and intracranial large arteries, endovascular thrombectomy should be undertaken when the procedure can be commenced between 6-24 hours after they were last known to be well if clinical and CT perfusion or MRI features indicate the presence of salvageable brain tissue. (Nogueira et al. 2017 [71], Albers et al. 2018 [72])

Practical Info

Which patients are likely to benefit?

Endovascular thrombectomy trials have shown striking consistency in treatment effect across important clinical and radiological subgroups, indicating that most patients with ischaemic stroke due to a large vessel occlusion will benefit when the procedure is commenced within 6 hours (and benefit extended to 7 hours 18 min in the HERMES meta-analysis) (Saver et al. 2016 [62]). Few patients in the initial randomised trials were treated beyond 6 hours. The subsequent DAWN and DEFUSE 3 randomised trials used advanced imaging selection with the aim of identifying patients who could benefit from later treatment (potentially up to 24 hours after stroke onset) (Nogueira et al. 2017 *[92]*, Albers et al. 2018 *[93]*). These trials required CT perfusion or MR diffusion imaging to identify patients with clinical-core mismatch (DAWN) or perfusion mismatch (DEFUSE 3). The DAWN imaging criteria (<21mL core if age >80, NIHSS≥10, <31mL core if age <80, NIHSS 10-19, <51mL core if age<80, NIHSS≥20) .were more restrictive than DEFUSE 3 criteria (core<70mL, mismatch ratio>1.8, mismatch volume>15mL). Almost all DAWN eligible patients are also eligible using DEFUSE 3 criteria and, compared to DAWN criteria, DEFUSE 3 criteria include ~60% additional patients. There was no heterogeneity in treatment benefit within DEFUSE 3 between patients who were or were not eligible for DAWN. Treatment effect in both trials did not differ between patients with delayed presentation after observed onset and patients with unwitnessed or 'wake-up' strokes.

As there was no suggestion of reduced treatment effect in DEFUSE 3 across the 6-16 hour treatment window, we have not differentiated 6-16hr versus 16-24hr selection criteria in the guideline recommendation. The volume based criteria do not account for regional eloquence which may be factored into decisions in clinical practice.

The HERMES pooled individual patient data meta-analysis (Goyal et al. 2016 [55]) showed that treatment benefit over standard care was consistent across the full spectrum of age. Elderly patients were included with no age limit in three of the randomised trials, provided they had independent pre-morbid function (mRS 0–2). There was a substantial mortality benefit in patients aged over 80, with no increase in severe disability. In clinical practice, judgement is required for patients with a degree of pre-morbid disability. Patients who are living at home but have some services which make them "mRS 3" may well benefit from treatment.

There was also benefit across the spectrum of clinical severity. There were relatively few very mild patients included with NIHSS < 6 and so confidence in this group is reduced. However, other sources of information indicate that patients with a large vessel occlusion who initially have mild symptoms can often deteriorate later, especially patients with carotid terminus or tandem occlusions (Mayza et al. 2018*[91]*). This deterioration may occur beyond the window for reperfusion therapies (Coutts et al. 2012 [50]), and so careful individualised judgement is required in these patients.

The target vessel occlusions are particularly those involving the internal carotid artery (ICA) and proximal middle cerebral artery (MCA "M1" – for this purpose defined as occlusion prior to the genu in the Sylvian fissure). Patients with "tandem" stenosis or occlusion of the extracranial carotid artery and an intracranial ICA/M1 occlusion also showed definite benefit, despite the increased technical challenges and potential requirement for carotid angioplasty or stenting in these patients.

Available evidence suggests that advanced imaging (e.g. CT perfusion) is helpful diagnostically and prognostically. Beyond 6 hours after stroke onset, advanced imaging with CT perfusion or MRI, processed using standardised automated software involving validated thresholds, is essential for patient selection, as indicated by the extended window trials DAWN and DEFUSE 3. Ideally this should occur at the initial hospital assessment to avoid futile transfers of patients ineligible for thrombectomy.

Procedural aspects

There are multiple stent retrievers available and no head-to-head comparisons have been made, although available data from the MR CLEAN trial suggested that the two most common devices Solitaire FR and TREVO produced similar results (Dippel et al. 2016 [61]). The stent retrievers can be used with proximal balloon guide occlusion and aspiration, distal access catheter aspiration, with and without simultaneous removal of the aspirating catheter and stent retriever. None of these techniques have been proven superior, and often more than one are required to achieve reperfusion. An alternative approach is suction (or aspiration) via a large bore catheter as studied in the THERAPY trial. This trial was stopped very early due to loss of equipoise in the trial population when the other trials reported positive results. Subsequently the ASTER trial showed similar results regardless of whether stent retrievers or aspiration catheters were used as the first-line strategy with a moderate number of patients requiring cross-over to the alternative strategy in both groups (Lapergue et al. 2017 *[96]*).

In observational studies, performing the procedure under general anaesthetic (GA) has repeatedly been associated with worse outcome than performing thrombectomy with the patient awake (Brinjikji et al. 2017 *[94]*, Campbell et al. 2018 *[97]*). Despite similar stroke severity in GA and no GA groups, these data may be confounded by sicker patients requiring general anaesthesia. However, there is concern regarding hypotension, which is very frequent during induction of general anaesthesia, and treatment delays. Three single centre randomised trials showed no difference, or even slight benefit, of GA versus conscious sedation using the same anaesthetic agents (Schönenberger et al. 2016 *[89]*, Lowhagen et al. 2017 *[90]*, Simonsen et al. 2018 *[95]*). These trials

achieved exceptionally fast GA induction (median 9 minutes delay when intubating the patients) and had strict protocols for maintaining blood pressure and other physiological parameters. If general anaesthesia is required due to patient agitation or challenging anatomy, close attention to maintaining normotension (systolic BP > 140 mmHg) is strongly advised. The majority of anterior circulation procedures can be performed awake with rates of general anaesthesia <10% in some randomised trials.

Systems of care

Individual patient data meta-analysis of the 5 HERMES randomised trials showed the critical impact of time to reperfusion on patient outcome. For every 9 minute increase in onset to reperfusion time, 1 in 100 patients suffered greater disability (>=1 point higher mRS at 3 months). (Saver et al. 2016 [62])

Given this critical time-dependence, workflow both before and after hospital arrival needs to be optimised. Protocols that formalise referral networks, patient transfer processes and the communication of key information such as imaging between treating hospitals are essential. Telemedicine has been a key facilitator of access to endovascular thrombectomy for rural patients. Units should monitor and benchmark metrics such as "door-to-puncture" and "imaging-to-puncture" times in order to troubleshoot processes and undertake continuous improvement. Transferring centres should monitor and benchmark "door-in-to-door-out" to ensure delays at initial centres are minimised.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

Within 6 hours of stroke onset, there is clear and high quality evidence that endovascular thrombectomy improves functional outcome (229 more patients had functional independence per 1000 stroke patients treated) and a trend towards lower mortality (44 fewer patients died per 1000 stroke patients treated), with no evidence of increased risk of symptomatic intracerebral haemorrhage (Goyal et al. 2016 [55]).

In the 6-24 hour treatment window, there is clear and high quality evidence that endovascular thrombectomy improves functional outcome (319 more patients had functional independence per 1000 stroke patients treated) and a trend towards lower mortality (51 fewer patients died per 1000 stroke patients treated). Symptomatic intracerebral haemorrhage did not differ significantly between the endovascular thrombectomy and standard medical care groups. Only ~9% in either group received intravenous alteplase in DAWN and DEFUSE 3 (Nogueira et al. 2017 *[92]*, Albers et al. 2018 *[93]*).

Certainty of the Evidence — High

Five independent randomised trials from different health care settings produced highly consistent results and have been combined in an individual patient data meta-analysis (Goyal et al. 2016 [55]). Subsequently, a further large trial (THRACE) has shown similar results and two trials that were stopped very early with low numbers (PISTE and THERAPY) demonstrated similar trends (Mocco et al. 2016 [66]; Muir et al. 2016 [67]).
Two subsequent high quality randomised trials of thrombectomy in an extended time window using imaging selection also showed major benefits in reduced disability (Nogueira et al. 2017 *[92]*, Albers et al. 2018 *[93]*).

Preference and values — No substantial variability expected

Patients would want to receive this intervention shown to improve functional outcomes.

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

In a systematic review published in 2017, 10 cost-utility analyses of endovascular thrombectomy for patients with acute ischaemic stroke were identified (Sevick et al. 2017*[99]*). In all but one study identified, it was found that endovascular thrombectomy combined with alteplase within 4.5-12 hours of symptom onset was either potentially cost saving or cost-effective (at the Canadian $50,000/QALY threshold) when compared to alteplase alone. The identified studies were conducted for North American and European settings. There were variations in results due to the perspective and time horizon of costs used in the analyses.

There is evidence from Australia that endovascular thrombectomy commenced within 4.5 hours of symptom onset is more effective and potentially cost saving than thrombolysis alone (Campbell et al. 2017*[98]*). In this simulation study that was based on data from the EXTEND-IA trial (Campbell et al. 2015), patients provided endovascular thrombectomy were estimated to have greater life expectancy and fewer DALYs lost over 15 years after stroke when compared to patients provided alteplase alone. Costs of inpatient care in the first 90 days were estimated to be US$4,365 less in those provided endovascular thrombectomy than alteplase alone. Sensitivity analyses were performed, and in the worst case scenario, it was estimated that endovascular thrombectomy would cost an additional US$7516 per DALY avoided or US$3818 per QALY gained when compared to alteplase in the first 90 days after stroke. These worst-case estimates were well within the usual willingness-to-pay (cost-effectiveness) thresholds.

The magnitude of benefit in the two new studies (Nogueira et al. 2017, Albers et al. 2018) versus standard care was at least as great as in the 0-6 hour thrombectomy trials and the cost-effectiveness demonstrated within 6 hours would therefore also apply between 6-24 hours.

Rationale

Endovascular thrombectomy is effective within 6 hours of stroke onset in a broad range of patients with ICA, proximal (M1) MCA or tandem occlusion of the cervical ICA and intracranial MCA without evidence of an effect of age, sex or clinical severity on treatment benefit (Goyal et al. 2016 [55]).
Between 6 and 24 hours after stroke onset, patients with ICA, M1 MCA or tandem occlusion **and** favourable CT perfusion or MR diffusion imaging benefit from endovascular thrombectomy. The two trials of thrombectomy beyond 6 hours (DAWN and DEFUSE 3) differed in inclusion criteria but DEFUSE 3 criteria (ischemic core <70mL with a mismatch ratio >1.8 and absolute mismatch >15mL) are broader and include virtually all DAWN-eligible patients. Although DAWN extended to 24hr and DEFUSE 3 only to 16hr, there was no evidence of reduced treatment effect over time in either trial and so we have elected not to differentiate between 6-16hr and 16-24hr.

Clinical Question/ PICO

Population: Adults with stroke onset > 6 hours
Intervention: Endovascular mechanical thrombectomy
Comparator: Standard care

Summary

Within 6 hours of stroke onset, there is clear and high quality evidence that endovascular thrombectomy improves functional outcome (229 more patients had functional independence per 1000 stroke patients treated) and a trend towards lower mortality (44 fewer patients died per 1000 stroke patients treated), with no evidence of increased risk of symptomatic intracerebral haemorrhage (Goyal et al. 2016 [55]).

In the 6-24 hour treatment window, there is clear evidence that endovascular thrombectomy improves functional outcome (319 more patients had functional independence per 1000 stroke patients treated) and a trend towards lower mortality (51 fewer patients died per 1000 stroke patients treated). Symptomatic intracerebral haemorrhage did not differ significantly between the endovascular thrombectomy and standard medical care groups. Only ~9% in either group received intravenous alteplase in DAWN and DEFUSE 3 (Nogueira et al. 2017 [72], Albers et al. 2018 [73]).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Endovascular mechanical thrombectomy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Functional independence [1] 90 days	Odds Ratio 5.04 (CI 95% 3.1 — 8.22) Based on data from 388	148 per 1000	467 per 1000	**High** Two trials terminated early	Endovascular mechanical thrombectomy beyond 6 hours improves

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Endovascular mechanical thrombectomy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
8 Critical	patients in 2 studies. [2] (Randomized controlled) Follow up: 90 days.	Difference: **319 more** per 1000 (CI 95% 202 more — 440 more)		but results consistent with previous 5 published trials [3]	functional independence in selected patients
Mortality 90 day 9 Critical	Odds Ratio 0.72 (CI 95% 0.43 — 1.19) Based on data from 388 patients in 2 studies. [4] (Randomized controlled) Follow up: 90 day.	**217** per 1000 Difference: **51 fewer** per 1000 (CI 95% 111 fewer — 31 more)	**166** per 1000	**Moderate** Due to serious imprecision [5]	Endovascular mechanical thrombectomy beyond 6 hours may reduce mortality
sICH 90 days 8 Critical	Odds Ratio 1.67 (CI 95% 0.64 — 4.33) Based on data from 388 patients in 2 studies. (Randomized controlled) Follow up: 90 days.	**37** per 1000 Difference: **23 more** per 1000 (CI 95% 13 fewer — 106 more)	**60** per 1000	**Moderate** Due to serious imprecision [6]	Endovascular mechanical thrombectomy beyond 6 hours may increase SICH slightly however numbers are low

1. Modified Rankin Scale 0-2 at 3 months
2. Primary study. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [93], [92],
3. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Both trials stopped earlier than scheduled, resulting in potential for overestimating benefits.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Relatively low patient numbers (388) but results consistent with existing meta-analysis of 5 previous trials. **Publication bias: No serious.** One of trials commercially sponsored.
4. Primary study. **Baseline/comparator:** Primary study. **Supporting references:** [93], [92],
5. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Wide confidence intervals. **Publication bias: No serious.** One of two trials commercially sponsored.
6. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Both trials stopped earlier than scheduled, resulting in potential for overestimating benefits.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Wide confidence intervals. **Publication bias: No serious.** One of the two trials was commercially sponsored.

Strong recommendation

In review

Eligible stroke patients should receive intravenous thrombolysis while concurrently arranging endovascular thrombectomy, with neither treatment delaying the other. (Goyal et al. 2016 *[76]*)

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

All the positive randomised trials administered intravenous alteplase to eligible patients prior to thrombectomy (Goyal et al. 2016 *[76]*). The safety profile did not appear to be affected by the concurrent use of thrombolytics but ongoing trials will examine this in detail. The aim of treatment is reperfusion, and data from HERMES suggest that the timing of alteplase relative to thrombectomy did not impact clinical outcome (Goyal et al. 2016 *[76]*). Hence alteplase must not delay

thrombectomy. However, in a proportion of cases thrombectomy will fail and these patients may still derive benefit from alteplase.

Certainty of the Evidence High

Five independent randomised trials from different health care settings produced highly consistent results and have been combined in an individual patient data meta-analysis (Goyal et al. 2016 *[76]*).

Preference and values No substantial variability expected

Improved functional outcome benefits are clinically significant and important to patients and carers.

Resources and other considerations No important issues with the recommended alternative

Resources considerations

Economic evaluations of this mechanical thrombectomy have not yet been conducted for an Australian setting. However, there is evidence from North American and European evaluations that mechanical thrombectomy combined with tPA was more effective and cost-saving (Aronsson et al. 2015 *[79]*; Lobotesis et al. 2016 *[81]*) or cost-effective (Ganesalingam et al. 2016 *[80]*) when compared to IV tPA alone. These findings were consistent despite regional differences in costs and how mechanical thrombectomy was performed.

Rationale

As with intravenous thrombolysis, time is brain and earlier removal of occlusion is more likely to lead to improved outcomes. Trials to date have administered intravenous thrombolysis prior to clot retrieval in all eligible patients (Goyal et al. 2016 *[76]*). However, endovascular thrombectomy is effective in patients with contraindications to intravenous thrombolysis (Goyal et al. 2016 *[76]*).

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Endovascular mechanical thrombectomy
Comparator: Standard medical care

Summary

Goyal et al. (2016) *[76]* conducted an individual patient meta-analysis that pooled results from five recent trials of endovascular thrombectomy. The included trials were different to previously published trials in that they all used CT or magnetic resonance imaging to target large vessel occlusions, emphasised fast treatment, and used second-generation neurothrombectomy devices with better recanalization rates and lower complications. The primary outcome was scores on the modified Rankin scale, analysed using ordinal logistic regression to estimate the odds that intervention would improve mRS scores by 1 or more points. Intervention was shown to increase the odds of improvement significantly (common odds ratio 2.49, 95% CI 1.76 to 3.53). The number needed to treat for one patient to have a reduction of their mRS score of 1 point or more was 2.6. The dichotomous outcome of mRS 0–2 vs 3–6 also showed a significant increase in functional independence (adjusted OR 2.71, 95% CI 2.07 to 3.55). There were no significant effects on 90-day mortality or symptomatic intracranial haemorrhage. The trials were generally of high quality, with blinded outcome assessment, and effects were consistent across trials.

A previous meta-analysis by Badhiwala et al. (2015) *[74]* included the same 5 trials as the Goyal et al. analysis but also included 3 earlier trials. The pooled results showed a significant increase in the odds of a reduction of mRS score (OR 1.56, 95% CI 1.14 to 2.13), and in the odds of functional independence (OR 1.71, 95% CI 1.18 to 2.49), although in both cases the effect appeared to be weaker than the comparable analysis in the Goyal et al. meta-analysis.

The stronger effects in the Goyal et al. analysis may result from the newer trials employing improved patient selection and achieving faster, more effective reperfusion as discussed above. There was a significant interaction between functional outcome and year of publication in the Badhiwala et al. analysis.

Outcome Timeframe	Study results and measurements	Comparator	Intervention	Certainty of the Evidence (Quality of evidence)	Plain text summary
Improved functional outcome [1] 3 months 8 Critical	Odds Ratio 2.49 (CI 95% 1.76 — 3.53) Based on data from 1,287 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	Difference: **385 more** CI 95%		**High** Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomized controlled trials with consistent effects. [2]	Endovascular mechanical thrombectomy improves functional outcome
Functional independence [3] 3 months 8 Critical	Odds Ratio 2.71 (CI 95% 2.07 — 3.55) Based on data from 1,278 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	**265** per 1000	**494** per 1000 Difference: **229 more** per 1000 (CI 95% 296 more — 162 more)	**High** Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomized controlled trials with consistent effects. [4]	Endovascular mechanical thrombectomy improves functional independence
Mortality 3 months 9 Critical	Odds Ratio 0.73 (CI 95% 0.47 — 1.13) Based on data from 1,279 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	**189** per 1000	**145** per 1000 Difference: **44 fewer** per 1000 (CI 95% 19 more — 90 fewer)	**High** Overall mortality did not differ with endovascular mechanical thrombectomy. However the subgroup aged >80 years did have a significant reduction in mortality. [5]	Endovascular mechanical thrombectomy has little or no effect on mortality overall with a significant reduction in patients aged > 80 years
Symptomatic intracranial haemorrhage [6] within 36 hours of treatment 8 Critical	Odds Ratio 1.07 (CI 95% 0.62 — 1.84) Based on data from 1,287 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	**43** per 1000	**46** per 1000 Difference: **3 more** per 1000 (CI 95% 33 more — 16 fewer)	**High** No difference in the rate of symptomatic haemorrhage [7]	Endovascular mechanical thrombectomy has little or no effect on symptomatic intracranial haemorrhage

1. improvement by at least 1 level of the modified Rankin score
2. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
3. modified Rankin Scale 0-2
4. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some

trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..

5. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
6. Hemorrhagic transformation of the infarct leading to significant clinical deterioration as defined per trials
7. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Endovascular mechanical thrombectomy + intravenous thrombolysis
Comparator: Intravenous thrombolysis alone

Summary

Goyal et al. (2016) *[76]* conducted an individual patient meta-analysis that pooled results from five recent trials of endovascular thrombectomy. The overall analysis showed a significant increase in odds of a reduced modified Rankin scale score (OR 2.49, 95% CI 1.76 to 3.53). A prespecified subgroup analysis of patients who had received alteplase treatment found a similar treatment effect (OR 2.45, 95% CI 1.68 to 3.57). There was non-significant heterogeneity (p = 0.43) between subgroups receiving or not receiving alteplase, suggesting that the effect of thrombectomy did not differ between the groups. As in the overall analysis, endovascular thrombectomy significantly improved the odds of functional independence and produced no significant differences in 90-day mortality.

Palesch et al. (2015) *[77]* reported 12-month outcomes from an earlier trial of endovascular therapy (IMS III), where all patients (in both the endovascular therapy and control groups) had received intravenous alteplase. At 12 months, the odds of functional independence following endovascular therapy were significantly improved for patients with severe strokes but showed no difference among patients with moderate stroke. However, the more recent trials included in the Goyal et al. analysis had substantially stronger early treatment effect with no heterogeneity across the spectrum of stroke severity. Two-year follow-up from the MR CLEAN trial has been reported in abstract form and demonstrated preserved treatment benefit with an 8% reduction in mortality that was not detected at 3 months.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention**	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Functional independence [1] 3 months 8 Critical	Odds Ratio 1.67 (CI 95% 1.37 — 2.05) Based on data from 1,090 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	270 per 1000	382 per 1000 Difference: **112 more** per 1000 (CI 95% 161 more — 66 more)	**High** Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomised controlled trials with consistent effects. [2]	Endovascular mechanical thrombectomy improves functional independence

Outcome Timeframe	Study results and measurements	Comparator	Intervention	Certainty of the Evidence (Quality of evidence)	Plain text summary
Mortality 3 months 9 Critical	Odds Ratio 0.75 (CI 95% 0.5 — 1.12) Based on data from 1,090 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	184 per 1000	145 per 1000 Difference: **39 fewer** per 1000 (CI 95% 18 more — 83 fewer)	**High** Overall mortality did not differ with endovascular mechanical thrombectomy. However the subgroup aged >80 years did have a significant reduction in mortality. [3]	Endovascular mechanical thrombectomy has little or no effect on mortality overall with a significant reduction in patients aged > 80 years
Improved functional outcome [4] 3 months 8 Critical	Odds Ratio 2.45 (CI 95% 1.68 — 3.57) Based on data from 1,090 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	CI 95%		**High** Endovascular thrombectomy in addition to alteplase improves functional outcome [5]	Endovascular mechanical thrombectomy + intravenous thrombolysis improves functional outcome

1. modified Rankin Scale 0-2
2. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
3. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
4. Improvement by at least 1 level on the modified Rankin scale
5. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..

Clinical Question/ PICO

Population: Adults with stroke ineligible for IV thrombolysis
Intervention: Endovascular mechanical thrombectomy
Comparator: Standard care

Summary

Goyal et al. (2016) *[76]* conducted an individual patient meta-analysis that pooled results from five recent trials of endovascular thrombectomy. The overall analysis showed a significant increase in odds of a reduced modified Rankin scale score (OR 2.49, 95% CI 1.76 to 3.53). A prespecified subgroup analysis of patients ineligible for alteplase (N = 188) found a similar effect (OR 2.43, 95% CI 1.30 to 4.55), with non-significant heterogeneity (p = 0.43) between patients eligible and not eligible for alteplase. Endovascular thrombectomy appears to be equally effective among patients eligible and ineligible for alteplase.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Endovascular mechanical thrombectomy	Certainty of the Evidence (Quality of evidence)	Plain text summary
Improved functional outcome [1] 3 months 8 Critical	Odds Ratio 2.43 (CI 95% 1.3 — 4.55) Based on data from 188 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	CI 95%		**High** Endovascular thrombectomy improves outcome in patients ineligible for alteplase [2]	Endovascular mechanical thrombectomy improves functional outcome in patients ineligible for intravenous thrombolysis
Functional independence [3] 3 months 8 Critical	Odds Ratio 2.05 (CI 95% 1.16 — 3.63) Based on data from 188 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	**223** per 1000	**370** per 1000 Difference: **147 more** per 1000 (CI 95% 287 more — 27 more)	**High** Robust statistical significance and no evidence of effect heterogeneity. [4]	Endovascular mechanical thrombectomy improves functional independence in patients ineligible for intravenous thrombolysis
Mortality 3 months 9 Critical	Odds Ratio 1.11 (CI 95% 0.6 — 2.07) Based on data from 188 patients in 5 studies. (Randomized controlled) Follow up: 3 months.	**225** per 1000	**231** per 1000 Difference: **6 more** per 1000 (CI 95% 150 more — 77 fewer)	**High** [5]	Endovascular mechanical thrombectomy in patients ineligible for intravenous thrombolysis has little or no effect on mortality

1. Improvement of at least 1 level on the modified Rankin scale
2. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
3. Modified Rankin Scale 0-2 at 3 months
4. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..
5. **Risk of Bias: No serious.** Inability to blind participants. Assessors blinded. Low risk of potential performance bias. Some trials stopped earlier than scheduled, resulting in potential for overestimating benefits.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.** One of five trials commercially sponsored, partial funding of other trials by commercial unrestricted grants..

Strong recommendation

In selected stroke patients with occlusion of the basilar artery, endovascular thrombectomy should be undertaken. (Kumar et al. 2015 *[86]*)

Practical Info

Basilar artery occlusion patients were excluded from the recent trials due to a mixture of lack of equipoise and concerns about increased heterogeneity that would occur if they were included. The AUST trial (Macleod et al. 2005 *[85]*) randomised 16 patients and showed a trend favouring treatment that was supported by meta-analysis of observational data, demonstrating that recanalisation was associated with improved outcome (Kumar et al. 2015 *[86]*). A clear difference between thrombolysis and

thrombectomy was not demonstrated in the BASICS registry although this preceded the availability of current generation devices (Schonewille et al. 2009 *[84]*). There are ongoing randomised trials (BASICS, BEST), but the observational data clearly demonstrate a large magnitude benefit of recanalisation, acceptable safety profile and a dire natural history. This forms the basis of a strong recommendation despite the absence of randomised trials. The time window for treatment of basilar artery occlusions is not well-established. Stroke onset in basilar artery occlusion can be stuttering, with initial vertigo, diplopia or dysarthria that later progresses to paralysis and/or coma. This may confound the usual definition of time of onset as "last known normal time" and onset of severe symptoms/coma may be more appropriate. The BASICS registry found that good outcomes were rare when coma had been present for more than 9 hours. Basilar artery occlusions are quite variable. Distal basilar occlusion is generally embolic in contrast to mid-basilar occlusion, where there is often an underlying atherosclerotic stenosis.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

Basilar artery occlusion has a dire prognosis untreated, with high mortality and disability. Meta-analysis of observational data (n=2056) demonstrated clear benefits of recanalisation with reduced rates of death (HR 0.49, 95%CI 0.44–0.55) and modified Rankin scale 4–6 (HR 0.67, 95%CI 0.63–0.72) (Kumar et al. 2015 *[86]*). Safety was acceptable.

Certainty of the Evidence — Moderate

The recommendation is based on a meta-analysis of observational studies. Although the risk of bias of observational studies may be higher, the large magnitude of benefits makes the certainty in effect estimates moderate. Randomised controlled trials are ongoing.

Preference and values — No substantial variability expected

Improved functional outcome benefits are clinically significant and important to patients and carers.

Resources and other considerations — Factor not considered

Rationale

Basilar artery occlusion has a dire prognosis untreated, with high mortality and disability. Meta-analysis of observational data demonstrated clear association between recanalisation and reduced death and dependency (Kumar et al. 2015 *[86]*). Safety was acceptable (Kumar et al. 2015 *[86]*). Although randomised trials are ongoing, the effect size of recanalisation and poor natural history justifies pursuit of endovascular thrombectomy (and intravenous thrombolysis in those presenting within 4.5 hours).

Clinical Question/ PICO

Population: Adults with basilar artery occlusion
Intervention: Endovascular mechanical thrombectomy
Comparator: Control

Summary

The BASICS study (Schonewille et al. 2009 *[84]*) assessed a prospective observational registry of patients with symptomatic and radiologically confirmed basilar artery occlusion. 619 patients were included from 48 international centres, receiving either antithrombotic treatment only (AT), primary intravenous thrombolysis (IVT) or intra-arterial therapy (IAT). The intra-arterial therapy available at that time included intra-arterial thrombolysis in 90% of patients and did not include the current generation of stent retriever and aspiration devices that have proven effective in the anterior circulation. Risk of poor outcome (modified Rankin scale score 4–6) was compared between treatments, adjusting for 6 baseline variables including age, National Institutes of Health Stroke Scale score, and time to treatment. Among patients with mild-to-moderate deficit, there were no significant differences between intravenous thrombolysis and antithrombotic treatment (relative risk 0.94, 95% CI 0.60 to 1.45) or intra-arterial therapy and antithrombotic treatment (relative risk 1.29, 95% CI 0.97 to 1.72). Patients treated with intra-arterial therapy had higher risk of poor outcome than those treated with intravenous thrombolysis (relative risk 1.49, 95% CI 1·00–2·23). For patients with severe deficit, both intra-arterial therapy and intravenous thrombolysis had non-significantly lower risk of poor outcome than

antithrombotic treatment, with no significant difference between IAT and IVT. 72% of patients treated with intra-arterial therapy had partial or complete recanalisation of the basilar artery and this was associated with a significantly lower risk of poor outcome (relative risk 0.75, 95% CI 0.66 to 0.85). The study was non-randomised and patients receiving intra-arterial therapy had greater baseline stroke severity, potentially increasing the rate of poor outcomes in the IAT group. The covariate-adjusted analyses are also unlikely to have fully corrected or baseline differences between treatment groups.

Kumar et al. (2015) *[86]* included 45 observational studies of reperfusion therapies for acute basilar artery occlusion in a meta-analysis. The included studies used either intravenous thrombolysis (IVT) or intra-arterial thrombolysis and/or endovascular therapy (IA/EVT). Recanalisation was associated with a lower risk of death or dependency overall (relative risk 0.67, 95% CI 0.63 to 0.72), although there were indications of significant publication bias. Estimates of relative risk were similar for IVT (0.68) and IA/EVT (0.67). Recanalisation rates were higher with IA/EVT (77%) than IVT (59%), although the review authors noted that a valid comparison between the treatment approaches was not possible given the study design, and that further evidence was required to determine the relative efficacy of the approaches.

In the AUST study (Macleod et al. 2005 *[85]*), 16 patients with basilar or vertebral artery occlusion were randomised to treatment with intra-arterial urokinase or control, with both groups receiving anticoagulant therapy. The trial was halted early due to slow recruitment and urokinase being withdrawn from sale. There was no significant difference in death and disability at 6 months (odds ratio 0.14, 95% CI 0.02 to 1.43).

Practice statement

Consensus-based recommendations
For patients with ischaemic stroke caused by occlusion in the M2 segment of the middle cerebral artery, endovascular thrombectomy may be considered based on individual patient and advanced imaging factors.

Endovascular thrombectomy should be performed by an experienced neurointerventionist with recognised training in the procedure (Conjoint Committee for Recognition of Training in Interventional Neuroradiology CCINR.org.au).

Evidence To Decision

Resources and other considerations

Implementation considerations
There are organisational indicators collected in the National Stroke Audit to determine whether participating hospitals have access to endovascular stroke therapy for clinically appropriate patients and, if the hospital does have access, whether this intervention is available on-site and if it is available for patients with stroke 24 hours a day, 7 days a week. Further organisational indicators are also collected on routine access to onsite neurosurgery. Clinical indicators are collected as part of the Australian Stroke Clinical Registry.

Rationale

The randomised trials included in the HERMES Collaboration included 130 patients with M2 occlusion (Menon et al 2019 *[100]*). These (M2) occlusions are highly variable. Individual patient meta-analysis indicated that successful reperfusion (mTICI 2b or 3) occurred in 59% of patients receiving clot retrieval. Benefits for patients regarding 90-day mRS 0-2 favoured intervention over medical care (aOR 2.39, 95%CI 1.08 to 5.28). Other outcomes favoured clot retrieval. Treatment effect was strongest in patients with proximal M2 occlusion and in dominant M2 segment occlusion. No sICH were found in the clot retrieval group (compared to 5 [7.9%] in the control arm). Meta-analysis of observational data have also reported similar benefits and no increased risk for patients with M2 vs M1 occlusions (Alexander et al 2020 *[101]*). We have therefore made a consensus-based recommendation that treatment of some patients with M2 occlusions is reasonable.

Dysphagia

Dysphagia (problems with swallowing) is a common consequence of acute stroke, with a reported incidence of 27% to 64% (Bath et al 2018*[108]*). Dysphagia is associated with an increased risk of complications, such as aspiration pneumonia, dehydration and malnutrition (Bath et al 2018 *[108]*). Dysphagia was also found to lead to poor clinical outcomes (chest infection, death, disability, discharge destination, longer length of stay), reinforcing the need for early detection and management (Bath et al 2018 *[108]*).

It is believed that early identification and appropriate subsequent management of dysphagia is crucial to patient outcomes. The most recent National Stroke Audit of Acute Services in Australia showed that 58% of stroke patients received formal swallow screening and 55% were screened or swallow assessment performed before given oral intake (medications, food and fluids) (Stroke Foundation 2019 *[28]*). Around 70% of patients received formal assessment from speech pathologists within 48 hours (Stroke Foundation 2019 *[28]*). A total of 116 hospitals out of 120 surveyed indicated that they had locally agreed management protocols for swallow dysfunction (Stroke Foundation 2019 *[28]*).

Weak recommendation

Updated evidence, no change in recommendation

People with acute stroke should have their swallowing screened, using a validated screening tool, by a trained healthcare professional. (Poorjavad et al 2014 *[113]*; Benfield et al 2020 *[134]*)

Practical Info

Four screening tools rated highly in the systematic reviews are: (1) Oral Pharyngeal and Clinical Swallowing Examination, (2) Bedside Aspiration Test, (3) The Gugging Swallowing Screen, and (4) The Toronto Bedside Swallowing Screening Test (TOR-BSST). In the literature, the terminology describing swallow screening tests and more comprehensive bedside clinical assessments are often used inconsistently and interchangeably. ~~Every attempt has been made to generate this recommendation from the evidence surrounding assessment procedures for the purposes of dysphagia diagnosis, rather than merely screening.~~

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Swallowing screening tools ~~(SSTs)~~ include a range of factors including demographics, medical history, global assessment of function, oral mechanism examination, and direct swallowing assessment. It is suggested that ~~a~~ direct observation of swallowing is a compulsory item within an screening tool. Most commonly this is via a water swallow test. The nature of non-swallowing items to be included for maximum validity is yet to be determined. The benefits of screening tool's ~~SSTs~~ outweigh any harm as an early indicator of aspiration and/or dysphagia risk. Screening tool's ~~SSTs~~ for use after acute stroke generally have a focus on aspiration rather than dysphagia more generally, which means that such tools are likely to have a role in preventing aspiration pneumonia which has life-threatening consequences. ~~Recent~~ Evidence demonstrates a reduction in pneumonia, the earlier the swallow screening is attended (Bray et al 2016 *[124]*) and a similar reduction in pneumonia the earlier clinical swallowing evaluation is conducted (Eltringham et al 2019 *[128]*). ~~As dysphagia can occur without aspiration, the review by Daniels et al. 2012 *[115]* did raise the question as to whether current SSTs are capable of detecting patients at risk of dysphagia itself. Evidence supporting the use of SSTs on other outcomes such as length of stay, nutritional and hydration status is sparse.~~

Certainty of the Evidence

Moderate

The evidence for swallow screening tools is moderate. The systematic review had stringent inclusion/exclusion criteria, however the quality and number of studies included in the review were variable.

Preference and values

No substantial variability expected

It is expected that patients would want early swallow screening to avoid potential complications.

Resources and other considerations

No important issues with the recommended alternative

Resources considerations

This recommendation may have implications for nursing resources to ensure training is provided and nurses are confident to conduct screening rapidly. ~~as it suggests screening be conducted within 4 hours compared to the 24 hours recommended in the~~

~~2010 guidelines.~~

Implementation considerations

There are clinical indicators collected in the National Stroke Audit on the provision of formal swallow screens for patients with stroke and, if these screens were performed, both the date and time also collected so the median time from the patient's arrival to the emergency department and the swallow screen can be reported ~~upon~~. An additional clinical indicator is collected to determine whether patients with stroke received a formal swallow screen before any oral medications, foods or fluids; this clinical indicator is included in the Acute Stroke Clinical Care Standard.

Rationale

A small number of ~~high-quality~~ studies have investigated the reliability and validity of swallow screening tools for the stroke population. A number of tools currently available meet most of the validity and reliability requirements for clinical use (i.e. they are simple, valid, reliable, sensitive, and specific tests for screening swallowing disorders in almost all acute alert stroke patients), although there is a need for further evidence about their impact on stroke patient outcomes (Benfield et al 2020 *[134]*; Hines et al 2016 *[133]*; Eltringham et al 2018 *[128]*; Smith et al 2018 *[131]*; ~~;~~Poorjavad et al~~.~~ 2014 *[113]*; Schepp et al~~.~~ 2012 *[114]*; Daniels et al~~.~~ 2012 *[115]*~~; Leder et al. 2012 [122]; Martino et al. 2014 [125]~~).

Clinical Question/ PICO

Population:	Adults with stroke
Intervention:	Swallow screen test
Comparator:	Reference standard (FEES or VF)

Summary

Swallow screen test may increase performance in identifying dysphagia.

Systematic reviews have found screening assessments vary greatly in terms of their methods, endpoints, and psychometric values. Poorjavad and Jalaie (2014) *[113]* in a systematic review concluded that there are four screening tools that have used high-quality methodologies to determine the validity, reliability, sensitivity and specificity when compared with instrumental measures of swallowing function. These four screening tools are the (1) Oral Pharyngeal and Clinical Swallowing Examination, (2) Bedside Aspiration Test, (3) The Gugging Swallowing Screen, and (4) The Toronto Bedside Swallowing Screening Test (TOR-BSST), and all have consistently scored well in terms of sensitivity and specificity.

Schepp et al. (2012) *[114]* had previously conducted a systematic review of swallowing screens for use after acute stroke. They included screening tools and assessments that did not require specialised training and skills and had been validated against a gold standard, and reported validity and reliability data. Only four tools met their criteria, with the TOR-BSST the only overlap with the review by Poorjavad and Jalaie (2014). Two of the screening tools had small sample sizes, while the TOR-BSST and Acute Stroke Dysphagia Screen (ASDS) were considered to have sufficient sample sizes. Reliability was high for both of these screening tools, as was sensitivity and NPV, but specificity and PPV values were not as strong. These authors highlight that evidence supporting the impact screening has on morbidity, mortality, and length of hospital stay is still to be produced.

Daniels et al. (2012) *[115]* conducted a systematic review focused on identifying valid items for inclusion in a swallowing screening tool (SST). It was noted that inclusion of a direct assessment of swallowing was associated with high-quality studies. Specifically, they noted that an essential item for inclusion was a water swallow test (WST); with cough and wet voice in response to the WST the essential predictors or aspiration. They did note that most current SST focus on aspiration risk and not dysphagia. The recommendation was for further research to determine the volume of water that should be used in the WST; whether it is an independent screening measure or should occur in conjunction with consideration of non-swallowing items; and whether it can predict dysphagia rather than just aspiration. Leder et al (2012) *[122]* reported on an observational study that suggested that the 90-cc WST (n = 75) and concluded that if 90-cc challenge is passed diet recommendations can be safely made without further objective dysphagia assessment. Martino 2014 *[125]* reported a high diagnostic performance of using water intake of 10 teaspoons and a lingual motor test.

A cohort study by Crary et al. (2013) *[112]* suggests that swallow frequency rates also have potential as a screening tool that can be used without requiring trained personnel. Based on a cohort of 63 acute stroke patients, a swallowing frequency rate <= 0.40 swallows per minute (SPM) had a sensitivity of 96% and specificity of 68% for identifying dysphagia. As an observational study with a small sample size, this provides low-quality evidence for swallowing frequency as a screening tool.

Hines et al (2016)*[133]* undertook an updated review including 15 studies revealing that nurse-initiated dysphagia screening is effective for reducing chest-infections in patients with dysphagia (OR 0.45, 95% CI 0.33 to 0.62; 5 studies, n = 4,519).

Park et al (2020)*[135]* included 8 studies (n = 1,206) and investigated the effectiveness of the Gugging Swallowing Screen (GUSS) for dysphagia screening. The use of GUSS for early systematic dysphasia screening by nurses resulted in a reduction in pneumonia rate compared to the control group (p = 0.004). Based on 5 of the studies (n= 276), the GUSS has a pooled sensitivity of 97% and specificity of 67% for identifying dysphagia.

The review by Benfield et al (2020)*[134]* included 20 studies describing 5 different test. No one test was found to be superior to others regarding accuracy and clinical utility. Pooling three studies (n=192) the GUSS was found to have high sensitivity (96%) but low specificity (65%).

Outcome Timeframe	**Study results and measurements**	**Comparator** Reference standard (FEES or VF)	**Intervention** Swallow screen test	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Performance in identifying dysphagia [1] 7 Critical	Based on data from: 392 patients in 6 studies. (Observational (non-randomized))	Screening tests' sensitivities ranged from 47 to 100%, while their specificity ranged from about 63 to 100%. Four screening tools that have consistently scored well in terms of sensitivity and specificity are Oral Pharyngeal and Clinical Swallowing Examination, Bedside Aspiration Test, The Gugging Swallowing Screen, and The Toronto Bedside Swallowing Screening Test (TOR-BSST)		**Moderate** Due to serious imprecision [2]	Oral Pharyngeal and Clinical Swallowing Examination, Bedside Aspiration Test, The Gugging Swallowing Screen, and TOR-BSST can be used as swallow screen tools.

1. Many of the screening tests had the endpoint of identifying aspiration - only some aimed to identify dysphagia
2. **Risk of Bias: No serious.** Only studies with high methodological quality was included in the analysis. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide range of sensitivity and specificity; no meta-analysis was performed. **Publication bias: No serious.**

Practice statement

Updated evidence, no change in recommendation

Consensus-based recommendation

People with acute stroke should have their swallowing screened within four hours of arrival at hospital and before being given any oral food, fluid or medication. (Bray et al. 2016 *[124]*; Ouyang et al 2020 *[137]*)

Rationale

Dysphagia is common in acute stroke patients. Early swallow screening by a trained health professional can potentially avoid complications such as aspiration and pneumonia. A nationwide, registry-based prospective cohort in England and Wales analysed data from 63,650 patients admitted with acute stroke, and found that people with the longest delay in swallow screen had a higher risk of pneumonia (Bray et al. 2016 *[124]*). Another international study using data from the HeadPoST randomised trial found increased rates of pneumonia and poor outcomes with longer times to screening compared to those who were screened <4 hours (Ouyang et al 2020 *[137]*). Swallow screen should be done before any oral food, fluid, or medication is given, ideally within four hours of admission ~~(based on working party consensus)~~.

Clinical Question/ PICO

Population: Adults with stroke

Intervention: Early swallow screen
Comparator: Usual care

Summary

A nation-wide, registry-based prospective cohort study in England and Wales analysed data from 63,650 patients admitted with acute stroke (Bray et al. 2016 *[124]*). The overall incidence of stroke associated pneumonia was 8.7%, and the median time from admission to dysphagia screening was 2.9 hours (IQR 1.3–5.7 hours). They found that patients with the longest delays in dysphagia screening (4th quartile, >= 345 minutes) had a higher risk of stroke-associated pneumonia (OR 1.36, 95%CI 1.20–1.53), compared with the shortest time (1st quartile, 0–79 minutes).

A review by Eltringham et al (2018)*[128]* with 12 mostly observational studies (n = 87,824) found early dysphagia screening may reduce the odds of stroke-associated pneumonia. 24/7 screening was found to reduce screening time from median 20 hours to 7 hours in one quasi experimental study (p = 0.001; n = 384). The risk of developing stroke-associated pneumonia increased with late dysphagia screening (2 studies, n = 75,926). Early dysphagia screening (less than 24 hrs of admission) was independently associated with decreased risk of stroke associated pneumonia (OR 0.68, 95% CI 0.52 to 0.89; 1 study, n = 12,276).

In a secondary analysis of the QASC trial, Middleton et al (2019)*[136]* (n = 1,126) found patients had greater odds of independence at 90 days (modified Rankin score of 0 or 1) if a swallow screen or assessment was completed within 24 hours of stroke unit admission (OR 1.8, 95% CI 1.3 to 2.6).

A multicentre cohort study conducted by Ouyang et al (2019)*[137]* (n = 11,093) used data from the HeadPoST RCT and found the median time from admission to dysphagia screening was 2.2 hrs (IQR 0.8 to 6.3). The frequency of pneumonia was associated with longer times to having a dysphagia screen, with median time for dysphagia screening being 3.0 hrs (IQR 1.0 to 11.4) for those who had pneumonia and 2.2 hrs (IQR 0.8 to 6.3) for those who did not have did not have pneumonia. Significant difference (p=0.001) in rates of pneumonia were found between those screened <4 hours (3.0%), 4-24 hrs (3.6%), and >24 hours (5.7%). Also significant difference (p<0.0001) in rates of a poor outcome (modified Rankin scale 3-6) were found between those screened <4 hours (35%), 4-24 hours (43%), and >24 hours (57%).

Weak recommendation

Updated evidence, no change in recommendation

All stroke patients who have failed swallow screening or who deteriorate should have a comprehensive assessment of swallowing performed by a speech pathologist. (Kertscher et al. 2014 *[116]*; O'Horo et al. 2015 *[118]*)

Practical Info

In the literature, the terminology describing swallow screening tests and more comprehensive ~~bedside~~ clinical swallowing evaluation are often used inconsistently and interchangeably. Every attempt has been made to generate this recommendation from the evidence surrounding swallowing assessment procedures undertaken by speech pathologists for the purposes of dysphagia diagnosis, rather than merely screening, which is often undertaken by non-speech pathologists.

There was limited information in the studies included in the more recent systematic reviews about what comprised a specialist swallow assessment, and no studies reported use of a validated clinical assessment tool.

When conducting a swallow assessment, it is important to be aware of the fear a patient may feel at the thought of food going down the wrong way, causing potential choking. Clinicians should consider how they will reassure the patient and how they talk~~e~~ to them about such an event. They should also keep in mind how a patient may feel if they do not 'pass' the swallow assessment.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Delay in speech pathologist clinical swallowing evaluation increases risk of stroke-associated pneumonia (Eltringham et al 2019 *[128]*). Patients in the slowest quartile for assessment had 1.98 (1.67-2.35) odds of stroke-associated pneumonia compared with patients receiving the quickest assessment. Delays in speech pathologist clinical assessment > 24 h were associated with an additional 4% absolute increase in stroke-associated pneumonia. ~~There are some bedside assessments that provide adequate sensitivity, specificity and predictive value to detect aspiration risk. In the absence of better tools, the 3-oz swallow test,~~

~~properly executed, seems to be the best currently available tool validated in more than one study (Kertscher et al. 2014 ; O'Horo et al. 2015 ; Mortenson et al. 2016 ; Kjaersgaard et al. 2014 ; Kjaersgaard et al. 2015). Volume-Viscosity Swallowing Test and Martino et al. Toronto Bedside Swallowing Screening Test best met criteria. An instrumental assessment remains the gold standard for detecting aspiration.~~
~~Evidence for bedside assessments or instrumental assessments reducing rates of pneumonia or leading to functional recovery and return to oral intake is limited.~~

Certainty of the Evidence Low

~~No randomized controlled trials examining a specific specialist swallow assessment tool and the impact on stroke-associated pneumonia was found. Meta-analysis in the systematic review examining stroke associated pneumonia was prohibited due to the heterogeneity of study designs, reporting methods of participant characteristics and the dominance of sample size of one study, so caution is recommended in drawing overall conclusons and generalizing.The evidence for bedside assessments being able to provide adequate predictive value for the presence of aspiration is low. A meta-analysis of the findings from the collective studies in two systematic reviews was not possible due to heterogeneity in study designs, populations and study endpoints.~~

The evidence to suggest clinical swallowing evaluations or instrumental assessments are effective in predicting the outcomes of pneumonia or return to oral intake remains ~~is very~~ low as there are too few studies of high quality that explore these endpoints.

Preference and values Substantial variability is expected or uncertain

Patients may prefer a non-invasive and low-risk process for evaluating their swallowing function and risk of aspiration. Clinicians may prefer the certainty of diagnosis that VFSS and FEES provide.

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

Resources considerations
There has been one study identified where a cost-effectiveness analysis of dysphagia assessment~~screening~~ in the acute post-stroke period has been conducted. In this study, the use of a videofluoroscopic swallowing study, a clinical bedside swallowing evaluation, or a combined approach were compared (Wilson et al. 2012 [87]). A decision-analysis model was used with information derived from multiple data sources, including meta-analyses and other relevant clinical studies. The strategy of having each patient undergo a videofluoroscopic swallowing study for dysphagia was more effective and less costly than the strategies of clinical ~~bedside~~ swallowing evaluation alone or as a combined approach. The videofluoroscopic swallowing study led to an outcome of 1.791 QALYs gained per person at an additional cost of US$1,853 (cost reference year 2010). The model was most influenced by the reduction in the risk of pneumonia attributable to the treatment of mild/moderate and severe dysphagia, the effectiveness of treatment with clinical bedside swallowing evaluation, the baseline probability of pneumonia, and the cost of a videofluoroscopic swallowing study.

Implementation considerations
There are clinical indicators collected in the National Stroke Audit ~~to determine the total number of patients with stroke who did not pass a formal swallow screen during their admission. There are also clinical indicators collected~~ on the provision of swallowing assessments by speech pathologists for patients with stroke and, if such an assessment was performed, the date and time of the assessment is collected so that the number of patients who received a swallow assessment within 24 hours of their admission to hospital can be reported. An additional clinical indicator is collected to determine whether patients received swallow assessments before any oral food, fluid or medication intake.

Rationale

There was limited information in the studies included in the systematic reviews about what comprised a specialist swallow assessment. One trial that added cough reflex testing to a standard clinical swallow evaluation showed no difference in the rates of pneumonia in patients randomized to receive the cough reflex test (Miles 2013 *[160]*). Although an instrumental assessment remains the gold standard for detecting aspiration it is unclear when this should be considered (Eltringham et al, 2019 *[128]*).

However, there is increasing evidence that a clinical swallow evaluation or consultation by a speech pathologist is associated with lower incidence of stroke-associated pneumonia. Assessment of swallowing ability occurred in 35% of patients in one large cohort (Ouyang et al (2019)*[137]*; n = 11,093). The median time from admission to dysphagia assessment was 12.5 hours (IQR 1.8 to 28.0).

The frequency of pneumonia was increased with longer times from admission to receiving a dysphagia assessment, with median time being 25.3 hours (IQR 15.1 to 51.6) for those who had pneumonia and 11.0 hours (IQR 1.7 to 26.9) for those who did not have pneumonia. Likewise, Eltringham et al (2019)*[128]* found a strong independent relationship between delay in speech pathologist clinical assessment and incidence of stroke-associated pneumonia; patients in the lowest quartile for assessment had 1.98 (1.67-2.35) odds of stroke-associated pneumonia compared with patients receiving the quickest assessment. Delays in speech pathologist clinical assessment over 24 hours were associated with an additional 4% absolute increase in stroke-associated pneumonia.

Overall~~y~~, consensus is that patients should be referred to a speech pathologist early after a failed screen or if the patient deteriorates so appropriate assessments can be made within 24 hours.

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Clinical swallowing evaluation
Comparator: Instrumental swallow exam

Summary

Two systematic reviews have examined a range of bedside swallow assessment for their potential as diagnostic tools, with reference standards being instrumental swallow exams such as fiberoptic endoscopic evaluation of swallowing (FESS) and videofluoroscopy (VFS) (Kertscher et al 2014 *[116]*; O'Horo et al 2015 *[118]*). Kertscher et al only included studies with high methodological quality, and identified Volume-Viscosity Swallowing Test and Toronto Bedside Swallowing Screening Test as appropriate screening tools with high sensitivity and acceptable specificity. O'Horo et al found individual studies reporting dysphonia assessments, abnormal pharyngeal sensation assessments, dual axis accelerometry, and 3 oz swallow test to be sensitive tools, but none of them was validated to be consistently sensitive.

Kjaersgaard et al (2014) *[119]* conducted a randomised controlled trial to determine how a clinical versus instrumental assessment would influence the rate of pneumonia in a group of acquired brain injury patient. Stroke participants represented a large proportion of this group. The comparison was between the Facial-Oral Tract Therapy (FOTT) approach and the instrumental measure FEES. The pneumonia rate was slightly higher for the comparator (FEES) than for those assessed with FOTT. However, there was no statistical comparison and the rates were both quite low in this relatively small sample. Kjaersgaard et al (2015) *[120]* reported on the return to oral intake outcomes for the cohort of participants reported in the 2014 study. They found that the type of initial assessment did not influence the time taken to commence oral intake, nor did it influence the time to full oral intake for those participants able to achieve this during their neurorehabilitation stay.

Mortensen and colleagues (2016) *[117]* reported on the diagnostic performance of the Swallowing Assessment of Saliva (SAS) based on FOTT approach. Comparison with FESS indicated that it was able to detect aspiration with a sensitivity of 91% and specificity of 88%. Therefore, the SAS as a bedside assessment tool for aspiration risk is comparable to FEES and is more likely to result in false positives rather than false negatives which is clinically preferable. However, the aim of the SAS was to identify patients at risk of aspiration, rather than to provide a comprehensive evaluation of dysphagia.

A systematic review by Smith et al 2018 *[131]* found insufficient evidence from randomized controlled trials to show whether implementation of a specific dysphagia screening protocol or a comprehensive specialist swallowing assessment involving cough reflex testing reduces the risk of death, dependency or pneumonia after stroke. However, Eltringham et al's 2019 *[128]* systematic review found increasing evidence that early dysphagia screening and comprehensive specialist swallow assessment do help to reduce the odds of stroke-associated pneumonia.

With respect to the timing of a comprehensive swallowing assessment by an speech-language pathologist, Bray (2016) *[124]* demonstrated that there was a strong dose-response relationship between a comprehensive swallowing assessment and stroke-associated pneumonia; the earlier dysphagia was assessed, the lower the risk of pneumonia. Patients with the longest delays in dysphagia assessment (4th quartile adjusted OR 2.01, 1.76 to 2.30) had a higher risk of stroke-associated pneumonia, with an absolute increase of pneumonia incidence of 1% per day of delay.

Ouyang et al (2019)*[137]* (n = 11,093) using data from the HeadPoST study found the median time from admission to dysphagia assessment was 12.5 hrs (IQR 1.8 to 28.0). The frequency of pneumonia was associated with longer times to having a dysphagia assessment, with median time for being 25.3 hrs (IQR 15.1 to 51.6) for those who had pneumonia and 11.0 hrs (IQR 1.7 to 26.9) for those who did not have did not have pneumonia.

Outcome Timeframe	**Study results and measurements**	**Comparator** Instrumental swallow exam	**Intervention** Clinical swallowing evaluation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Pneumonia until discharge 8 Critical	n/a Based on data from 559 patients in 2 studies. (Randomized controlled)	65 per 1000	105 per 1000 Difference: 40 more per 1000 CI 95%	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision [1]	The findings are based on two studies which had conflicting findings about the direction of the effect. We are uncertain whether assessment by clinical bedside swallow exam increases or decreases the risk of pneumonia to patients
Performance in diagnosing dysphagia/ aspiration 7 Critical	Based on data from: 10,850 patients in 53 studies. (Observational (non-randomized))	Pooled analysis could not be performed due to heterogeneity in study designs, different ways in which assessments were implemented, heterogeneity in statistical analysis and different endpoints for the reference and/or index tests.		**Moderate** Due to serious imprecision [2]	Very few bedside assessments can allow detection of dysphagia/ aspiration compared with gold standard.

1. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** due to no statistical analysis was presented by the authors of the RCT, The direction of the effect is not consistent between the included studies ;. **Indirectness: Serious.** Differences between the population of interest and those studied - this study included a mixed ABI population, not stroke specific and represented an extremely severe group of stroke survivors.. **Imprecision: Serious.** No 95%CI. **Publication bias: No serious.**
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** No meta-analysis of an individual tool - few studies validating same tools.

Strong recommendation

In review

For stroke survivors with swallowing difficulties, behavioural approaches such as swallowing exercises, environmental modifications, safe swallowing advice, and appropriate dietary modifications should be used early. (Geeganage et al. 2012 *[108]*)

Practical Info

Where stroke patients require modified texture foods and thickened fluids, these should be prescribed using nationally agreed descriptors (Cichero et al. 2017 *[126]*).

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Behavioural interventions such as swallowing exercises, environmental modifications (e.g. upright positioning for feeding), safe swallowing advice, and appropriate dietary modifications improve swallowing function after stroke. The systematic review incorporating 5 studies found that dysphagia significantly improved by the end of treatment (157 less dysphagia per 1000 patients treated but no statistically significant difference in the outcome of death) (Geeganage et al. 2012 *[108]*). However, due to heterogeneity in the nature of the behavioural interventions delivered, it is difficult to draw strong conclusions about the defining characteristics of the intervention.

A subsequent low-quality randomised controlled trial (no blinding of assessor or therapist) examining swallowing outcomes based on the time of initiation of active treatment found that stroke patients who received early intervention (within 3 days of stroke) had better swallowing outcomes and lower rates of pneumonia than those who commenced treatment at 2 weeks or 1

month after stroke (Bakhtiyari et al. 2015 *[109]*).

Certainty of the Evidence Low

The quality of the systematic review itself was high using the Cochrane methodology. Only 5 studies were grouped under the heading of "behavioural interventions" and the nature of the interventions differed amongst the studies, which limits the recommendations able to be made from the review. The randomised controlled trial was of low quality with no assessor or therapist blinding and small participant numbers.

Preference and values No substantial variability expected

We believe that most if not all patients will want behavioural interventions for their dysphagia.

Resources and other considerations Factor not considered

Rationale

Despite the judgement that evidence to date is of low quality (due to large heterogeneity in interventions), a strong recommendation is made for behavioural approaches, as a significant reduction in swallowing dysfunction was reported with minimal to no reported risks. Similarly, it is recommended that patients receive regular behavioural interventions for dysphagia as soon as possible after stroke even if the evidence to support the exact timing and intensity of interventions is lacking.

Clinical Question/ PICO

Population: All stroke patients with dysphagia
Intervention: Postural techniques and swallow strategies (compensatory -direct)
Comparator: Control

Summary

Bath et al (2018) *[108]* updated a Cochrane review and included 9 studies of behavioural interventions to improve dysphagia. Overall, behavioural interventions were found to significantly reduce dysphagia at the end of the trials (OR 0.45, 95% CI 0.28 to 0.74; 6 studies, n=511 participants) and improve swallowing ability (SMD -0.56, 95% CI -1.07 to -0.05; 3 studies; n=121 participants; 3 studies). Two studies were identified which ~~to~~ specifically focus on postural techniques and swallowing strategies. Carnaby et al (2006) undertook a multicomponent intervention which included diet modification as needed. A standard low-intensity intervention (swallowing compensation strategies and diet prescription three times weekly for up to a month) was compared to high-intensity intervention (as per low-intensity but seen at least daily) versus usual care. Both intervention groups had a significant rise in the proportion of patients regaining swallowing function by 6 months compared to usual care. However, high-intensity therapy led to increased proportion of patients who returned to a normal diet (p=0.04) and recovered swallowing (p=0.02) by 6 months compared to both usual care and low-intensity therapy. The other study by Song et al (2004) reported rehabilitation training (characterised by swallowing and ingesting training) lead to improved swallow function compared to control group (p< 0.01).

Jeon et al (2020)*[151]* conducted a small (n=34) trial reported upper cervical mobilisation in conjunction with neuromuscular electrical stimulation improved swallowing function compared to electrical stimulation and sham mobilisation. Further larger trials are required.

Bakhtiyari et al (2015) *[109]* conducted a 3-arm randomised controlled trial investigating the optimal time to introduce behavioural intervention for dysphagia, blinding patients to group allocation but not therapists or assessors. All groups were similar at baseline. Findings suggested that early intervention significantly reduced dysphagia and frequency of pneumonia as compared to both the medium and late-onset groups. The early intervention group also required fewer intervention sessions.

Combined, the systematic review and recent randomised trial suggest that compensatory interventions (postural techniques and swallowing strategies) during swallowing practice may reduce dysphagia, and that earlier intervention is preferable to delayed intervention.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Postural techniques and swallow strategies	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Dysphagia at end of trial 7 Critical	Based on data from: 481 patients in 4 studies. [1] (Randomized controlled)	Four comparisons from three studies (Carbaby 2006, Song 2004, Zheng 2014) noted in the Cochrane review by Bath (2018) found the proportion with dysphagia at the end of trial was 32.7% in the intervention group vs 48% in the control group. One additional small study by Jeon 2020 also reported improved swallowing function.o		**Low** Due to serious risk of bias [2]	Behavioral interventions such as postural techniques and swallow strategies may decrease dysphagia at end of trial

1. Systematic review [108].
2. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, 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, Incomplete data and/or large loss to follow up. **Inconsistency: No serious. Indirectness: No serious.** The outcome time frame in studies were insufficient. **Imprecision: No serious. Publication bias: No serious.**

Weak recommendation against

In review

For stroke survivors with dysphagia, non-invasive brain stimulation should only be provided within a research framework. (Pisegna et al. 2016 *[110]*)

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Non-invasive brain stimulation may improve swallowing function in unilateral strokes but further research is needed before use in clinical practice. A systematic review and meta-analysis revealed a moderate and significant pooled effect size overall, with larger effect sizes associated with stimulation to the non-affected hemisphere (Pisegna et al. 2016 *[110]*). No conclusions could be drawn about the most effective duration for stimulation treatment, benefits of transcranial direct current stimulation vs repetitive transcranial magnetic stimulation, long-term efficacy and long-term safety.

Certainty of the Evidence

Low

The quality of the systematic review itself was high (Pisegna et al. 2016 *[110]*). It was methodologically sound and included only studies that met specific inclusion criteria including quality ratings. However, the authors themselves state that specific and definitive conclusions cannot be made from only eight small and clinically heterogeneous trials (heterogeneity in the studies' treatment protocols, outcome measurements and patient characteristics).

Preference and values

Substantial variability is expected or uncertain

Patients' experiences of non-invasive brain stimulation have not been explored. There may be some variation in accepting this intervention considering its unclear benefits.

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

Non-invasive brain stimulation is showing promising results in improving swallowing function in clinical trials. However, the most effective stimulation paradigms with respect to stimulation type, location, intensity and duration have not been determined. Endpoint benefits and harms such as death, nutrition status and pneumonia have also not been well researched. For this reason, non-invasive brain stimulation should only be used with patients in a clinical research framework.

Clinical Question/ PICO

Population: All stroke patients with dysphagia
Intervention: Transcranial direct current stimulation
Comparator: Sham or control

Summary

A systematic review by Cheng et al (2020)*[132]* included 26 studies (n=852) assessing the impact of three forms of neurostimulation (transcranial direct current stimulation [tDCS], repetitive transcranial magnetic stimulation [rTMS] and pharyngeal electrical stimulation [PES]) as a treatment for dysphagia post-stroke. Overall there was a moderate significant effect from tDCS (SMD 0.65, 95% CI 0.25 to 1.04; 7 studies, n = 203) as compared to sham. Stimulation on the contralesional hemisphere appeared to be the most effective.

Marchina et al (2020)*[145]* included 7 studies (n=217) reported a more modest effects based on validated dysphagia scales (SMD 0.31; 95% CI 0.03 to 0.59). Subgroup analysis found studies with low intensity were effective (SMD 0.44, 95% CI, 4 studies, n=121) whereas those of high intensity were not (SMD 0.15, 95% CI -0.30 to 0.61; 3 studies, n=96). There was no difference between studies in acute vs chronic patients nor which hemisphere to stimulate.

A Cochrane review by Bath et al (2018)*[108]* included two small studies on tDCS. There was no difference in the proportion of participants with dysphagia at the end of the trial (OR 0.29, 95% CI 0.01 to 8.39; 1 study, n = 14) and ~~did not~~ improvement in swallowing ability (SMD -0.33, 95% CI -2.22 to 1.56; 2 studies, n = 34).

Chiang et al (2018)*[141]* included four studies (n = 112) investigating tDCS and found significantly improved post-stroke dysphagia (SMD 0.61, 95% CI 0.14 to 1.08). Network meta-analysis of different neurostimulation therapy also found a moderate effect size (SMD 0.61, 95% CI 0.09 to 1.13). tDCS was found to be third out of the 4 neurostimulations therapies analysed in terms of best treatment with a cumulative probability of 7.4%. No significant adverse safety event was reported. A small (n=28) subsequent study by Wang et al (2020)*[148]* investigates the effects of tDSC combined with conventional swallow training on swallow function. The anodal tDCS group exhibited greater improvement than the sham group on the functional dysphagia scale with the use of both thin and thick barium sulphate. Functional oral intake scale (FOIS) immediately after the intervention improved for both groups, with greater improvement in the tDCS group (3.07 ± 0.29, p = 0.001).

Overall, studies to date suggest that transcranial direct current neurostimulation may improve dysphagia. However, further robust studies are needed to improve the certainty of evidence.

Outcome Timeframe	**Study results and measurements**	**Comparator** Sham or control	**Intervention** tDCS	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Dysphagia [1] 8 Critical	Measured by: PAS, DOSS, MASA, SSA, DSRS, FDS, FOIS, VDS High better Based on data from: 203 patients in 7 studies. [2] (Randomized controlled)	Difference: **SMD 0.65 higher** (CI 95% 0.25 higher — 1.04 higher)		**Low** Due to serious risk of bias [3]	tDCS probably improves effect of treatment

1. various measures used including penetration aspiration scale, Dysphagia Outcome and Severity Scale, Mann Assessment of Swallowing Ability, etc.
2. Systematic review [132] . **Baseline/comparator:** Control arm of reference used for intervention.
3. **Risk of Bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, 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, Incomplete data and/or large loss to follow up, Selective outcome reporting, due to [reason]. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Weak recommendation against

In review

For patients with stroke, acupuncture should not be used for treatment of dysphagia in routine practice other than as part of a research study. (Long et al. 2012 *[107]*)

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

A systematic review and meta-analysis of 72 RCTs (3208 patients in the treatment group and 2926 patients in the control group) showed that acupuncture as an adjunct to conventional therapy was significantly more effective than conventional treatment without acupuncture in the recovery of swallowing function (OR=5.17, 95% CI 4.18 to 6.38; p<0.00001) (Long et al. 2012 *[107]*). No information about harm from the acupuncture treatment was reported

Certainty of the Evidence

Very low

The quality of evidence was judged by the working party and the authors of the systematic review as very low due to serious methodological issues, poor reporting of interventions and small sample sizes in the included studies (Long et al. 2012 *[107]*). It is considered of insufficient quality to make recommendations about using acupuncture without further well-designed clinical trials.

Preference and values

Substantial variability is expected or uncertain

There may be some variation in patients' willingness to receive acupuncture, especially given inadequate evidence and lack of information on the harm/discomfort.

Resources and other considerations

Factor not considered

Rationale

Whilst the available literature demonstrates significant positive effects of acupuncture for the recovery of swallowing function, studies to date are of inadequate quality to support a stronger recommendation of this as a treatment for dysphagia.

Clinical Question/ PICO

Population: All stroke patients with dysphagia
Intervention: Acupuncture
Comparator: No acupuncture

Summary

Long and Wu (2012) *[107]* conducted a meta-analysis of studies investigating the effectiveness of acupuncture to treat dysphagia after stroke. While their meta-analysis was conducted on 72 studies, the authors acknowledged that the methodological rigor was not strong for the majority of studies. Forty-two of the RCTs had a water swallow test as their criteria for dysphagia presence/absence, and only 4 had a strong methodology. Meta-analysis was conducted on all 3 study groups (n=72; n=42; n=4). In all analyses acupuncture was found to be an effective treatment for reducing dysphagia after

stroke, However, the odds ratio was smallest when only taking into consideration the 4 methodologically strong studies.

Ye et al (2017)*[139]* included 71 studies (n=6,010) found the efficacy of acupuncture for reducing dsyphagia was higher than the control group (RR 1.17, 95% CI 1.13 to 1.21; 58 studies, n=4809; moderate heterogeneity I^2=62%).

Bath et al (2018)*[108]* conducted an updated Cochrane review including 11 studies of acupuncture. Proportion of participants with dysphagia at end of trial was significantly lower (OR 0.31, 95% CI 0.20 to 0.49; 8 studies, n=676) although testing for subgroup differences did not yield significant results. Acupuncture did not improve swallowing ability (SMD -0.55, 95% CI -1.20 to 0.11; 6 studies, n=496; I^2 = 91%).

Li et al (2018)*[138]* included 29 studies (n=2,190) and found acupuncture improved risk of dysphagia (RR 1.33, 95% CI 1.25 to 1.43). Adverse events were not documented.

Li and Deng (2019) *[127]* included 17 RCTs (n=1,479) and found that acupuncture combined with swallowing therapy was significantly more effective than swallowing therapy alone in the recovery of swallowing function. All studies were conducted in China and only one study was published in English. Adverse events (aspiration pneumonia, malnutrition and dehydration) were slightly higher in the control group as reported in 6 RCTs but numbers were too low to allow accurate statistical analysis. Acupuncture related adverse events (e.g. mild vomiting, ecchymosis and haematoma) occurred rarely and were not severe. No medium to long term outcomes were reported.

Huang et al (2020)*[140]* included 16 studies (n=1,216) and found electroacupuncture in combination with conventional swallowing therapy was significant for effective rate of dysphagia (OR 5.40, 95% CI 3.78 to 7.72; 12 studies, n=968), reduced problems with water swallow test (MD -0.78, 95% CI -1.07 to -0.50; 3 studies, n=196; moderate heterogeneity I^2=66%), and improved dysphagia on video fluoroscopic swallowing study (MD 1.47, 95% CI 1.11 to 1.84; 2 studies, n=228). The incidence of aspiration pneumonia was lower with combined intervention (OR 0.20, 95% CI 0.06 to 0.61; 2 studies, n=170). Adverse events were reported in 2 studies, 10/16 participants reported non-severe symptoms such as pain and hematoma, and 6/16 developed a cough (all in the control group). Overall quality of studies was poor with high risk of selection bias, detection bias and reporting bias. No medium to long term outcomes were reported.

The evidence to-date is still emerging in regards to the effectiveness of acupuncture as a treatment for dysphagia, but studies to-date suggest that it may be a useful treatment to reduce dysphagia. Overall quality of evidence is low and further high quality trials are needed. (Tian et al 2019 *[150]*)

Outcome Timeframe	**Study results and measurements**	**Comparator** No/ or sham acupuncture	**Intervention** Acupuncture	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Clinical effectivenss rate 7 Critical	Relative risk 1.26 (CI 95% 1.19 — 1.34) Based on data from 1,075 patients in 14 studies. [1] (Randomized controlled) Follow up: unclear.	325 per 1000	410 per 1000 Difference: **85 more** per 1000 (CI 95% 62 more — 111 more)	**Low** Due to very serious risk of bias, Due to serious indirectness, Due to serious publication bias [2]	Acupuncture may improve clinical effectivenss rate
Swallowing function assessment [3] 8 Critical	High better Based on data from: 776 patients in 9 studies. (Randomized controlled) Follow up: unclear.		Difference: **SMD 1.17 higher** (CI 95% 0.76 higher — 1.58 higher)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness [4]	We are uncertain whether acupuncture increases or decreases swallowing function assessment due inconsistency across studies.

1. Systematic review. **Baseline/comparator:** Systematic review. **Supporting references:** [127], Note: calcuated from supplemental data.
2. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel (but hard to do for acupuncture). **Inconsistency: No serious.** Initially heterogeneity was high based on 15 trials (I=64.4%) which disappeared after removing one trial. . **Indirectness: No**

serious. lack of clear information in terms of range of follow-up times for each of the studies. **Imprecision: No serious. Publication bias: Serious.** Asymmetrical funnel plot. Begg's and Egger's test also significant but further trim-and-fill analysis was undertaken with no significant differences..
3. Studies used water swallow test (3 studies); videofluoroscopic study (1 study); standardised swallowing assessment (2 studies); dysphagia outcome and severity scale (one study) or Fujishima Ichiro's dysphagia scale (2 studies)
4. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2=85.5%. Sensitivity analysis found 4 of 9 trials contributed and when removed SMD was 1.40 95%1.18-1.61; I2=53.8%. **Indirectness: Serious.** Timeframes not reported. **Imprecision: No serious. Publication bias: No serious.**

Weak recommendation against

In review

For stroke survivors with dysphagia, surface neuromuscular electrical stimulation should only be delivered by clinicians experienced in this intervention, and be applied according to published parameters in a research framework. (Chen et al. 2016 *[102]*)

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Surface neuromuscular stimulation of swallowing (NMES) as an intervention for dysphagia may improve swallowing function for some stroke survivors, but further research is needed before routine use in standard clinical practice. A systematic review and meta-analysis by Chen et al. (2016) *[102]*, which included 8 studies, found improvements in swallowing function after NMES intervention plus swallow therapy compared to swallow therapy alone. Measures such as pharyngeal transit time and biomechanical laryngeal excursion showed significant improvements in the NMES group, with a pooled effect size of SMD 1.27, 95% CI 0.51 to 2.02. Three included studies that compared NMES alone to swallowing therapy showed no significant differences (SMD 0.25, 95% CI -0.16 to 0.65). A separate 3-armed RCT by Huang et al, (2014) *[103]* demonstrated a significant improvement on the Functional Dysphagia Scale for the combined NMES and swallow therapy group compared with NMES alone or swallow therapy alone.

NMES appears to be most effective when combined with swallowing therapy. No harm or adverse events were reported with surface NMES.

Certainty of the Evidence

Low

There was significant heterogeneity in the studies included in the systematic review (Chen et al, 2016 *[102]*). They varied in quality with issues relating to sample size, statistical analysis, lack of standardised treatment protocols regarding treatment intensity and NMES treatment parameters. Due to this serious inconsistency and serious risk of bias, the quality of the evidence was judged to be low.

Preference and values

Substantial variability is expected or uncertain

Patient comfort associated with receiving surface NMES was not reported in any of the studies, and should be considered before recommending this intervention.

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

Patients may want to be offered surface NMES as a treatment option for dysphagia but there is weak evidence to support its clinical

use. It is an intervention that requires additional training and the exact parameters or combinations of treatments that result in the best outcomes remain unclear. Recent findings would indicate that the most likely benefit would come from NMES in combination with swallowing therapy. Further clinical research is needed before a stronger recommendation can be made.

Clinical Question/ PICO

Population: All stroke patients with dysphagia
Intervention: Surface neuromuscular electrical stimulation
Comparator: Usual care / placebo / sham

Summary

Chen et al (2016) *[102]* conducted a systematic review and meta-analysis of randomised and quasi-randomised controlled trials of neuromuscular electrical stimulation (NMES). Eight studies were included. Comparing NMES plus swallow therapy to swallow therapy alone, measures of swallowing function such as pharyngeal transit time and biomechanical laryngeal excursion showed significant improvements in the NMES group (SMD 1.27, 95% CI 0.51 to 2.02; 6 studies, n=243; high heterogeneity I^2=85%).-Three included studies that compared NMES alone to swallowing therapy showed no significant differences (SMD 0.25, 95% CI -0.16 to 0.65).

An updated Cochrane review by Bath et al (2018)*[108]* explored the impact of a range of interventions for dysphagia. Six studies (n=312) investigated NMES, one study combined NMES and swallow therapy, while the others compared NMES with traditional dysphagia therapy. NMES did not improve swallowing abilitiy (SMD -1.34, 95% CI -3.39 to 0.71; 2 studies, n = 100) or reduce the proportion of participants with dysphagia at the end of the trial (OR 0.51, 95% CI 0.18 to 1.49; 2 studies, n = 76). But NMES was-effective for reducing pharyngeal transit time (MD -0.23, 95% CI -0.39 to -0.08; 3 studies, n = 126; moderate heterogenity I^2 = 63%; low certainty of evidence).

A review by Alamer et al (2020)*[146]* investigated the effectiveness of neuromuscular electrical stimulation on post-stroke dysphagia. Eleven RCTs were identified (n = 784) which were of moderate quality but due to the heterogeneity of interventions, meta-analysis was not possible. All but one study observed an increased swallow function and no complications were reported.

A review by Chiang et al (2018)*[141]* exploring the impact of neurostimulation therapies included 5 studies (n = 313) investigating NMES. Pairwise and network meta-analysis found significantly improved poststroke dysphagia (SMD 0.76, 95% CI 0.26 to 1.26; moderate heterogeneity I^2 = 65% and SMD 0.82, 95% CI 0.42 to 1.23 respectively). Among the 4 neurostimulations therapies analysed and the placebo, NMES was placed after rTMS in terms of best treatment with a cumulative probability of 22.4%. No significant adverse safety events were reported.

Carnaby et al (2020)*[147]* conducted a double-blind placebo controlled trial (n=53) in acute care comparing McNeill Dysphagia Therapy Program (MDTP) in addition to NMES, MDTP plus sham NMES, and usual care. All groups received standardised behavioural swallowing therapy by a speech pathologist. MDTP alone (plus sham NMES) demonstrated a greater reduction in swallowing severity compared to MDTP + NMES or usual care (effect size 1.37, 95% CI 0.68 to 2.07). There was no difference between groups in the proportion demonstrating dysphagia post-treatment, however, MDTP alone had fewer patients with dysphagia identified during modified barium swallow study. Both MDTP and MDTP + NMES significantly improved oral intake level compared to usual care.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care / placebo / sham	**Intervention** Surface neuromuscular electrical stimulation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Proportion of participants with dysphagia at end of trial 8 Critical	Odds Ratio 0.51 (CI 95% 0.18 — 1.49) Based on data from 76 patients in 2 studies. [1] (Randomized controlled)	667 per 1000	505 per 1000 Difference: **162 fewer** per 1000 (CI 95% 402 fewer — 82 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Surface neuromuscular electrical stimulation may decrease proportion of participants with dysphagia at end of trial

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care / placebo / sham	**Intervention** Surface neuromuscular electrical stimulation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Swallowing function After treatment: 2-4 weeks 8 Critical	Measured by: Various - pharyngeal transit time, biomechanical laryngeal excursion, bolus velocity High better Based on data from: 243 patients in 6 studies. [3] (Randomized controlled) Follow up: 2-4 weeks of treatment.	Difference: **SMD 1.27 higher** (CI 95% 0.51 higher — 2.02 higher)		**Low** Due to serious inconsistency, Due to serious risk of bias [4]	Surface neuromuscular electrical stimulation (plus swallow therapy) may improve swallowing function

1. Systematic review [108] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious.** The outcome time frame in studies were insufficient. **Imprecision: Serious.** Low number of patients, Wide confidence intervals. **Publication bias: No serious.**
3. Systematic review [102] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel in 6/8 included studies, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors in 2/8 included studies, resulting in potential for detection bias, Inadequate sequence generation/ generation of comparable groups in 2/8 studies (quasi-randomisation), resulting in potential for selection bias. **Inconsistency: Serious.** The magnitude of statistical heterogeneity was high, with I^2: 85%. Excluding one study with a higher effect size gave a smaller but still significant effect size (0.93). **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Weak recommendation against

In review

For stroke survivors with dysphagia, pharyngeal electrical stimulation is not routinely recommended. (Bath et al. 2016 *[104]*; Scutt et al. 2015 *[105]*)

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is no strong evidence to support the use of pharyngeal electrical stimulation (PES) as a treatment for dysphagia following stroke. A recent large randomised controlled trial of 141 patients (Bath et al. 2016 *[104]*) failed to confirm previously reported positive outcomes for PES as an intervention for dysphagia after stroke. A previous meta-analysis of three small randomised controlled trials (n=73) had indicated PES resulted in significantly lower levels of penetration-aspiration and clinical dysphagia at 2 weeks post treatment than sham, but suggested it may be effective for patients with more severe dysphagia (Scutt et al. 2015 *[105]*). No adverse events were reported in any studies investigating PES as a treatment for dysphagia.

Certainty of the Evidence

Low

The meta-analysis of PES was methodologically sound, setting strict inclusion criteria and including only those where patient datasets were supplied, which then resulted in them reporting only three studies (Scutt et al. 2015 *[105]*). The authors acknowledged that the findings are preliminary due to the small numbers of studies included, the use of VFSS as the method of determining penetration-aspiration, and the lack of long-term follow-up (Scutt et al. 2015 *[105]*). The subsequent larger randomised trial reporting outcomes on PES was also methodologically sound, but as the authors themselves acknowledge, the participant attrition was higher than is preferable and, while attempts were made to blind participants to their treatment, this

may not have been achieved nor was there blinding of therapists (Bath et al. 2016 *[104]*). However, the assessors were blinded to the intervention arm.

Preference and values Substantial variability is expected or uncertain

Patient comfort associated with receiving PES was not reported in any of the studies and should be considered. It should be noted that failure to insert the catheter and withdrawal of consent were two reasons for participant attrition in the randomised controlled trial investigating PES in acute and subacute settings, which may reflect patient preferences regarding nasopharyngeal catheter insertion.

Resources and other considerations Factor not considered

Rationale

The meta-analysis and randomised controlled trial reports that had positive findings in relation to PES as a treatment for dysphagia were of low quality, and a larger randomised controlled trial with stronger methodology failed to confirm that PES is an effective intervention for all survivors of stroke with dysphagia. In addition, patient comfort and acceptance of an intervention that requires insertion of a nasopharyngeal catheter is unknown, and there are multiple contraindications for the use of PES as a routine treatment that clinicians need to consider. Therefore, further clinical trials are required to support the use of PES in dysphagia post-stroke, with consideration of patient comfort and acceptance of the treatment included in these trials before it should be considered for implementation into clinical practice. We believe that at this stage few people will want PES due to the invasive nature of the treatment and the lack of benefit of the intervention.

Clinical Question/ PICO

Population: All stroke patients with dysphagia
Intervention: Pharyngeal electrical stimulation
Comparator: Sham

Summary

Pharyngeal electrical stimulation (PES) differs from neuromuscular electrical stimulation (NMES) as an intervention tool as it is more invasive requiring the insertion of a catheter with a pair of bipolar titanium ring electrodes housed in the tube (similar to a nasogastric tube) to deliver the electrical stimulation to the pharynx. A Cochrane review by Bath et al (2018)*[108]* explored the impact of a range of interventions for dysphagia and many outcomes were addressed by the 4 PES studies (n = 312). No effect was found for-proportion of people with dysphagia at end of trial (OR 0.55, 95% CI 0.15 to 2.11; 3 studies, n = 66), swallowing ability (SMD 0.06, 95% CI -0.22 to 0.34; 3 studies, n = 194), or penetration aspiration (SMD -0.17, 95% CI -0.53 to 0.19; 4 studies, n = 177). There was also no effect on pharyngeal transit time or-chest infections based on small single studies.

A review by Chiang et al (2018)*[141]* exploring the impact of a range of interventions found 3 studies (n = 190) investigating PES using pairwise and network meta-analysis found no significant improvement for post-stroke dysphagia.

One of the studied included in the review was the largest and most well-controlled RCT (n=141) comparing PES and sham interventions in a stroke population with mixed severity of dysphagia did not find PES to improve swallowing function in comparison to sham, and there was no impact on rate of respiratory tract infections, severity of stroke disability, or death (Bath et al 2016 *[104]*).

Outcome Timeframe	**Study results and measurements**	**Comparator** Sham	**Intervention** Pharyngeal electrical stimulation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Proportion of participants with dysphagia at end of trial 7 Critical	Odds Ratio 0.55 (CI 95% 0.15 — 2.11) Based on data from 66 patients in 3 studies. [1] (Randomized controlled)	781 per 1000	662 per 1000 Difference: **119 fewer** per 1000 (CI 95% 432 fewer — 102 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Pharyngeal electrical stimulation has little or no difference on proportion of participants with dysphagia at end of trial
Swallowing ability 7 Critical	Measured by: Dysphagia Severity Rating Scale, Functional Oral Intake Scale, Dysphagia Outcome and Severity Scale (DOSS) or water swallowing test Based on data from: 194 patients in 3 studies. [3] (Randomized controlled)	Difference: **SMD 0.06 higher** (CI 95% 0.22 lower — 0.34 higher)		**Moderate** Due to serious risk of bias [4]	Pharyngeal electrical stimulation has little or no difference on swallowing ability
Penetration aspiration score 7 Critical	Measured by: VFSS, FEES, PAS Lower better Based on data from: 177 patients in 4 studies. [5] (Randomized controlled)	Difference: **SMD 0.17 lower** (CI 95% 0.53 lower — 0.19 higher)		**Moderate** Due to serious risk of bias, Due to serious imprecision, Due to serious imprecision [6]	Pharyngeal electrical stimulation probably has little or no difference on penetration aspiration score

1. Systematic review [108] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Low number of patients. **Publication bias: No serious.**
3. Systematic review [108] . **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Low number of patients. **Publication bias: No serious.**
5. Systematic review [108] . **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Low number of patients. **Publication bias: No serious.**

Practice statement

Consensus-based recommendations

- Until a safe swallowing method is established for oral intake, patients with dysphagia should have their nutrition and hydration assessed and managed with early consideration of alternative non-oral routes.
- Patients with dysphagia on texture-modified diets and/or fluids should have their intake and tolerance to the modified diet monitored regularly due to the increased risk of malnutrition and dehydration.
- Patients with dysphagia should be offered regular therapy that includes skill and strength training in direct therapy (with food/fluids) and indirect motor therapy which capitalises on the principles of neural plasticity to improve swallowing skills.
- Patients with persistent weight loss, dehydration and/or recurrent chest infections should be urgently reviewed.
- All staff and carers involved in feeding patients should receive appropriate training in feeding and swallowing techniques.
- All staff should be appropriately trained in the maintenance of oral hygiene, including daily brushing of teeth and/or dentures and care of gums.

Please also refer to the topic Early Nutrition in Managing Complications.

Rationale

Patients with dysphagia are at increased risk of malnourishment, dehydration and aspiration pneumonia, reinforcing the need for close monitoring. Furthermore, any modification from regular liquids and solid diets contributed to reduced hydration at discharge for patients with dysphagia in acute settings (Crary et al. 2016 *[123]*). Therefore, the hydration and nutrition status should be regularly monitored and managed.

Acute antithrombotic therapy

Antithrombotic therapies include the use of antiplatelets and anticoagulants.

Antiplatelet agents inhibit platelet adhesion and aggregation, and anticoagulants reduce the propagation of a thrombus in an intracerebral artery (Sandercock et al. 2014 *[164]*; Sandercock et al. 2015 *[161]*). Therefore early use of antithrombotics may, theoretically, decrease the volume of infarcted cerebral tissue and so decrease the neurological deficit, risk of disability and death. Additionally, they may reduce the risk of early recurrent thromboembolic stroke. However, these benefits could be offset by the possibility of increased risk for intracerebral haemorrhage (Sandercock et al. 2014 *[164]*; Sandercock et al. 2015 *[161]*).

Common anticoagulant agents include unfractionated heparin, low-molecular-weight heparins, heparinoids, and oral vitamin K antagonists. The most commonly used antiplatelet agent in Australia is aspirin. Clopidogrel and dipyridamole are also used by itself or in combination with aspirin. The uses of glycoprotein IIb-IIIa inhibitors, cilostazol, and thromboxane A2 synthase inhibitor are investigated in the literature, but they are not included in our evidence review due to limited applicability to the Australia healthcare setting.

In Australia, the National Stroke Audit of Acute Services showed that 76% of stroke patients received hyperacute aspirin therapy and 70% of ischaemic stroke patients received aspirin within 48 hours of admission (Stroke Foundation 2019 *[28]*).

Strong recommendation

Patients with ischaemic stroke who are not receiving reperfusion therapy should receive antiplatelet therapy as soon as brain imaging has excluded haemorrhage. (Sandercock et al. 2014 *[164]*)

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Aspirin was shown to have small but statistically significant benefit in outcomes of death (9 fewer per 1000), death and dependency (13 fewer per 1000), and recurrent stroke (7 fewer per 1000) (Sandercock et al. 2014 *[164]*). It was shown to increase symptomatic intracranial haemorrhage but the effect was small (2 more per 1000 patients) (Sandercock et al. 2014 *[164]*).

Certainty of the Evidence

High

The evidence is based on large RCTs with low risk of bias, reporting consistent results.

Preference and values

No substantial variability expected

Patients that are not receiving reperfusion therapy are likely to want to receive aspirin as it reduces death and dependency.

Resources and other considerations

No important issues with the recommended alternative

<u>Resources considerations</u>

In decision analytic modelling conducted for an Australian setting, it was found that treatment with aspirin within 48 hours of ischaemic stroke was cost-effective compared to no aspirin, costing an additional AU$1,847 per DALY avoided (cost reference year 1997) (Mihalopoulos et al. 2005 *[169]*).

<u>Implementation consideration</u>

There are clinical indicators collected in the National Stroke Audit on the provision of aspirin given as hyperacute therapy for patients with ischaemic stroke and, if aspirin was provided, the date and time the treatment was given is collected so that the number of patients who receive aspirin within 48 hours of their admission can be reported.

Rationale

High-quality evidence shows that aspirin significantly reduces death and dependency and recurrent stroke, with a small increase in intracranial haemorrhage in patients of ischaemic stroke who are not receiving reperfusion therapy.

Clinical Question/ PICO

Population: Adults with acute ischaemic stroke
Intervention: Aspirin
Comparator: Placebo or no treatment

Summary

Sandercock et al (2014) *[164]* conducted a systematic review and meta-analysis of immediate oral antiplatelet therapy for acute ischaemic stroke. Eight randomised controlled trials with 41,483 patients were included. The two largest trials, contributing 98% of the data, used 300mg or 160mg aspirin. Aspirin was associated with a small but significant reduction in death or dependence (OR 0.95, 95% CI 0.91 to 0.99) at the end of follow-up (up to 6 months). There were also significant reductions in death and recurrent stroke, as well as a significant increase in symptomatic intracranial haemorrhages that was small in absolute terms due to the low overall risk. The review authors rated the risk of bias as low. Although one of the large trials contributing the majority of the data was unblinded, outcomes were self-reported by patients or assessed by a blinded interviewer, and a pilot study suggested that the majority of patients did not remember the treatment they had received at 6-month follow-up.

Rothwell et al (2016) *[160]* conducted an individual patient data analysis of the effects of aspirin on risk of recurrent stroke following TIA or ischaemic stroke. Data for aspirin following acute stroke predominantly came from the two largest trials included in the Sandercock et al (2014) review. Time course analysis of the risk of recurrent ischaemic stroke following aspirin treatment was conducted. For patients with mild or moderately severe neurological deficits, there was a non-significant reduction in risk in the first 24 hours following aspiring treatment, with significant reductions by day 2 that remained significant at day 3, days 4-6 and days 7-14. Risks were not significantly different after 14 days.

While dual antiplatelet therapy with aspirin and clopidogrel has been shown to be beneficial for mild stroke and TIA (Hao et al 2018*[171]*) intensive antiplatelet therapy with three agents (aspirin, clopidogrel and dipyridamole) compared to single (clopidogrel) or dual (aspirin and dipryidamole) therapy has not. Bath et al (2018) *[173]* conducted an international RCT (N=3096) of intensive antiplatelet therapy commenced within 48 hours of an ischaemic stroke or TIA. Results showed indidence and severity of recurrent stroke or a TIA within 90 days did not differ (cOR 0.90, 95%CI 0.67-1.20, p=0.47) but did increase number and severity of bleeding complications (cOR 2·54, 95% CI 2·05-3·16, p<0·0001). The trial was stopped early on recommendation of the data monitoring committee and triple antiplatelet therapy cannot be recommended.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no treatment	**Intervention** Aspirin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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
Recurrent stroke [1] During treatment 8 Critical	Odds Ratio 0.77 (CI 95% 0.69 — 0.87) Based on data from 40,850 patients in 3 studies. (Randomized controlled) Follow up: 5 days to 3	31 per 1000	24 per 1000 Difference: **7 fewer** per 1000 (CI 95% 9 fewer — 4 fewer)	High	Aspirin decreases recurrent stroke

Outcome Timeframe	Study results and measurements	Comparator Placebo or no treatment	Intervention Aspirin	Certainty of the Evidence (Quality of evidence)	Plain text summary
	months of treatment.				
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

1. Recurrent ischaemic/unknown stroke during treatment period

Strong recommendation against

Acute antiplatelet therapy should not be given within 24 hours of thrombolysis administration with the exception of patients who require stent implantation as part of acute stroke therapy. (Zinkstok et al. 2012 *[168]*)

Practical Info

After stent implantation for acute stroke therapy it is often necessary to use antiplatelet agents within 24 hours of thrombolysis. Intravenous aspirin is a useful option for patients who may be anaesthetised or have dysphagia.
For extracranial stents it may be possible to use a single antiplatelet in the first 24 hours, pending repeat imaging to exclude haemorrhagic transformation, especially if brain infarct volume is expected to be large.

Evidence To Decision

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

Addition of intravenous aspirin to alteplase versus alteplase alone showed no improvements in favourable outcomes (defined as modified Rankin Scale 0–2) and an increase in symptomatic intracranial haemorrhage (28 more per 1000) (Zinstok et al. 2012 *[168]*).

Certainty of the Evidence — Moderate

The quality of evidence is moderate as it comes from only one study, which terminated early before reaching the powered sample size.

Preference and values — No substantial variability expected

Patients would not want to receive this treatment as it increases symptomatic intracranial haemorrhage with no evidence of benefits.

Resources and other considerations — Factor not considered

Rationale

Based on moderate quality of evidence, concurrent use of antiplatelets with alteplase probably increases symptomatic intracranial haemorrhage with no apparent benefits. Therefore, acute antiplatelet therapy should be deferred when thrombolysisis given. Exceptions may include patients with stent implantation.

Clinical Question/ PICO

Population: Adult stroke patients treated with alteplase
Intervention: Early antiplatelet therapy
Comparator: No additional therapy

Summary

A randomised trial (Zinstok and Roos 2012 *[168]*) comparing addition of intravenous aspirin to alteplase versus alteplase alone was halted early due to increased numbers of symptomatic intracranial haemorrhage in the aspirin group, with no evidence of benefit on the primary endpoint of a favourable outcome (score of 0-2 on the modified Rankin Scale).

Outcome Timeframe	Study results and measurements	Comparator No additional therapy	Intervention Early antiplatelet therapy	Certainty of the Evidence (Quality of evidence)	Plain text summary
Death 3 months 9 Critical	n/a Based on data from 564 patients in 1 studies. (Randomized controlled) Follow up: 3 months.	97 per 1000	112 per 1000 CI 95%	**Low** Due to very serious imprecision [1]	early antiplatelet therapy (within 24h) may increase death
Favourable outcome [2] 3 months 8 Critical	Odds Ratio 0.91 (CI 95% 0.66 — 1.26) Based on data from 564 patients in 1 studies. (Randomized controlled) Follow up: 3 months.	572 per 1000	549 per 1000 Difference: **23 fewer** per 1000 (CI 95% 103 fewer — 55 more)	**Moderate** Due to serious imprecision [3]	early antiplatelet therapy (within 24h) probably has little or no difference on favourable outcome
Symptomatic intracranial haemorrhage [4] 8 Critical	Relative risk 2.78 (CI 95% 1.01 — 7.63) Based on data from 564 patients in 1 studies. (Randomized controlled) Follow up: 3 months.	16 per 1000	44 per 1000 Difference: **28 more** per 1000 (CI 95% 106 more — 0 fewer)	**Moderate** Due to serious imprecision [5]	early antiplatelet therapy (within 24h) probably increases symptomatic intracranial haemorrhage

1. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** The study was terminated early due to futility and didn't reach the powered sample size N = 600, Only data from one study; no relative effect estimate. **Publication bias: No serious.**
2. Modified Rankin score 0-2
3. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** The study was terminated early due to futility and didn't reach the powered sample size N = 600., Only data from one study. **Publication bias: No serious.**
4. Neurological deterioration of 4 points or more increase on the NIHSS in combination with intracranial haemorrhage on follow-up CT scan without other obvious causes for the deterioration
5. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** The study was terminated early due to futility and didn't reach the powered sample size N = 600., Only data from one study. **Publication bias: No serious.**

Strong recommendation against

Routine use of anticoagulation in patients without cardioembolism (e.g. atrial fibrillation) following TIA/stroke is not recommended. (Sandercock et al. 2015 *[161]*; Whiteley et al. 2013 *[167]*)

Evidence To Decision

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

Anticoagulation was shown to significantly reduce recurrent stroke but to increase symptomatic intracranial haemorrhage to a similar extent (8 cases per 1000 patients) (Sandercock et al. 2015 *[161]*). These effects appeared to produce a neutral effect on death and dependency at follow-up of greater than a month (Sandercock et al. 2015 *[161]*).

Certainty of the Evidence — High

Quality of evidence is high – multiple large randomised controlled trials reporting consistent results.

Preference and values — No substantial variability expected

Patients are unlikely to want to receive routine anticoagulation considering its lack of benefits.

Resources and other considerations — Factor not considered

Rationale

High-quality evidence suggests that anticoagulants did not show any benefits in death and dependency in patients with acute ischaemic stroke (Sandercock et al. 2015 *[161]*; Whiteley et al. 2013 *[167]*). Therefore, routine use of anticoagulation in patients with no indication of potential benefits from it is not recommended.

Clinical Question/ PICO

Population: Adults with acute ischaemic stroke
Intervention: Anticoagulant
Comparator: Placebo or no treatment

Summary

A Cochrane review by Sandercock et al (2015) *[161]* assessed the effectiveness of early anticoagulation following acute ischaemic stroke. 24 trials with 23,748 participants were included. Meta-analysis of 8 trials reporting death or dependence with a follow-up greater than 1 month showed no difference in the odds of death or dependency (OR 0.99, 95% CI 0.93 to 1.04). There was substantial heterogeneity in this analysis, with low-molecular-weight heparins and subcutaneous heparinoids showing non-significant benefit and direct thrombin inhibitors showing non-significant harms. While anticoagulants significantly decreased recurrent stroke during the treatment period, they also significantly increased symptomatic intracranial haemorrhage and these two effects appeared to produce no difference in overall death or dependency.

Based on various international guidelines that recommend targeting of heparin treatment at stroke patients with high risk of venous thrombotic events or low risk of haemorrhagic events, Whiteley et al (2013) *[167]* conducted an individual patient data meta-analysis of the 5 largest randomised controlled trials of heparin treatment. They found no evidence that patients predicted to be at higher risk of thrombotic events or lower risk of haemorrhagic events benefited from treatment with heparins. They suggested that existing guidelines recommending targeted selection of patients for heparin treatment be revised.

Butcher et al (2020)*[177]* compared dabigatran with aspirin in patients (N=305) with TIA or minor (NIHSS 0-9) noncardioembolic ischaemic stroke commencing within 72 hours of onset. The primary outcome was symptomatic hemorrhagic transformation (HT) based on MRI within 30 days which failed to occur in either group. Asymptomatic petechial HT occured in 7.8% dibigatran group copmared to 3.5% in aspirin group (RR 2.3, 95%CI 0.78-6.8).

Outcome Timeframe	Study results and measurements	Comparator Placebo or no treatment	Intervention Anticoagulant	Certainty of the Evidence (Quality of evidence)	Plain text summary
Death or dependence End of follow-up 9 Critical	Odds Ratio 0.99 (CI 95% 0.93 — 1.04) Based on data from 22,125 patients in 8 studies. (Randomized controlled) Follow up: >30 days.	599 per 1000	597 per 1000 Difference: 2 fewer per 1000 (CI 95% 18 fewer — 9 more)	**Moderate** Due to serious inconsistency [1]	Anticoagulant probably has little or no difference on death or dependence
Death End of follow-up 9 Critical	Odds Ratio 1.05 (CI 95% 0.98 — 1.12) Based on data from 22,776 patients in 11 studies. (Randomized controlled) Follow up: > 30 days.	205 per 1000	213 per 1000 Difference: 8 more per 1000 (CI 95% 3 fewer — 19 more)	**High**	Anticoagulant has little or no difference on death
Recurrent stroke [2] During treatment 8 Critical	Odds Ratio 0.76 (CI 95% 0.65 — 0.88) Based on data from 21,605 patients in 11 studies. (Randomized controlled) Follow up: 7 to 30 days of treatment.	36 per 1000	28 per 1000 Difference: 8 fewer per 1000 (CI 95% 12 fewer — 4 fewer)	**High**	Anticoagulant decreases recurrent stroke
Symptomatic intracranial haemorrhage During treatment 8 Critical	Odds Ratio 2.55 (CI 95% 1.95 — 3.33) Based on data from 22,943 patients in 16 studies. (Randomized controlled) Follow up: 7 to 30 days of treatment.	5 per 1000	13 per 1000 Difference: 8 more per 1000 (CI 95% 5 more — 11 more)	**High**	Anticoagulant increases symptomatic intracranial haemorrhage

1. **Inconsistency: Serious.** Point estimates vary widely. **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
2. Recurrent ischaemic or unknown stroke during treatment period

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 *[171]*)

Practical Info

Importantly, trials commenced treatment within 12 or 24 hours of symptom onset and the risk of recurrent stroke is highest in the first few days so treatment should commence within 24 hours. Patients who received thrombolysis and those with an indication for anticoagulation (e.g. AF) were excluded from the trials. Patients with more severe stroke or low risk TIA were not included in 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 *[172]*)

It is worth considering proton pump inhibitor use (e.g. pantoprazole to avoid potential CYP2C19 interactions) to protect against erosive gastritis in these patients. The role of antiplatelet resistance testing remains uncertain but this could be considered in selected patients at high risk of thrombotic complications (e.g. after stent implantation).

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

This recommendation applies to minor stroke and high risk TIA patients 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 *[171]*).

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 *[171]*). 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. *[166][170]*

Certainty of the Evidence — Moderate

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

Preference and values — No substantial variability expected

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

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

<u>Resources considerations</u>

In an economic evaluation of patients with acute TIA or minor stroke with a high risk of recurrence, it was found that clopidogrel plus aspirin, compared to aspirin alone, was cost-effective at an additional cost of US$5,200 per QALY gained (cost reference year 2011), and was cost-saving when the cost of the generic clopidogrel drug was used (Pan et al. 2014 *[165]*). 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.

Rationale

This recommendation applies to minor stroke and high risk TIA patients 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 acute stroke
Intervention: Clopidegrol and aspirin
Comparator: Aspirin

Summary

A systematic review (Hao et al 2018 *[171]*) of 3 major trials (10301 patients) investigating dual antiplatelet therapy (clopidogrel plus aspirin) compared to mono antiplatelet (aspirin alone) found dual antiplatelet therapy produced significant reductions in the risk of recurrent stroke (RR 0.70, 95% CI 0.61 to 0.80) with a very small increase in major bleeding (RR 1.71, 95% CI 0.92-3.20). Trials found improvement in modified Rankin Scale and quality of life with dual antiplatelet therapy. *[162][[163]*

Outcome Timeframe	**Study results and measurements**	**Comparator** Aspirin	**Intervention** Clopidegrol and aspirin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Non fatal recurrent stroke 90 days 8 Critical	Relative risk 0.7 (CI 95% 0.61 — 0.8) Based on data from 10,301 patients in 3 studies. (Randomized controlled) Follow up: 90.	63 per 1000	44 per 1000 Difference: **19 fewer** per 1000 (CI 95% 25 fewer — 13 fewer)	**High**	Dual antiplatelet therapy decreases recurrent stroke
Mortality 90 days 8 Critical	Relative risk 1.27 (CI 95% 0.73 — 2.23) Based on data from 9,690 patients in 2 studies. (Randomized controlled) Follow up: 90 days.	5 per 1000	6 per 1000 Difference: **1 more** per 1000 (CI 95% 2 fewer — 4 more)	**Moderate** Due to serious imprecision [1]	Dual therapy probably has little or no impact on mortality
Major bleeding 90 days 8 Critical	Relative risk 1.71 (CI 95% 0.92 — 3.2) Based on data from 10,075 patients in 3 studies. (Randomized controlled) Follow up: 90 days.	3 per 1000	5 per 1000 Difference: **2 more** per 1000 (CI 95% 0 fewer — 7 more)	**Moderate** Due to serious risk of bias and some inconsistency [2]	Dual antiplatelet therapy probably results in a very small, possibly important increase in moderate or major extracranial bleeding.
Severe functional disability measure by modified Rankin Scale (mRS: 2-5) 7 Critical	Relative risk 0.9 (CI 95% 0.81 — 1.01) Based on data from 9,690 patients in 2 studies. (Randomized controlled) Follow up: 90 days.	142 per 1000	128 per 1000 Difference: **14 fewer** per 1000 (CI 95% 27 fewer — 1 more)	**Moderate** Due to serious imprecision [3]	Dual antiplatelet therapy possibly has a small but important benefit on patient function.
Poor quality of life measured by EQ-5D index score of 0.5 or less 7 Critical	Relative risk 0.81 (CI 95% 0.66 — 1.01) Based on data from 5,131 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	68 per 1000	55 per 1000 Difference: **13 fewer** per 1000 (CI 95% 23 fewer — 1 more)	**Moderate** Due to serious imprecision [4]	Dual antiplatelet therapy probably has a s mall important benefit on quality of life.

1. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients. **Publication bias: No serious.**
2. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No**

serious.
3. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

Weak recommendation

New

Aspirin plus ticagrelor commenced within 24 hours may be used in the short term (first 30 days) in patients with minor ischaemic stroke or high-risk TIA to prevent stroke recurrence. (Johnston et al 2020 *[174]*)

Practical Info

Included patients were those with minor stroke (NIHSS <5) or high risk TIA. Treatment commenced within 24 hours of symptom onset with a loading dose of ticagrelor (180-mg) followed by 90 mg twice daily plus aspirin (loading dose 300 to 325 mg on the first day followed by 75 to 100 mg daily). Patients were excluded from the trial if intravenous thrombolysis or mechanical thrombectomy was planned or undertaken or if there was planned use of anticoagulation or specific antiplatelet therapy other than aspirin. Additional exclusion criteria included hypersensitivity to ticagrelor or aspirin, a history of atrial fibrillation or ventricular aneurysm or a suspicion of a cardioembolic cause of the TIA or stroke, planned carotid endarterectomy that required discontinuation of the trial medication within 3 days after randomization, a known bleeding diathesis or coagulation disorder, a history of intracerebral hemorrhage, gastrointestinal bleeding within the past 6 months, or major surgery within 30 days.

It is reasonable to consider a proton pump inhibitor (e.g. pantoprazole 40mg) for the duration of dual antiplatelet therapy, although this has not been specifically assessed in a stroke cohort requiring dual antiplatelet therapy.

Finally the **use of ticagrelor for minor stroke and TIA is off-label** and product information refers to cardiac indications although the dose is the same.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Dual therapy was shown to reduce combined stroke and death primarily due to the reduction of ischaemic stroke. There was no difference in mRS >1 or death alone. Dual therapy led to higher rate of bleeding although absolute numbers were small e.g. severe bleeding 28 v 7. Benefit of treatment is expected with NNT of 92 to prevent one stroke or death and severe bleeding event expected after NNH 263. (Johnston et al 2020 *[174]*)

Certainty of the Evidence

Moderate

The quality of evidence across primary outcomes is moderate due to data coming from one trial. Safety outcomes are low certainty due to very small numbers.

Preference and values

Substantial variability is expected or uncertain

Patients (and their family/carer for those with communication impairments) are likely to prefer the benefits of reduced risk of stroke recurrence over possible harm (small risk of bleeding). However, some people may have different views regarding the balance between benefits and harms.

There was some variation in heath professional preference for ticagrelor with a few members of the working group questioning the recommendation based on the strength of the balance between benefit and harms.

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

Resources considerations

No cost-effective studies specific to secondary stroke prevention dual therapy with ticagrelor were found. Currently ticagrelor is significantly more expensive than generic clopidogrel so is likely to be less cost effective.

Rationale

Ticagrelor plus aspirin reduces the risk of early (within first 30 days) ischaemic stroke compared to aspirin alone in people with minor stroke or high risk TIA. Furthermore, ticagrelor added to aspirin was superior to aspirin alone in preventing disabling stroke or death at 30 days and reduced the total burden of disability owing to ischemic stroke recurrence (Amarenco et al. 2020 *[178]*). Dual therapy increases the risk of severe bleeding although absolute numbers are low (28 v 7 in >5,000 participants in each arm). Dual therapy may be considered depending on comorbidities (e.g. recent MI) or clopidogrel intolerance/potential inefficacy, however, due to the current cost of ticagrelor and data based on one albeit large trial, clopidogrel base therapy has a stronger recommendation in this patient population. Further trials directly comparing ticagrelor plus aspirin versus clopidogrel plus aspirin are needed.

Clinical Question/ PICO

Population: Adults with acute stroke
Intervention: Ticagrelor and aspirin
Comparator: Aspirin

Summary

Johnston et al (2020)*[174]* conducted a large (N=11,016) international trial of ticagrelor plus aspirin vs aspirin alone. Participants had mild-to-moderate acute non-cardioembolic ischemic stroke (NIHSS 0-5) or high risk TIA (ABCD2 scale 6 or 7) or symptomatic intracranial or extracranial stenosis (>50% narrowing) and commenced treatment within 24 hours of symptom onset. Participants were excluded if they planned to undergo thrombolysis or thrombectomy, planned anticoagulation or carotid surgery, history of AF or suspicion of cardioembolic stroke. Participants in the intervention group received a loading dose of ticagrelor (180mg) and aspirin (300-325mg) followed by daily dose of ticagrelor (90mg) and aspirin (75-100mg). Outcomes were measured at 30 days given risk of recurrence is greatest early after stroke/TIA. Dual therapy was shown to reduce combined stroke and death (HR 0.83, 95%CI 0.71–0.96) primarily due to the reduction of ischaemic stroke (HR 0.79, 95%CI 0.68–0.93). There was no difference in mRS >1 (OR 0.98, 95%CI 0.89–1.07). Dual therapy led to higher rate of bleeding although absolute numbers were small e.g. intracranial hemorrhage or fatal bleeding 22 v 6 (HR 3.66, 95%CI 1.48-9.02), severe bleeding 28 v 7 (HR 3.99, 95%CI 1.74-9.14). Benefit of treatment is expected with NNT of 92 to prevent one stroke or death and severe bleeding event expected after NNH 263.

A pre-specified analysis of the THALES trial found ticagrelor added to aspirin was superior to aspirin alone in preventing disabling stroke or death (mRS >1) at 30 days (hazard ratio 0.83, 95%CI 0.69 to 0.99) and reduced the total burden of disability owing to ischemic stroke recurrence (odds ratio of shift in mRS burden 0.77, 95%CI 0.65 to 0.91) (Amarenco et al. 2020 *[178]*).

A previous study by Johnston et al (2016)*[175]* reported a non statistical difference in the time to occurrence of stroke, MI or death within 90 days with ticagrelor alone compared to aspirin (HR 0.89, 95%CI 0.78-1.01, p=0.07). Ischaemic stroke occurred in 5.8% treated with ticagrelor vs 6.7% treated with aspirin (HR 0.87, 95%CI 0.76-1.00). Major bleeding and ICH was similar between groups. Ticagrelor is PBS listed in Australia for cardiac indications and is superior to clopidogrel in the cardiac group. However, single-agent ticagrelor was not superior to aspirin in patients with mild stroke or high risk TIA but may have similar bleeding risk.(Johnston et al. 2016 *[175]*).

Wang et al (2019)*[176]* also explored effects of ticagrelor plus aspirin but compared it to clopidogrel plus aspirin. This phase II trial (26 Chinese centres, N=675 participants) enrolled similar patients with minor stroke (NIHSS 0-3), high risk TIA (ABCD2 scale 4-6) or >50% symptomatic stenosis and also commenced within 24 hours. At 90 days, high platelet reactivity occurred less in ticagrelor/aspirin group than clopidogrel/aspirin (12.5% vs 29.7%; RR 0.40; 95%CI 0.28 to 0.56; P<0.001) and also in patients carrying CYP2C19 loss-of-function alleles. While not powered to detect clinical benefits, the secondary outcome of stroke occurred in 21 (6.3%) in ticagrelor/aspirin group vs 30 (8.8%) of the clopidogrel/aspirin group (HR 0.70, 95%CI 0.40 to 1.22; P=0.20).

Outcome Timeframe	**Study results and measurements**	**Comparator** Aspirin	**Intervention** Ticagrelor and aspirin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Composite stroke or death 30 days 9 Critical	Hazard Ratio 0.83 (CI 95% 0.71 — 0.96) Based on data from 11,016 patients in 1 studies. [1] (Randomized controlled) Follow up: 30 days.	63 per 1000	53 per 1000 Difference: **10 fewer** per 1000 (CI 95% 18 fewer — 2 fewer)	**Moderate** Due to serious imprecision and single trial [2]	Dual antiplatelet therapy decreases poor outcome (recurrent stroke or death)
Recurrent ischaemic stroke 30 days 8 Critical	Hazard Ratio 0.79 (CI 95% 0.68 — 0.93) Based on data from 11,016 patients in 1 studies. [3] (Randomized controlled) Follow up: 30 days.	63 per 1000	50 per 1000 Difference: **13 fewer** per 1000 (CI 95% 20 fewer — 4 fewer)	**Moderate** Due to serious imprecision and single trial [4]	Ticagrelor and aspirin probably decreases recurrent ischaemic stroke
Disability (mRS>1) 30 days 7 Critical	Odds Ratio 0.98 (CI 95% 0.89 — 1.07) Based on data from 11,016 patients in 1 studies. [5] (Randomized controlled) Follow up: 30 days.	232 per 1000	233 per 1000 Difference: **1 fewer** per 1000 (CI 95% 7 fewer — 4 more)	**Moderate** Due to serious imprecision and single trial [6]	Ticagrelor and aspirin probably has little or no difference on disability
Severe bleeding 30 days 8 Critical	Hazard Ratio 3.99 (CI 95% 1.74 — 9.14) Based on data from 11,016 patients in 1 studies. [7] (Randomized controlled) Follow up: 30 days.	1 per 1000	5 per 1000 Difference: **4 more** per 1000 (CI 95% 1 more — 8 more)	**Low** Due to very serious imprecision and single trial [8]	Ticagrelor and aspirin probably worsens severe bleeding

1. Primary study[174]. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: No serious. Imprecision: Serious.** Only data from one study, Wide confidence intervals, few safety outcomes.
3. Primary study[174]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: No serious. Imprecision: Serious.** Only data from one study, Wide confidence intervals, few safety outcomes.
5. Primary study[174]. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: No serious. Imprecision: Serious.** Only data from one study, Wide confidence intervals, few safety outcomes.
7. Primary study[174]. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: No serious. Imprecision: Very serious.** Only data from one study, Wide confidence intervals, few safety outcomes, Low number of patients.

Acute blood pressure lowering therapy

Acute stroke, whether due to infarction or haemorrhage, is associated with high blood pressure (Bath et al 2014 *[180]*), and 68% of stroke patients have a history of high blood pressure on admission (Stroke Foundation 2019 *[28]*). In acute ischaemic stroke, high blood pressure appears to adversely affect outcomes through increasing the risk of cerebral oedema (Bath et al 2014 *[180]*). In acute intracerebral haemorrhage, the blood pressure often becomes elevated and may be associated with haematoma expansion (Bath et al 2014 *[180]*). However, previous analyses of large trials showed that both low and high blood pressure after a stroke were associated with poor outcomes (Bath et al 2014 *[180]*). Therefore, the precise target of blood pressure in treating acute stroke patients needs to be determined.

Weak recommendation against

Intensive blood pressure lowering in the acute phase of care to a target SBP of < 140 mmHg is not recommended for any patient with stroke. (Bath and Krishnan 2014 *[180]*)

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 < 140 mmHg (Bath and Krishnan 2014 *[180]*) and in the ATACH-2 trial there was no benefit of lowering to < 140 mmHg and increased renal adverse effects (Qureshi 2016 [105]).

Certainty of the Evidence

High

The evidence has multiple high-quality randomised controlled trials (Bath and Krishnan 2014 *[180]*).

Preference and values

No substantial variability expected

No substantial variability was identified or expected.

Resources and other considerations

Factor not considered

Rationale

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

Clinical Question/ PICO

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

Summary

A systematic review by Tsivgoulis et al 2015 *[183]*, found a trend towards reduced death and dependency with intensive BP reduction to a target of 140mmHg in patients with intracerebral haemorrhage (p=0.06). INTERACT-2 was the largest trial and found a significant benefit in ordinal analysis of the modified Rankin Scale (an outcome that was not testable in the meta-analysis). The ATACH-2 trial evaluated more intensive BP reduction to a target of 120mmHg and the control group was very similar to the INTERACT intervention arm with a mean achieved BP ~140mmHg. There was no benefit of lowering BP below 140mmHg and an increase in renal adverse events.(Qureshi et al 2016 *[181]*).

A systematic review by Carandini et al (2017)*[188]* included 6 studies (n = 4,375) and found no difference in risk of death at 3 months between intensive vs standard BP treatment (RR 0.99, 95% CI 0.83 to 1.17; n = 4294). Additionally, there was no difference for disability (RR 0.96, 95% CI 0.89 to 1.03; 5 studies, n = 4212) and no difference in non-fatal serious advense events (RR 1.07, 95% CI 0.90 to 1.28; 3 studies, n = 4194; moderate heterogeneity I^2= 60%). Other reviews are consistent

(Lattanzi et al 2017 *[191]*, Boulouis et al 2017*[186]*, Gong et 2017*[184]* and Zhang et at 2017*[187]*).

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 0.87 (CI 95% 0.76 — 1) Based on data from 3,315 patients in 4 studies. [2] (Randomized controlled)	543 per 1000	545 per 1000 Difference: 2 more per 1000 (CI 95% 47 more — 43 fewer)	**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
2. Systematic review [183] . **Baseline/comparator:** Control arm of reference used for intervention.

Clinical Question/ PICO

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

Summary

Two systematic reviews from Lee et al (2015) *[179]* and Bath et al (2014) *[180]* showed that there was no overall effect of treatment on death or dependancy. No differences were observed when analysed by the subgroup of ischaemic stroke either. There was no difference in early neurological deterioration when lowering blood pressure based on two studies (OR 0.58, 95%CI 0.09 to 3.82) (Bath et al 2014 *[180]*). There was no difference in recurent stroke (RR 1.00, 95%CI 0.54 to 1.84; four trials, n=5,843) or recurrent vascular events (RR 0.90, 95%CI 0.65 to 1.25; six trials, n=7,915) at 3 or 6 months after treatment (Lee et al 2015 *[179]*).

Nasi et al (2019)*[189]* (n = 218) investigated maintaining three ranges of systolic blood pressure (SBP) control within the first 24 hours: 140-160 mmHg, 161-180 mmHg, 181-200 mmHg. There was no difference in good clinical outcome (mRS 0-2 at 90 days) across all three groups of blood pressures (51% vs 52% vs 39%, P = 0.27). Adverse effects related to SBP appeared confined to groups 2 and 3 which were the higher SBP ranges; all associated with the infusion of norepinephrine. Symptomatic intracranial hemorrhage was more frequent in the groups with higher SBP (1% vs 2.7% vs 9.1%, P = 0.048).

Zhang et al (2019)*[190]* (n = 4,071) conducted a pre-specified secondary analysis of the China Antihypertensive Trial in Acute Ischaemic Stroke (CATIS) and found no overall effect of early treatment on death or major disability at 14 days or at hospital discharge. However, commencing antihypertensive treatment within 24 hours was associated with decreased risk of recurrent stroke (OR 0.44, 95% CI 0.25 to 0.77) in patients with a history of hypertension. No association was observed in patients without a history of hypertension (OR 3.43, 95% CI 0.94 to 12.55).

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]	Odds Ratio 1 (CI 95% 0.92 — 1.08) Based on data from	409	409	**High**	Blood pressure lowering has little or no difference on death and dependency

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Blood pressure lowering	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
9 Critical	11,015 patients in 8 studies. [2] (Randomized controlled)	per 1000	per 1000 Difference: **0 fewer** per 1000 (CI 95% 19 more — 20 fewer)		
Recurrent stroke 3 or 6 months 7 Critical	Relative risk 1 (CI 95% 0.54 — 1.84) Based on data from 5,843 patients in 4 studies. [3] (Randomized controlled) Follow up: 3 or 6 months.	**20** per 1000	**20** per 1000 Difference: **0 fewer** per 1000 (CI 95% 9 fewer — 17 more)	**High**	Acute blood pressure lowering has little or no difference on recurrent stroke

1. mRS > 1 or > 2 depending on definition in individual trials
2. Systematic review [180] with included studies: ENOS 2014, PRoFESS 2009, RIGHT 2013, CHHIPS 2009, SCAST 2011, Eveson 2007, VENTURE 2013, CATIS 2013. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [179] . **Baseline/comparator:** Primary study. From control arm of the substudy of PRoFESS trial (Bath et al 2009; Stroke Vol 40, no 11.).

Weak recommendation

In patients with intracerebral haemorrhage, blood pressure may be acutely reduced to a target systolic blood pressure of around 140 mmHg (but not substantially below). (Tsivgoulis et al. 2014 *[183]*; Qureshi et al. 2016 *[181]*)

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The evidence for this recommendation is based on the systematic review by Tsivgoulis et al. *[183]*, which was heavily weighted by results from a large randomised controlled trial INTERACT2 (N = 2794). In INTERACT2, the primary end point of death or major disability at three 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 *[182]*). 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) (Anderson et al. NEJM 2013 *[182]*). ATACH-II trial control group was very similar to the INTERACT-2 "intensive" group with a mean achieved blood pressure ~140 mmHg. In the ATACH-II trial there was no benefit of more intensive lowering with a target of 120 mmHg systolic, and increased renal adverse events. We have therefore recommended a BP target of 140 mmHg but not substantially below. (Qureshi et al. 2016 *[181]*).

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

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

Data from a meta-analysis (Tsivgoulis et al. 2016 *[183]*), together with results from ATACH-2 (Qureshi et al. 2016 *[181]*), suggests that in patients with mild to moderate intracerebral haemorrhage, a SBP target of 140 mmHg (but not lower), is probably safe and associated with better patient outcomes, as demonstrated by a shift in mRS at 90 days.

Clinical Question/ PICO

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

Summary

A systematic review by Tsivgoulis et al 2015 *[183]*, found a trend towards reduced death and dependency with intensive BP reduction to a target of 140mmHg in patients with intracerebral haemorrhage (p=0.06). INTERACT-2 was the largest trial and found a significant benefit in ordinal analysis of the modified Rankin Scale (an outcome that was not testable in the meta-analysis). The ATACH-2 trial evaluated more intensive BP reduction to a target of 120mmHg and the control group was very similar to the INTERACT intervention arm with a mean achieved BP ~140mmHg. There was no benefit of lowering BP below 140mmHg and an increase in renal adverse events.(Qureshi et al 2016 *[181]*).

A systematic review by Carandini et al (2017)*[188]* included 6 studies (n = 4,375) and found no difference in risk of death at 3 months between intensive vs standard BP treatment (RR 0.99, 95% CI 0.83 to 1.17; n = 4294). Additionally, there was no difference for disability (RR 0.96, 95% CI 0.89 to 1.03; 5 studies, n = 4212) and no difference in non-fatal serious advense events (RR 1.07, 95% CI 0.90 to 1.28; 3 studies, n = 4194; moderate heterogeneity I^2= 60%). Other reviews are consistent (Lattanzi et al 2017 *[191]*, Boulouis et al 2017*[186]*, Gong et 2017*[184]* and Zhang et at 2017*[187]*).

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 0.87 (CI 95% 0.76 — 1) Based on data from 3,315 patients in 4 studies. [2] (Randomized controlled)	543 per 1000	545 per 1000 Difference: 2 more per 1000 (CI 95% 47 more — 43 fewer)	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
2. Systematic review [183] . **Baseline/comparator:** Control arm of reference used for intervention.

Weak recommendation

Pre-existing antihypertensive medication may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 *[180]*)

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 *[180]*). 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 stroke
Intervention: Continue pre-stroke antihypertensives
Comparator: Stop pre-stroke antihypertensives

Summary

Bath et al (2014) *[180]* conducted a systematic review of the effectiveness of altering blood pressure in acute stroke patients. In a total of 2,860 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.

Woodhouse et al (2017) *[185]* identified two studies which was also identified in the previous systematic review and conducted an individual patient data meta-analysis (n = 2,860). Additional findings were a significant association between continuation of treatment and the recurrence of ischemic stroke by the end of treatment (OR 2.27, 95% CI 1.17 to 4.39), however, the association was not present with recurrent ICH (OR 0.35, 95% CI 0.09 to 1.31) nor with recurrent stroke of any type (OR 1.41, 95% CI 0.85 to 2.34). Additionally, there was no significant difference for death or institutionalisation (OR 1.10, 95% CI 0.93 to 1.30).

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]	Odds Ratio 1.06 (CI 95% 0.91 — 1.24) Based on data from 2,860 patients in 2 studies. [2]	567 per 1000	581 per 1000	High	continue pre-stroke antihypertensives may have little or no difference on death or

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**
9 Critical	(Randomized controlled)	Difference: **14 more** per 1000 (CI 95% 52 more — 23 fewer)			dependency

1. mRS > 1 or > 2 depending on definition in individual trials
2. Systematic review [180] with included studies: ENOS 2014, COSSACS 2010. **Baseline/comparator:** Control arm of reference used for intervention.

Practice statement

Consensus-based recommendations

- All acute stroke patients 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.

Surgery for ischaemic stroke

Patients with a large cerebral infarction generally have a poor prognosis (Cruz-Flores et al. 2012 *[194]*. Hemicraniectomy for ischaemic stroke should be considered for large life-threatening, space-occupying brain oedema or middle cerebral artery (MCA) infarcts; so-called 'malignant infarction' as the condition is associated with 80% mortality due to herniation during the first week, despite maximal conservative treatment in the intensive care unit (ICU), including osmotherapy, barbiturates, and hyperventilation (Juttler et al. 2014 *[193]*). Conservative management of brain oedema is not supported by clinical trials (Juttler et al. 2014 *[193]*).

Strong recommendation

Updated evidence, no change in recommendation

Selected patients aged 60 years and under with malignant middle cerebral artery territory infarction should undergo urgent neurosurgical assessment for consideration of decompressive hemicraniectomy. When undertaken, hemicraniectomy should ideally be performed within 48 hours of stroke onset. (Cruz-Flores et al. 2012 *[194]*; Reinink et al. 2021 *[199]*)

Practical Info

Malignant cerebral oedema after acute ischaemic stroke is associated with significant morbidity and mortality risk. Patients potentially eligible for surgical decompression (based on clinical severity and/or brain imaging criteria) should be identified early and referred for neurosurgical opinion. Stroke centres with no onsite neurological expertise should be particularly proactive in arranging early referral of potentially eligible patients to a neurosurgical centre. Careful discussion with patients' family or next of kin is strongly advised, including a review of the patient's premorbid health, functional status, and previously stated wishes. In patients with malignant middle cerebral artery territory infarction, the surgical technique recommended is hemicraniectomy with durotomy. Native or synthetic cranioplasty is usually performed approximately 6 weeks post-decompression depending on surgical preference.

In patients with massive cerebellar infarction and relative sparing of the brainstem, despite the absence of randomised controlled data, there is a general consensus that patients without significant pre-existing disability should be considered for posterior fossa decompression surgery given the more favourable natural history of isolated cerebellar infarction.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There is a clear benefit of surgery in terms of survival for those aged 60 years and under (386 fewer deaths per 1000 patients treated) (Cruz-Flores et al. 2012 *[194]*) and a higher rate of a favourable outcome (mRS 0-3) at one year (Reinink et al 2021 *[199]*).

Certainty of the Evidence

Moderate

The overall quality of evidence is moderate.

Preference and values

Substantial variability is expected or uncertain

Most patients treated with hemicraniectomy will survive with at least long term moderate disability due to the underlying stroke, and this should be discussed prior to treatment. This surgery is potentially life saving, and other considerations including the patient circumstances and wishes need to be taken into account should this treatment be a viable option.

Resources and other considerations

Important issues, or potential issues not investigated

<u>Resources considerations</u>

In a study conducted in the Netherlands, Hofmeijer et al. (2013) *[196]* found that surgical decompression for space-occupying hemispheric infarction was not cost-effective at an additional cost of €60,000 per QALY gained compared to best alternative medical treatment (cost reference year 2009). In this economic evaluation, the HAMLET randomised controlled trial data were incorporated into a Markov model with a time horizon of three years.

In a modelled cost-utility analysis conducted from the UK National Health Service perspective, hemicraniectomy surgery was compared to medical treatment (use of hyperosmotic agents, artificial ventilation, hyperventilation and sedatives). Costs of hemicraniectomy surgery and medical management were included and were based the average costs in the UK for acute care

and long term costs that were estimated based on data from published literature (reference year 2015 Pound Sterling). QALYs were estimated based on modified Rankin Scale scores. At 1-year post intervention, hemicraniectomy was found to be more costly and more effective (average cost=£39,474, average QALY= 0.35) compared to medical treatment (average cost= £12,651; average QALY= 0.12). The ICER value of £116,595 per QALY gained for hemicraniectomy was larger than the typical willingness to pay threshold of £20,000–£30, 000 in the UK (Bhattacharyya et al. 2019 *[198]*)

No similar studies have been conducted in Australia.

Rationale

There is a clear benefit in terms of increased survival and favourable outcomes with surgery. There is no evidence of heterogeneity across subgroups. Almost all of the patients had surgery within 48 hours.

Clinical Question/ PICO

Population: Adults < 60 y.o. with malignant middle cerebral artery infarct
Intervention: Hemicraniectomy
Comparator: Medical treatment

Summary

A 2012 Cochrane review by Cruz-Flores et al *[194]* included 3 trials (total N = 134) assessing the effectiveness of decompressive surgery following acute ischaemic stroke with cerebral oedema. All 3 trials were restricted to patients aged 60 years or younger. Meta-analysis showed significant decreases in the risk of death (OR 0.19, 95% CI 0.09 to 0.37) and the risk of death or severe disability (modified Rankin scale scores > 4) at 12 months (OR 0.26, 95% CI 0.13 to 0.51). However, there was no significant difference in death or disability defined as modified Rankin scores > 3, suggesting that patients that do survive tend to have at least moderate disability. All 3 trials included in the review were stopped early, meaning the effect sizes found in the meta-analysis may be overestimated. Vahedi et al published a subgroup analysis from these 3 trials limited to patients who received decompressive hemicraniectomy within 48 hours of stroke onset (Vahedi et al 2007 *[197]*). In addition to a survival benefit, this analysis demonstrated an improvement in rates of severe disability (modified Rankin scale scores >4) at 12 months (OR 0.10, 95% CI 0.04 to 0.27), as well as moderate disability (modified Rankin scale scores >3) at 12 months (OR 0.33, 95% CI 0.13 to 0.86).

Reinink et al (2021)[199] included eight published and one unpublished studies (n=543 total participants) and undertook an individual patient meta-analysis (from seven included studies, n=488). Surgical decompression decreased the chance of death (aOR 0.16, 95% CI 0.10 to 0.24; 7 studies, n=488) and increased chance of a favourable outcome [mRS 0-3] at one year (aOR 2.95, 95% CI 1.55 to 5.60; 7 studies, n=488) based on all age groups combined. There was no statistical heterogeneity in treatment effect based on age outcome [mRS 0-3](OR 3.52, 95%CI 1.63 to 7.58 <60 years compared with OR 2.56, 95%CI 0.65 to 10.07 >60 years; p=0.48), although this is discussed in more detail in the recommendation for patients > 60 years of age. There was also no heterogeneity based on sex, aphasia, NIHSS score at baseline, vascular territories involved, or time to randomization, although only 32 patients were randomised greater than 48 hours from symptom onset.

Outcome Timeframe	**Study results and measurements**	**Comparator** Medical treatment	**Intervention** Hemicraniectomy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death at end of follow-up (all ages) 12 months of follow-up 9 Critical	Odds Ratio 0.16 (CI 95% 0.1 — 0.24) Based on data from 488 patients in 7 studies. (Randomized controlled) Follow up: 12 months.	709 per 1000	280 per 1000 Difference: 429 fewer per 1000 (CI 95% 513 fewer — 340 fewer)	**Moderate** Due to risk of bias [1]	Hemicraniectomy probably decreases death at end of follow-up

Outcome Timeframe	Study results and measurements	Comparator Medical treatment	Intervention Hemicraniectomy	Certainty of the Evidence (Quality of evidence)	Plain text summary
Favourable functional outcome (mRS 0-3) patients <60 years old 12 months of follow-up 9 Critical	Odds Ratio 3.52 (CI 95% 1.63 — 7.58) Based on data from 235 patients in 6 studies. (Randomized controlled) Follow up: 12 months.	197 per 1000	463 per 1000 Difference: 266 more per 1000 (CI 95% 89 more — 453 more)	**Moderate** Due to imprecision, Due to risk of bias [2]	Hemicraniectomy probably improves functional outcome (mRS 0-3)

1. **Risk of Bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/ lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Low number of patients, Wide confidence intervals. **Publication bias: No serious.**
2. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/ lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Wide confidence intervals. **Publication bias: No serious.**

Weak recommendation

Updated evidence, no change in recommendation

Decompressive hemicraniectomy may be considered in highly selected stroke patients over the age of 60 years, after careful consideration of the pre-morbid functional status and patient preferences. (Reinink et al. 2021 *[199]*)

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is evidence from a small number of trials that hemicraniectomy in patients over the age of 60 with malignant middle cerebral artery territory infarction improves the odds of favourable outcome (mRS 0-3) and reduced mortality.

Certainty of the Evidence

Moderate

The certainty of evidence is low to moderate.

Preference and values

Substantial variability is expected or uncertain

Approximately a third of survivors after hemicraniectomy in the > 60 age group had severe disability (mRS = 5, i.e. nursing home level of care), therefore it is important to discuss with patients and/or their carers in terms of their preferences.

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. See resource consideration in recommendation for hemicraniectomy for those aged under 60 years.

Rationale

There is evidence from individual patient data meta-analysis involving five trials (n=252) that hemicraniectomy in patients over the age of 60 with malignant middle cerebral artery territory infarction improves the odds of a favourable outcome (mRS 0-3) and reduced mortality at one year. However, there remains some uncertainty given the variability in trials and the relatively high prevalence of very severe disability in survivors. Careful consideration of risks, benefits and individual patient preferences are needed.

Clinical Question/ PICO

Population: Adults > 60 y.o. with malignant middle cerebral artery infarct
Intervention: Hemicraniectomy
Comparator: Medical treatment

Summary

Reinink et al (2021)*[199]* explored surgical decompression for space-occupying hemispheric infarction with seven studies and 488 participants. Surgical decompression decreased the chance of death (aOR 0.16, 95% CI 0.10 to 0.24; 7 studies, n=488) and increased chance of a favourable outcome [mRS 0-3] at one year (aOR 2.95, 95% CI 1.55 to 5.60; 7 studies, n=488) across all patient groups. There was no evidence of heterogeneity of treatment outcome based on age (OR 3.52, 95%CI 1.63 to 7.58 <60 years; 6 studies compared with OR 2.56, 95%CI 0.65 to 10.07 >60 years; 5 studies; p=0.48). However, the analysis of patients >60 years of age (from 5 trials) showed considerable variability between trials in the proportion of patients reaching a favourable outcome (mRS≤3 at 1 year) following surgery. The highest proportion of favourable outcome was seen in the unpublished DEMITUR trial (66%), while the proportions observed in the other studies ranged from 0 to 12.5%, noting that most studies had small absolute numbers in this subgroup.

Outcome Timeframe	**Study results and measurements**	**Comparator** Medical treatment	**Intervention** Hemicraniectomy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Favourable functional outcome (mRS 0-3) [1] 12 months 9 Critical	Odds Ratio 2.56 (CI 95% 0.65 — 10.07) Based on data from 253 patients in 5 studies. [2] (Randomized controlled) Follow up: 12 months.	102 per 1000	225 per 1000 Difference: 123 more per 1000 (CI 95% 33 fewer — 432 more)	**Moderate** Due to imprecision, Due to risk of bias [3]	Hemicraniectomy may improve functional recovery (mRS 0-3)
Death within 12 months 12 months 9 Critical	Odds Ratio 0.22 (CI 95% 0.12 — 0.35) Based on data from 235 patients in 5 studies. [4] (Randomized controlled) Follow up: 12 months.	737 per 1000	381 per 1000 Difference: 356 fewer per 1000 (CI 95% 485 fewer — 242 fewer)	**Moderate** Due to serious imprecision - single study [5]	Hemicraniectomy increases survival at 12 months

1. mRS 0-4 at 6 months
2. Primary study. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [199],
3. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study, Low number of patients, Wide confidence intervals. **Publication bias: No serious.**
4. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [199],
5. **Risk of Bias: No serious.** Incomplete data and/or large loss to follow up. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**

Practice statement

Consensus-based recommendation
For selected patients with large cerebellar infarction threatening brainstem and 4th ventricular compression, decompressive surgery should be offered.

Management of cerebral oedema

Conservative treatment of cerebral oedema often include care in the intensive care unit (ICU), including osmotherapy, barbiturates, and hyperventilation (Juttler et al. 2014 *[193]*). Conservative management of brain oedema is not supported by clinical trials (Juttler et al. 2014 *[193]*).

Weak recommendation against

Corticosteroids are not recommended for management of stroke patients with brain oedema and raised intracranial pressure. (Sandercock et al. 2011 *[195]*)

Evidence To Decision

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

There is evidence that corticosteroids are of no benefit in the treatment of brain oedema and raised intracranial pressure in stroke.

Certainty of the Evidence — High

The evidence comes from a Cochrane meta-analysis of 8 randomised trials and the quality of the studies is considered high.

Preference and values — No substantial variability expected

It is unlikely that patients would want to receive a treatment shown to improve intracranial pressure with no apparent benefits.

Resources and other considerations — Factor not considered

Rationale

In eight randomised controlled trials no benefit was found for the use of corticosteroids for managing patients with brain oedema and raised intracranial pressure.

Clinical Question/ PICO

Population: Corticosteroids for acute ischaemic stroke
Intervention: Corticosteroids
Comparator: Placebo

Summary

Sandercock et al (2011) *[195]* conducted a Cochrane review of the effectiveness of corticosteroids in acute ischaemic stroke, including 8 randomised trials (N = 466). Trials were double-blinded with placebo controls but details on randomisation and allocation concealment were generally unclear. Meta-analysis showed no significant difference in the odds of death by 12 months (OR 0.87, 95% CI 0.57 to 1.34) or within one month (OR 0.97, 95% CI 0.63 to 1.47). Due to

the small numbers of included trials and patients, the review authors noted that there is insufficient evidence to rule out benefit from corticosteroid treatment but at present there is no evidence to support the use of corticosteroids.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death within one month 1 month 9 Critical	Odds Ratio 0.97 (CI 95% 0.63 — 1.47) Based on data from 466 patients in 8 studies. [1] (Randomized controlled)	**281** per 1000	**275** per 1000 Difference: **6 fewer** per 1000 (CI 95% 83 fewer — 84 more)	**High**	Corticosteroids have little or no effect on death within one month
Death End of follow-up 9 Critical	Odds Ratio 0.87 (CI 95% 0.57 — 1.34) Based on data from 466 patients in 8 studies. [2] (Randomized controlled) Follow up: 2 weeks to 12 months.	**379** per 1000	**347** per 1000 Difference: **32 fewer** per 1000 (CI 95% 121 fewer — 71 more)	**High**	Corticosteroids have little or no effect on death

1. Systematic review [195] with included studies: Bauer 1973, Norris 1976, Mulley 1978, Ogun 2001, McQueen 1978, Gupta 1978, Norris 1986, Patten 1972. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [195] with included studies: Norris 1976, Norris 1986, Bauer 1973, McQueen 1978, Mulley 1978, Ogun 2001, Patten 1972, Gupta 1978. **Baseline/comparator:** Control arm of reference used for intervention.

Practice statement

Consensus-based recommendation
In stroke patients with brain oedema and raised intracranial pressure, osmotherapy and hyperventilation can be trialled while a neurosurgical consultation is undertaken.

Intracerebral haemorrhage (ICH) management

ICH accounts for 11% to 22% of incident strokes and half of all stroke deaths (Feigin et al. 2009 *[200]*). In general, the management of ICH is similar to that for ischaemic stroke, e.g. rapid assessment, stroke unit care, routine investigations, and prevention of complications. This section addresses medical and surgical management specific to patients with ICH.

Medical interventions

Potential medical interventions aim to reduce haematoma growth, which is strongly associated with worse patient outcomes. Reversal of coagulopathy and control of blood pressure are the main strategies currently available.

The incidence of intracranial haemorrhage (ICH) in the first year of warfarin therapy has been reported to be 1.9% (Hylek et al. 2007 *[206]*). Despite the availability of reversal agents for warfarin, the risk of disability and death is higher than other causes of intracerebral haemorrhage. The incidence of intracerebral haemorrhage with direct oral anticoagulants (DOACs) is significantly lower than with warfarin. Mortality was similar to warfarin-related bleeds in the era prior to specific reversal agents for DOACs. It remains to be seen whether these reversal agents are able to reduce morbidity associated with DOAC-related intracerebral haemorrhage.

Evidence on edaravone, cerebrolysin and tranexamic acid has also been identified, but it was insufficient to make recommendations (Yang et al. 2011 *[201]*; Bajenaru et al. 2010 *[202]*; Sprigg et al. 2014 *[203]*).

Management of blood pressure is particularly important in ICH as an elevated blood pressure is common in ICH patients and may increase haematoma expansion. However, the optimal target of blood pressure remains controversial.

Weak recommendation

- For stroke patients with warfarin-related intracerebral haemorrhage, prothrombin complex concentrate should be urgently administered in preference to standard fresh frozen plasma to reverse coagulopathy. (Steiner et al. 2016 *[204]*)
- Intravenous vitamin K (5–10 mg) should be used in addition to prothrombin complex to reverse warfarin but is insufficient as a sole treatment. (Steiner et al. 2016 *[204]*)

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Although prothrombin complex concentrate has clear superiority in rapid normalisation of coagulopathy, and probably reduces the risk of haematoma expansion (which is the rationale for treating), the effects on mortality and functional independence are less clear (Steiner et al. 2016 *[204]*).

Certainty of the Evidence

Moderate

The evidence comes from one well-conducted randomised controlled trial. The evidence for coagulopathy reversal is very robust but weaker for haematoma expansion and mortality reduction due to sample size.

Preference and values

No substantial variability expected

Most patients would want to receive the treatment considering the high mortality rate of warfarin-related ICH and little harm of the treatment.

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

Warfarin-related intracerebral haemorrhage has a high mortality rate, and mortality is associated with high rates of haematoma expansion following presentation. The INCH trial compared fresh frozen plasma (20 mL/kg) with intravenous four-factor prothrombin complex concentrate (PCC – 30 IU/kg), in patients presenting within 12 hours of ICH and with INR of greater than 1.9. Rates of INR normalisation (to less than 1.3) were achieved in 67% of PCC patients within 3 hours, as opposed to 9% of controls (Steiner et al. 2016 *[204]*). The trial was stopped early due to lower rates of haematoma expansion in the PCC group. Mortality rates within 48 hours from haematoma expansion were 0 and 5 (22%) in the PCC and FFP groups respectively (Steiner et al. 2016 *[204]*). Treatment with prothrombin complex concentrate should be administered with time-critical urgency.

All patients in this trial received 10 mg of intravenous vitamin K. Although no randomised controlled trial data exist to support using vitamin K, replenishing vitamin K prevents 'rebound' elevation of the INR by promoting hepatic synthesis of vitamin K-dependent clotting factors. The intravenous route has a more rapid onset than oral dosing, however up to 24 hours is required for effect, and therefore vitamin K cannot be the sole approach to warfarin-associated ICH.

Clinical Question/ PICO

Population: Adults with intracranial haemorrhage related to vitamin K antagonists
Intervention: Prothrombin complex concentrate
Comparator: Fresh frozen plasma

Summary

Steiner et al (2016) *[204]* conducted a randomised open-label trial comparing fresh frozen plasma (FFP) to prothrombin complex concentrate (PCC) for patients with intracranial haemorrhage related to vitamin K antagonists. The trial was terminated after 50 patients had been included due to safety concerns, with greater haematoma expansion in the FFP group. Patients receiving PCC were significantly more likely to have a normalised international normalised ratio (INR) within 3 hours (OR 30.6, 95% CI 4.7 to 197.9) and showed significantly lower haematoma expansion. There were no significant differences in functional independence or death by 90 days. The early stopping of the trial suggests a risk of bias, particularly a risk that the differences in haematoma expansion could be overestimated. The early stopping may also have limited the power of the study to detect differences in clinical outcomes.

Note: Steiner et al (2016) *[204]* did not report a relative effect estimate for deaths, instead it reported the results of a log-rank test based on time-to-event data. The log-rank test was non-significant, p = 0.14. The relative risk reported here was manually calculated from the raw numbers of events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Fresh frozen plasma	**Intervention** Prothrombin complex concentrate	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
INR ≤1·2 within 3 h 3 hours 7 Critical	Odds Ratio 30.6 (CI 95% 4.7 — 197.9) Based on data from 50 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	87 per 1000	745 per 1000 Difference: **658 more** per 1000 (CI 95% 222 more — 863 more)	**Moderate** Due to serious risk of bias, Due to serious imprecision, Upgraded due to Large magnitude of effect and reasons for bias limited [1]	Prothrombin complex concentrate may improve the chances of INR reduction to ≤1·2 within 3 h in patients with warfarin related ICH
Death 90 days 9 Critical	Relative risk 0.53 (CI 95% 0.2 — 1.4) Based on data from 50 patients in 1 studies. [2] (Randomized controlled) Follow up: 90 days.	348 per 1000	184 per 1000 Difference: **164 fewer** per 1000 (CI 95% 278 fewer — 139 more)	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Prothrombin complex concentrate may decrease death in patients with warfarin related ICH, compared with standard FFP

Outcome Timeframe	Study results and measurements	Comparator Fresh frozen plasma	Intervention Prothrombin complex concentrate	Certainty of the Evidence (Quality of evidence)	Plain text summary
Functional independence [4] 90 days 8 Critical	Odds Ratio 1.7 (CI 95% 0.4 — 6.8) Based on data from 50 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	391 per 1000	522 per 1000 Difference: **131 more** per 1000 (CI 95% 187 fewer — 423 more)	Low Due to serious risk of bias, Due to serious imprecision [5]	Prothrombin complex concentrate may increase functional independence
Haematoma expansion [6] 24 hours 7 Critical	Measured by: blood in brain (mL) Lower better Based on data from: 50 patients in 1 studies. (Randomized controlled) Follow up: 24 hours.	Difference: **MD 16.4 lower** (CI 95% 2.9 lower — 29.9 lower)		Low Due to serious risk of bias, Due to serious imprecision [7]	Prothrombin complex concentrate may decrease haematoma expansion

1. **Risk of Bias: Serious.** Missing intention-to-treat analysis, Trial stopping earlier than scheduled (but due to harm), Inadequate/lack of blinding of participants (but unlikely to effect outcomes of death, INR measures). **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Only data from one study. **Publication bias: No serious. Upgrade: Large magnitude of effect.**
2. Primary study[204]. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Risk of Bias: Serious.** Missing intention-to-treat analysis, Trial stopping earlier than scheduled (but due to harm), Inadequate/lack of blinding of participants (but unlikely to effect outcomes of death, INR measures). **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Only data from one study, Low number of patients. **Publication bias: No serious.**
4. mRS score of 0-3
5. **Risk of Bias: Serious.** Missing intention-to-treat analysis, Trial stopping earlier than scheduled (but due to harm), Inadequate/lack of blinding of participants (but unlikely to effect outcomes of death, INR measures). **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
6. Haemoatoma expansion commonly occurs in warfarin related ICH, and is a well-recognised surrogate marker for increased risk of death and ppor outcome
7. **Risk of Bias: Serious.** Missing intention-to-treat analysis, Trial stopping earlier than scheduled (but due to harm), Inadequate/lack of blinding of participants (but unlikely to effect outcomes of death, INR measures). **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study, Wide confidence intervals. **Publication bias: No serious.**

Weak recommendation

Stroke patients with intracerebral haemorrhage related to direct oral anticoagulants should urgently receive a specific reversal agent where available. (Pollack et al. 2016 *[207]*; Connolly 2016 *[208]*)

Practical Info

Idarucizumab is currently available as a specific reversal agent for dabigatran and is administered as a single IV bolus of 5 g, with an immediate reversal of the anticoagulant effect of dabigatran and no prothrombotic effect.

Andexanet alfa has been approved for use overseas for the reversal of apixaban and rivaroxoban, but it is not yet available in Australia.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

Two recent cohort trials have assessed the safety and efficacy of reversal agents for direct oral anticoagulants. Both trials show rapid and near complete reversal of anticoagulant effects following administration of reversal agents, without any prothrombotic effect (Pollack et al. 2016 *[207]*; Connolly 2016 *[208]*).

Certainty of the Evidence — Low

Evidence is from two single-group prospective cohort studies (Pollack et al. 2016 *[207]*; Connolly 2016 *[208]*). Although this means less certainty in its effects, it would be unethical to have a randomised controlled trial. Around a third of the population investigated had intracranial bleeding. Whether reversal of anticoagulant effect translates into improved outcome for intracerebral haemorrhage patients remains to be determined.

Preference and values — No substantial variability expected

Patients are likely to prefer to receive reversal agents compared to no treatments, considering the severity of the condition and little harm of the agents.

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

Although no randomised trial data support use, the mortality rate of DOAC-associated intracranial haemorrhage appears similar to warfarin-related haemorrhage. It is therefore reasonable to utilise specific reversal agents in this setting. Two cohort studies have examined the effect of andexanet alfa and idarucizumab, which respectively reverse factor Xa inhibitors (apixaban, rivaroxaban, edoxaban or enoxaparin) and dabigatran (Pollack et al. 2016 *[207]*; Connolly 2016 *[208]*). Around a third of the patient cohort in each study comprised patients with intracranial bleeding (intracerebral haemorrhage, subdural haemorrhage and subarachnoid haemorrhage). These two cohort studies demonstrated the rapid and complete reversal of abnormal coagulation parameters, without any prothrombotic effect. Treatment should be given emergently when this scenario is encountered, as the risk of haematoma expansion is greatest in the first few hours.

Clinical Question/ PICO

Population: Adults with ICH related with DOACs
Intervention: Reversal agents
Comparator: No treatment

Summary

Two recent cohort trials have assessed the safety and efficacy of reversal agents for direct oral anticoagulants. Both trials were single group prospective cohort studies. Pollack et al (2015) *[207]* assessed intravenous idarucizumab, a reversal agent for dabigatran, reporting an interim analysis based on 90 participants out of a planned 300 in the RE-VERSE AD trial. The 90 included patients either had uncontrollable or life-threatening bleeding (group A, including 18 patients with intracranial bleeding) or required surgery requiring normal haemostasis (group B). The primary endpoint was percentage reversal of dabigatran's anticoagulant effects, measured using dilute thrombin time or ecarin clotting time. Dilute thrombin time was normalized in 98% of group A patients and 93% of group B, while ecarin clotting time was normalised for 89% of group A and 88% in group B. Only 1 patient had a thrombotic event early (<= 72 hours) after idarucizumab administration.

In the ANNEXA-4 trial, Connolly et al (2016) *[208]* evaluated andexanet, a reversal agent for factor Xa inhibitors. 67 patients included in an interim safety analysis had acute major bleeding (28 with intracranial bleeding) following administration of a factor Xa inhibitor - apixaban, rivaroxaban, or enoxaparin. Anti-factor Xa activity following bolus administration was decreased by 89% from baseline among patients receiving rivaroxaban and 93% among patients

receiving apixaban. At 12 hours after andexanet infusion, 37 out of 47 patients had good or excellent clinical hemostatis.12 out of 67 patients had thrombotic events during 30-day follow-up.

Both trials show rapid and near complete reversal of anticoagulant effects following administration of reversal agents, without a prothrombotic effect.

Strong recommendation against

For stroke patients with intracerebral haemorrhage previously receiving antiplatelet therapy, platelet transfusion should not be administered. (Baharoglu et al. 2016 *[205]*)

Evidence To Decision

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

There were increased rates of death and disability (162 more patients with mRS 4–6 per 1000 patients treated), with consistent evidence of harm in both dichotomised modified Rankin Scale and shift analysis (Baharoglu et al. 2016 *[205]*).

Certainty of the Evidence — Moderate

One large randomised controlled trial of low risk of bias (downgraded due to only one study available) (Baharoglu et al. 2016 *[205]*).

Preference and values — No substantial variability expected

Patients would not want to receive a therapy shown to increase death and disability.

Resources and other considerations — Factor not considered

Rationale

Only one large randomised controlled trial examined the effectiveness of platelet transfusion on the outcome of patients with intracerebral haemorrhage (ICH) previously taking antiplatelet therapy (Baharoglu et al. 2016 *[205]*). Patients presenting within 6 hours of ICH were randomised to routine care or platelet transfusion within 90 minutes of neuroimaging. The odds of death and dependency at three months were higher in the platelet transfusion group, and the risk of haematoma expansion was not decreased.

Clinical Question/ PICO

Population: Adults with intracerebral haemorrhage taking antiplatelet before
Intervention: Platelet transfusion
Comparator: Standard care

Summary

Baharoglu et al (2016) *[205]* conducted a multicentre open-label randomised trial (N = 190) of platelet transfusion after acute intracerebral haemorrhage in people taking antiplatelet therapy. The intervention group received platelet transfusion within 6 hours of intracerebral haemorrhage while the control group received standard care. While the trial was open label, outcome assessors were blind to treatment allocation and allocation concealment was clearly reported.

The primary analysis showed significantly increased odds of a shift towards death or dependence at 3 months (modified Rankin scale scores) following platelet transfusion (adjusted common OR 2.05, 95% CI 1.18 to 3.56). Patients receiving platelet transfusion also had significantly increased odds of a poor outcome at 3 months (mRS score 4-6, OR 2.04, 95% CI 1.12 to 3.74), with a nonsignificant decrease in survival and increase in serious adverse events. These findings suggest platelet transfusion should not be used following acute intracerebral haemorrhage.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Platelet transfusion	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death or dependence [1] 90 days 9 Critical	Odds Ratio 2.04 (CI 95% 1.12 — 3.74) Based on data from 190 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	559 per 1000	721 per 1000 Difference: **162 more** per 1000 (CI 95% 28 more — 267 more)	**Moderate** Due to serious imprecision [2]	Platelet transfusion probably increases death or dependence following intracerebral haemorrhage in patients previously taking antiplatelet therapy
Survival [3] 90 days 9 Critical	Odds Ratio 0.62 (CI 95% 0.33 — 1.19) Based on data from 190 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	774 per 1000	680 per 1000 Difference: **94 fewer** per 1000 (CI 95% 243 fewer — 29 more)	**Moderate** Due to serious imprecision [4]	Platelet transfusion may decrease survival following intracerebral haemorrhage in patients previously taking antiplatelet therapy
Serious adverse events [5] 90 days 7 Critical	Odds Ratio 1.74 (CI 95% 0.96 — 3.17) Based on data from 190 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	295 per 1000	421 per 1000 Difference: **126 more** per 1000 (CI 95% 8 fewer — 275 more)	**Moderate** Due to serious imprecision [6]	Platelet transfusion may increase serious adverse events following intracerebral haemorrhage in patients previously taking antiplatelet therapy

1. Dependence defined as mRS 4-6. Primary outcome in trial was 'shift' on the mRS by ITT - that was also significant (adjusted common OR 2·05, 95% CI 1·18–3·56; p=0·0114)
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. Imprecision: Serious.** Only data from one study, 190 participants, Wide confidence intervals. **Publication bias: No serious.**
3. ITT
4. **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. Imprecision: Serious.** Wide confidence intervals, Only data from one study. **Publication bias: No serious.**
5. These are reported from the as treated analysis
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Only data from one study. **Publication bias: No serious.**

Weak recommendation

For stroke patients with intracerebral haemorrhage, blood pressure may be acutely reduced to a target systolic blood pressure of around 140 mmHg (but not substantially below) (see Acute blood pressure lowering therapy).

Surgical interventions

The aim of surgery for intracerebral haemorrhage is to reduce the volume of haemorrhage, prevent rebleeding, and remove the mass effect so that tissue damage is reduced (Gregson et al. 2012 *[214]*). However, the true effectiveness, timing and practice of operative neurosurgical interventions remain unclear. In recent years, intraventricular thrombolysis has also been investigated for the management of intraventricular haemorrhage, which has a mortality rate of 50–80% and is traditionally managed by cerebrospinal fluid drainage (Naff et al. 2011 *[215]*).

Weak recommendation against

In review

For stroke patients with supratentorial intracerebral haemorrhage (lobar, basal ganglia and/or thalamic locations), routine surgical evacuation is not recommended outside the context of research. (Mendelow et al. 2013 *[211]*; Gregson et al. 2012 *[214]*)

Practical Info

In patients with acute neurological deterioration considered to predominantly be due to obstructive hydrocephalus as a complication of the haematoma (as opposed to the intracerebral haemorrhage itself), neurosurgical placement of an external ventricular drain is often offered and is commonly accepted as beneficial, although randomised controlled trial evidence to support this is lacking.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is evidence for potential benefit from surgery for supratentorial (lobar, basal ganglia and/or thalamic) haematomas from some randomised trials but the largest and best-designed trials have been neutral (Mendelow et al. 2013 *[211]*; Xiao et al. 2012 *[212]*; Gregson et al. 2012 *[214]*). Crossover from medical to surgical treatment is a frequent confounding factor in interpretation.

Certainty of the Evidence

Low

The quality of the evidence is poor. Although one meta-analysis demonstrates a statistically significant benefit from surgery, individual studies in this meta-analysis had non-overlapping confidence intervals (Mendelow et al. 2013 *[211]*). Furthermore, another meta-analysis found no statistically significant difference in outcomes (Gregson et al. 2012 *[214]*).

Preference and values

Substantial variability is expected or uncertain

Some variation due to differences in the cultural or personal preferences of patients or substitute decision-makers may be expected.

Resources and other considerations

Factor not considered

Rationale

Although a meta-analysis suggested net benefit from surgery for lobar haematomas (Mendelow et al. 2013 *[211]*), there are several drawbacks including concerns about the quality of the evidence and the resource-intensive nature of the intervention. Similarly, studies of surgery for basal ganglia and/or thalamic haematomas have reported nonsignificant results compared with conservative management (Gregson et al. 2012 *[214]*). This therapy should therefore be carefully considered in each situation.

Clinical Question/ PICO

Population: Patients with Basal ganglia/thalamic haematomas
Intervention: Surgery

Comparator: Conservative treatment

Summary

An individual patient data meta-analysis by Gregson et al (2012) *[214]* compared surgery and conservative treatment in patients with basal ganglia or thalamic haematomas. Of the eight studies included in the meta-analysis, three were of similar size (>190 patients each) and the rest were smaller (<30 patients each). Of the three larger studies, two had point estimates suggesting overall harm with surgery, although the CIs for the OR crossed the null 1.0. It was the third study which had a point estimate showing benefit with surgery, with a CI for the OR that did not cross 1.0, which drove the overall point estimate of effect towards benefit with surgery, with a CI for the overall OR that crossed 1.0. Overall, surgery possibly reduces unfavourable outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conservative treatment	**Intervention** Surgery	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Unfavourable outcome [1] 3-6 months 9 Critical	Odds Ratio 0.84 (CI 95% 0.65 — 1.1) Based on data from 1,379 patients in 8 studies. (Randomized controlled) Follow up: 3-6 months.	782 per 1000	751 per 1000 Difference: 31 fewer per 1000 (CI 95% 16 more — 82 fewer)	**Moderate** Due to serious inconsistency [2]	Surgery possibly reduces the likelihood of an unfavourable outcome in patients with basal ganglia and thalamic haematomas.

1. Death/vegetative state/severe disability (i.e. not independent outside the home) or Rankin score >=3 or Barthel index <=90. Outcome of NOT achieving "Excellent" outcome was used for Chen 2001
2. **Risk of Bias: No serious.** Unable to tell from meta-analysis (Gregson). **Inconsistency: Serious.** Point estimates vary widely,The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., The magnitude of statistical heterogeneity was high, with I^2:70.8 %., , The direction of the effect is not consistent between the included studies. The point estimate for the overall result is in favour of the intervention group, but this appears to be driven by a single study (Wang), with all of the other studies' point estimates suggesting outcomes less favourable then reported by Wang et al. with intervention. . **Indirectness: No serious. Publication bias: No serious.** Smaller studies did not have particularly favourable outcomes with surgery therefore probably not biased against publication for neutral/negative studies. .

Clinical Question/ PICO

Population: Patients with lobar haematoma
Intervention: Surgery
Comparator: Conservative treatment

Summary

A meta-analysis by Mendelow et al (2013) *[211]* showed that in patients with lobar haematomas, surgery probably reduces the rate of an unfavourable outcome slightly compared with initial conservative treatment (OR 0.74, 95% CI 0.64-0.86). In the meta-analysis by Mendelow et al, the confidence intervals for several of the contributing studies did not overlap, reducing the degree of precision of the estimate of effect. Conversely, crossover between the immediate surgery and delayed surgery groups may reduce the apparent impact of surgery on this outcome.

In a randomised trial by Xiao et al (2012) *[212]*, patients (N = 36) with large (>70ml) lobar haematomas had CT-based haematoma puncture and aspiration (removing, an average of 1/3 of the haematoma volume) prior to haematoma evacuation via craniectomy. Survival at 12 months was better in those who had prior puncture and aspiration (58.3%) compared with patients who only had craniectomy without prior puncture and aspiration (20.8%). However, patients in

the puncture and aspiration group had their craniectomy on average 60 mins earlier than the group that proceeded directly to craniectomy, introducing the possibility that the improved survival was related to earlier surgery rather than initial haematoma puncture and aspiration.

Overall, although there is some degree of uncertainty, surgery may reduce unfavourable outcomes in patients with lobar haematoma.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conservative treatment	**Intervention** Surgery	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Unfavourable outcome [1] Not specified 8 Critical	Odds Ratio 0.74 (CI 95% 0.64 — 0.86) Based on data from 3,366 patients in 15 studies. (Randomized controlled) Follow up: Unclear.	665 per 1000	595 per 1000 Difference: **70 fewer** per 1000 (CI 95% 34 fewer — 105 fewer)	**Low** Due to serious inconsistency, Due to serious indirectness [2]	Surgery for patients with lobar haematomas may reduce the rate of unfavourable outcome slightly.

1. Very difficult to see what the definition of this was in Mendelow et al. They updated a meta-analysis (their Ref 37) which was published in a book, and the Cochrane review used 'death or dependency' in 2008. Presumably the latter is not the outcome used in the current meta-analysis or they would have used this terminology rather than 'unfavourable outcome'. It's unlikely there would have been enough data for them to apply the STICH II prognosis-based outcome in the meta-analysis.
2. **Risk of Bias: No serious.** Difficult to determine from the meta-analysis (Mendelow et al.). **Inconsistency: Serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high, with I^2:67 %.. **Indirectness: Serious.** Differences between the intervention/comparator of interest and those studied (due to a variety of different interventions included in the meta-analysis). **Imprecision: No serious.** **Publication bias: No serious.**

Weak recommendation against

For stroke patients with intraventricular haemorrhage, the use of intraventricular thrombolysis via external ventricular drain catheter is not recommended outside the context of research. (Gregson et al. 2012 *[214]*; Naff et al. 2011 *[215]*)

Evidence To Decision

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

Intraventricular haemorrhage thrombolysis is not recommended. Previously published evidence does not demonstrate improved clinical outcomes, and suggests increased risk of symptomatic haemorrhage (King et al. 2012 *[213]*; Naff et al. 2011 *[215]*). The MISTIE III trial has been reported in abstract form only and found a reduced risk of death with intraventricular thrombolysis but no reduction in disability. There were no safety concerns. Further trials are planned.

Endoscopic surgery for intraventricular haemorrhage is not recommended. Evidence does not demonstrate improved clinical outcomes (Gregson et al. 2012 *[214]*; Chen et al. 2011 *[216]*).

Certainty of the Evidence Low

The studies included have small sample sizes and variable outcome measures.

Preference and values Substantial variability is expected or uncertain

It is uncertain if patients would want a treatment option with unclear benefits.

Resources and other considerations Factor not considered

Rationale

There are few studies assessing intraventricular thrombolysis or endoscopic surgery for ventricular haemorrhage (King et al. 2012 *[213]*; Gregson et al. 2012 *[214]*; Naff et al. 2011 *[215]*; Chen et al. 2011 *[216]*). These studies include small numbers of patients, have variable outcome measures and do not demonstrate long-term clinical benefit from such interventions.

Clinical Question/ PICO

Population: Adults with intraventricular haemorrhage complicating parenchymal haemorrhage
Intervention: Surgery
Comparator: Conservative treatment

Summary

In patients with intraventricular haemorrhage complicating parenchymal haemorrhage, a meta-analysis by Gregson et al (2012) *[214]* showed that surgery probably reduces the rate of an unfavourable outcome. A small randomised controlled trial (N = 48) by Chen et al (2010) *[216]* investigated endoscopic surgery compared with external ventricular drainage surgery for intraventricular haemorrhage caused by thalamic haemorrhage. However, it showed little difference in critical clinical outcomes such as death and disability.

Outcome Timeframe	**Study results and measurements**	**Comparator** Conservative treatment	**Intervention** Surgery	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Unfavourable outcome [1] Unclear 8 Critical	Relative risk 0.77 (CI 95% 0.45 — 1.31) Based on data from 547 patients in 7 studies. (Randomized controlled) Follow up: Various.	888 per 1000	684 per 1000 Difference: 204 fewer per 1000 (CI 95% 488 fewer — 275 more)	Moderate Due to serious imprecision (statistically nonsignificant outcome) [2]	Surgery for intraventricular haematomas complicating parenchymal haematomas possibly decreases the rate of unfavourable outcome.

1. Various definitions used in the individual studies included in the meta-analysis.
2. **Risk of Bias: No serious.** Difficult to tell from meta-analysis. **Inconsistency: No serious.** I^2=0. **Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

Clinical Question/ PICO

Population: Adults with intraventricular haemorrhage complicating parenchymal haemorrhage
Intervention: Intraventricular thrombolysis

Comparator: Placebo

Summary

Naff et al (2011) *[215]* investigated the use of rtPA for intracerebral haemorrhage in a randomised controlled trial (N = 48) and showed potential small benefits and large adverse effects. A small randomised controlled trial with 16 participants by King et al (2012) *[213]* used intraventricular urokinase but no statistically significant differences were found in 6-month mortality, 30-day NIHSS score and 30-day mRS score.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Intraventricular thrombolysis	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death 30 days 8 Critical	Relative risk 0.85 (CI 95% 0.28 — 2.55) Based on data from 48 patients in 1 studies. (Randomized controlled) Follow up: 30 days.	227 per 1000	193 per 1000 Difference: **34 fewer** per 1000 (CI 95% 163 fewer — 352 more)	**Moderate** Due to serious imprecision [1]	Intraventricular rtPA administration probably has little or no effect on mortality in patients with large ventricular haemorrhages due to extension of spontaneous small supratentorial intracranial haemorrhage.
Adverse events - Ventriculitis 30 days 7 Critical	Relative risk 0.85 (CI 95% 0.12 — 5.52) Based on data from 48 patients in 1 studies. (Randomized controlled) Follow up: 30 days.	91 per 1000	77 per 1000 Difference: **14 fewer** per 1000 (CI 95% 80 fewer — 411 more)	**Moderate** Due to serious imprecision [2]	intraventricular thrombolysis probably has little or no difference on adverse events - ventriculitis
Adverse events - Symptomatic bleeding 30 days 7 Critical	Relative risk 5.08 (CI 95% 0.66 — 39.02) Based on data from 48 patients in 1 studies. (Randomized controlled) Follow up: 30 days.	45 per 1000	229 per 1000 Difference: **184 more** per 1000 (CI 95% 15 fewer — 1,711 more)	**Moderate** Due to serious imprecision [3]	intraventricular thrombolysis probably increases adverse events - symptomatic bleeding

1. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Low number of patients, Only data from one study, Wide confidence intervals. **Publication bias: No serious.**
2. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: No serious.**

Practice statement

Consensus-based recommendations

- For selected patients with large (> 3 cm) cerebellar haemorrhage, decompressive surgery should be offered. For other infratentorial haemorrhages (< 3 cm cerebellar, brainstem) the value of surgical intervention is unclear.
- Ventricular drainage as treatment for hydrocephalus is reasonable, especially in patients with decreased level of consciousness.
- In previously independent patients with large supratentorial haemorrhage and deteriorating conscious state, haematoma evacuation may be a life-saving measure but consideration of the likely level of long term disability is required.

Practical Info

The natural history of a large cerebellar haematoma (or ischaemic stroke) is compression of the 4th ventricle causing acute hydrocephalus. Direct brainstem compression can also occur. Deterioration in conscious state can be precipitous and once comatose it can be difficult to rescue the situation so these patients require close monitoring and careful consideration of the timing of surgery.

Rationale

There are no randomised trials of posterior fossa decompression and there are unlikely to be trials performed for this condition. Decompressive craniectomy and evacuation of the haematoma is regarded as a life-saving procedure and those who survive the initial pressure-related complications can make an excellent functional recovery. In the absence of randomised trial data, the high risk of early death associated with a large cerebellar haematoma and the observational data suggesting good functional recovery in those who survive the initial pressure-related complications support surgical decompression.

Surgery for brainstem haematoma is not felt to be beneficial due to the poor prognosis and technical challenges of evacuation without causing further injury to vital structures.

In patients where acute neurological deterioration is attributed to obstructive hydrocephalus as a complication of intracerebral haemorrhage (as opposed to deterioration due to the haematoma itself), neurosurgical placement of an external ventricular drain is often offered and is commonly accepted as beneficial, although randomised controlled trial evidence to support this is lacking.

Although we have recommended against routine surgical intervention for supratentorial intracerebral haemorrhage, the neutral trials included selected patients in whom the treating team had equipoise about the need for surgical intervention. The major supratentorial ICH surgery trials STICH I and STICH II were not designed to answer the question "is haematoma evacuation superior to no haematoma evacuation", but were pragmatic trials designed to answer the question "is an early surgical approach superior to initial conservative therapy in patients deemed by the supervising neurosurgeon to not require immediate surgery" (Mendelow et al. 2013 *[211]*; Mendelow et al. 2005 *[217]*). STICH I explicitly invoked the uncertainty principle: "patients were eligible… if the responsible neurosurgeon was uncertain about the benefits of either treatment" (Mendelow et al 2005 *[217]*). In STICH I, 26% of patients crossed over to surgery, mostly because of neurological deterioration. In STICH II, 21% crossed over (also mostly due to neurological deterioration). Thus, the conclusion of the STICH I and STICH II trials was that early surgical intervention for ICH is not superior to delayed surgical intervention upon deterioration in patients deemed initially to not require surgery. It remains probable that surgical intervention can be a life-saving procedure in certain patients, however this has not been demonstrated in a randomised controlled trial. In the absence of a randomised trial, the longer term post-surgical morbidity of survivors remains uncertain. Careful consideration of the prognosis for functional outcome and the patient's expressed attitude to disability (if known) are required when determining the best course of management.

Oxygen therapy

Whilst healthy adults with normal cerebral circulation can compensate for mild hypoxia through an increase in cerebral flow, this is difficult in patients whose brain is already ischaemic (Roffe et al. 2011 *[222]*). Mild hypoxia is common in stroke patients (affecting up to 63% of stroke patients after admission) and is associated with neurological deterioration (Roffe et al. 2011 *[222]*). On the other hand, oxygen supplementation has its problems. There is evidence from animal models and *in vitro* studies that oxygen encourages the formation of toxic free radicals, leading to further damage to the ischaemic brain.

Weak recommendation against

Updated

For acute stroke and Transient Ischaemic Attack (TIA) patients who have SpO_2 >92% on room air, the routine use of supplemental oxygen is not recommended. (Chu et al 2018 *[220]*; Ding et al 2018 *[219]*)

We had added further details on oxygen thresholds and provided additional updated information in the Key information, Rationale and Practical info. No change to overall grade of recommendation.

Practical Info

Most of the included trials used simple nasal prongs rather than face masks which may be more effective but more uncomfortable for patients. It can also be a challenge for patients who are confused to tolerate them in situ. There was considerable variability in the levels of oxygen provided (2-10L/min). The trials also didn't use thresholds for treatment with baseline SpO_2 readings commonly between 94-96% with potential harms found over 96% SpO_2. Hypoxic is defined as SpO_2 <92% on room air so oxygen therapy may be considered in such cases (see consensus statement for treatment targets).

Evidence To Decision

Benefits and harms

Important harms

Supplemental oxygen in those who are normoxic (SpO_2>92% on room air) does not improve neurological outcome as measured on NIHSS nor functional outcomes as measured by mRS but may increase mortality if administered to patients with an SpO_2 >96%. (Chu et al 2018 *[220]*)

Certainty of the Evidence

Moderate

The overall quality is moderate to high.

Preference and values

No substantial variability expected

Most patients would probably choose to avoid unnecessary oxygen treatment, particularly as there is the potential for important harms.

Resources and other considerations

Important issues, or potential issues not investigated

Oxygen therapy is usually readily available and tubing and nasal prongs/face masks relatively cheap but are all additional costs to the health service. No formal economic analysis was identified or undertaken.

Rationale

Moderate to high quality evidence shows lack of benefit for routine use of oxygen supplementation for acute stroke patients who are normoxic (SpO_2 >92% on room air) and possible increase death if SpO_2 >96% (Chu et al 2018 *[220]*, Ding et al 2018*[219]*). Considering the extra cost incurred and lack of benefit, routine use of supplemental oxygen in patients who are normoxic cannot be recommended.

Clinical Question/ PICO

Population: Adults with acute ischaemic stroke

Intervention: Early routine oxygen supplementation
Comparator: Room air

Summary

Ding et al 2018*[219]* included 11 RCTs and 6366 patients and found no change overall in any outcome of interest (mRS, BI scale, mortality, or NIHSS). Possible short term effects based on NIHSS was limited by small sample size.

Chu et al 2018*[220]* included 25 RCTs from mix populations (7 RCTs were stroke specific populations). Liberal versus conservative therapy did not chang functional status ie. mRS score >2 (5 trials [4 stroke & 1 TBI], OR 1.00; 0.92-1.09, and OR 1.02; 0.96-1.07 using 3 trials only of low risk of bias/high quality evidence), nor change in hospital-acquired infections (7 trials [3 stroke & 4 sepsis, MI and critical care], OR 1.04; 0.93-1.16, High quality evidence), but did slightly increase mortality during hospital stay (RR1.21, 1.03-1.43, 14 more per 1000 based on effect size of all included trials projected to incidence in stroke population), at 30 days (RR1.14, 1.01-1.28, 18 more per 1000, again extrapolating using effects for all populations) and at longest follow up (RR1.10, 1.00-1.20, 24 more per 1000) -High quality evidence overall. Individually calculating stroke specific mortality both in hospital and at longest follow up revealed non-significant trend to harm (higher mortality) with supplemental oxygen (RR1.28; 0.96-1.70 and RR1.09; 0.95-1.25 respectively). Baseline SpO_2 levels was 94-96% where harms appear to over-ride any possible benefits but specific thresholds were not used in the included studies.

Outcome Timeframe	**Study results and measurements**	**Comparator** Room air	**Intervention** Early routine oxygen supplementation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death End of follow-up 9 Critical	Relative risk 1.09 (CI 95% 0.95 — 1.25) Based on data from 6,130 patients in 5 studies. (Randomized controlled) Follow up: 3-12 months.	112 per 1000	122 per 1000 Difference: **10 more** per 1000 (CI 95% 6 fewer — 28 more)	**High** Two of 5 trials had risk of bias but the largest trial was low risk [1]	Early routine oxygen supplementation may increase mortality in acute stroke
Death In hospital 9 Critical	Relative risk 1.28 (CI 95% 0.96 — 1.7) Based on data from 6,288 patients in 5 studies. (Randomized controlled) Follow up: in hospital or within 7 days.	26 per 1000	33 per 1000 Difference: **7 more** per 1000 (CI 95% 1 fewer — 18 more)	**Moderate** Due to serious imprecision and two of 5 trials had risk of bias although largest trial was low risk [2]	Early routine oxygen supplementation may have risk of increased death in hospital
Disability (mRS >2) 3 -6 months 8 Critical	Relative risk 1.02 (CI 95% 0.96 — 1.07) Based on data from 5,426 patients in 3 studies. [3] (Randomized controlled) Follow up: 3-6 months.	480 per 1000	490 per 1000 Difference: **10 more** per 1000 (CI 95% 19 fewer — 34 more)	**High** [4]	Early routine oxygen supplementation probably has little or no difference on disability (mRS >2)

1. **Risk of Bias: Serious.** one study classes as high risk, largest trial was low risk. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
2. **Risk of Bias: Serious.** included two trials with risk of bias. Other trials had low risk, . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. Publication bias: No serious.**
3. Systematic review [220] . Only including 3 of the 4 stroke trials with low risk of bias as per table4a in Chu et al 2018.. **Baseline/comparator:** Systematic review.
4. **Risk of Bias: No serious.** based on three included trials with low risk of bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Weak recommendation against

For acute ischaemic stroke patients, hyperbaric oxygen therapy is not recommended. (Bennett et al. 2014 *[218]*)

Practical Info

HBO is expensive and there are limited facilities available for stroke patients.

Evidence To Decision

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

No benefit of hyperbaric oxygen was found in the outcomes of death or functional outcome in acute ischaemic stroke patients (Bennett et al. 2014 *[218]*).

Certainty of the Evidence — Low

The overall quality of evidence is low for the outcome of death (downgraded due to small sample size and serious risk of bias) but very low for functional outcome (due to very serious risk of bias, and inconsistency in results and in measurement) (Bennett et al. 2014 *[218]*).

Preference and values — Substantial variability is expected or uncertain

It is unclear if patients would want to receive this intervention with uncertain benefits.

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

Access to hyperbaric oxygen treatment is limited outside of major metropolitan centres and treatment can be costly.

Rationale

Low-quality evidence shows ambivalent results for hyperbaric oxygen therapy for acute stroke patients (Bennett et al. 2014 *[218]*). Considering the extra cost incurred and uncertainty in the benefit, routine use of supplemental oxygen cannot be recommended. However, hyperbaric oxygen may be considered for patients with stroke due to air embolism.

A small study of patients with ICH (n=79) reported hyperbaric oxygen therapy improved functional outcomes at 6 months (Xu et al 2018 *[221]*) but further studies are needed in this population.

Clinical Question/ PICO

Population: Adults with acute ischaemic stroke
Intervention: Hyperbaric oxygen therapy
Comparator: Standard practice

Summary

Bennet et al (2014) *[218]* conducted a Cochrane review of hyperbaric oxygen therapy in acute stroke patients. They did not find evidence of improved clinical outcomes. However, the overall quality of evidence was insufficient to exclude the possibility of clinical benefits and well-designed studies in the future can provide a clearer answer.

Xu et al (2018) *[221]* compared early hyperbaric oxygen therapy to normobaric oxygen therapy in 79 patients with haemorrhagic stroke and diabetes. A trend to good outcomes (Barthel Index 95-100; mRS <2, NIHSS <3) were noted at the end of the 30 day treatment period which reached significance (all outcomes) at 6 months. Complications (ear-ache and or claustrophobia) were similar between groups.

Outcome Timeframe	Study results and measurements	Comparator Standard practice	Intervention Hyperbaric oxygen therapy	Certainty of the Evidence (Quality of evidence)	Plain text summary
Death 3-6 months 9 Critical	Relative risk 0.97 (CI 95% 0.34 — 2.75) Based on data from 144 patients in 4 studies. [1] (Randomized controlled) Follow up: 3- to 6-months.	85 per 1000	82 per 1000 Difference: **3 fewer** per 1000 (CI 95% 56 fewer — 149 more)	**Low** Due to serious imprecision, Due to serious risk of bias [2]	hyperbaric oxygen therapy may have little or no difference on death
Functional outcome 1 to 365 days 7 Critical	Based on data from: 705 patients in 11 studies. (Randomized controlled) Follow up: 1 to 365 days.	Four of 14 scale measures of disability and functional performance indicated improvement following HBOT.		**Very low** Due to very serious risk of bias and serious inconsistency [3]	We are uncertain whether hyperbaric oxygen therapy increases or decreases functional outcome

1. Systematic review [218] . **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Small sample sizes. **Publication bias: No serious.**
3. **Risk of Bias: Very serious.** These trials varied in methodological quality, and only six provided full reports of completed trials in a peer-reviewed publication, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, 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, Incomplete data and/or large loss to follow up. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies, and various measurement tools and timeframes. **Indirectness: No serious. Imprecision: No serious.** no data pooled for this outcome. **Publication bias: No serious.**

Practice statement

Updated

Consensus-based recommendation

If supplemental oxygen is required (SpO_2 <93% on room air) a target oxygen saturation of 94-96% is reasonable, or 88-92% if the patient is at risk of hypercapnic respiratory failure. (Beasley et al 2015 *[223]*)

We have made a change to the threshold to consider oxygen therapy from <95% to <93% on room air. We have also added a target level if oxygen therapy is provided.

Rationale

There is little evidence to guide thresholds for 'normal' oxygen saturation with consensus that supplemental oxygen therapy should commence if SpO_2 <92% on room air, titrated to target a SpO_2 of 94-96% *[223]*. Current evidence suggests an increased risk of mortality with supplemental oxygen administration in patients with SpO_2 >96% *[220]*. Further evidence may reveal subgroups who may benefit from more aggressive therapy.

Neuroprotection

Most of the current strategies for treatment of ischaemic stroke are based on re-establishing perfusion through the blocked blood vessels, using pharmacologic and mechanical thrombolysis. Conversely, neuroprotection targets biochemical pathways that lead to cell injury and death in ischaemia in order to rescue salvageable nervous tissue.

Despite encouraging data in experimental animal models, no clinical trials have demonstrated any significant benefit of neuroprotective agents in human stroke patients. There are too few data on other groups of agents, including colony-stimulating factors (including erythropoietin, granulocyte colony-stimulating factor and analogues), theophylline, aminophylline, caffeine and analogues, edaravone, minocycline, and arundic acid (ONO2506). Hypothermia has been studied for its potential neuroprotective effects, including physical cooling or use of paracetamol to reduce body temperature, but evidence supporting it is also limited.

Practice statement

Consensus-based recommendation
For stroke patients, putative neuroprotective agents, including hypothermic cooling, are not recommended outside the context of research.

Rationale

A large number of neuroprotective agents have been studied in clinical trials; however, none have demonstrated clear benefits and hence cannot be recommended for routine use (Ladurner et al. 2005 *[229]*; Muir et al. 2004 *[230]*; Krams et al. 2003 *[231]*; Muir et al. 2003 *[232]*; Diener et al. 2008 *[233]*; Lyden et al. 2007 *[234]*; Davalos et al. 2012 *[224]*; Chamorro et al. 2014 *[225]*; Ginsberg et al. 2013 *[226]*; Saver et al. 2015 *[228]*; Heiss et al. 2012 *[227]*). The ESCAPE NA-1 trial provided some evidence of benefit of nerinetide in patients in the pre-specified subgroup of patients not treated with alteplase (Hill et al 2020 *[236]*). However, further trials will be required to establish the role of this medication in clinical practice.

Practice statement

Consensus-based recommendation
Patients with acute ischaemic stroke who were receiving statins prior to admission can continue statin treatment.

Rationale

Small studies suggest that receiving statin therapy prior to stroke may have a neuroprotective effect (Blanco et al. 2007 *[235]*). However, this preliminary evidence precludes a stronger recommendation. Further large interventional studies reporting consistent results are needed to clarify the role of statin therapy for neuroprotection in acute stroke patients.

Glycaemic therapy

Hyperglycaemia after stroke is found in one-third of patients, although the reported incidence varies between 8% and 83% depending on the cohort and definition (Capes et al. 2001 *[251]*). Previously undetected diabetes is found in 16–24% of patients admitted with stroke (Gray et al. 2004 *[252]*; Kernan et al. 2005 *[253]*). Observational data indicate that hyperglycaemia fluctuates in the first 72 hours in both non-diabetic and diabetic patients, even with current best practice (Allport et al. 2006 *[254]*). Observational data also reveal poorer outcomes for non-diabetic patients with hyperglycaemia (Capes et al. 2001 *[251]*). Glucose intolerance after stroke is also common (approximately 25%) (Kernan et al. 2005 *[253]*; Allport et al. 2006 *[254]*) and linked to higher stroke recurrence (Vermeer et al. 2006 *[255]*).

There is now good evidence that hyperglycaemia needs management regardless of the patient's diabetic status (Bellolio et al. 2014 *[249]*; Ntaios et al. 2014 *[247]*; Middleton et al. 2011 *[256]* and Drury et al. 2014 *[257]*). Implementation of effective glycaemic control requires education of nursing staff across all shifts, which can be challenging. Glucometers also need to be readily available. National Stroke Audits report that 91% of Australian stroke hospitals have locally agreed protocols for glucose control in place (Stroke Foundation 2019 *[28]*).

Strong recommendation

All stroke patients should have their blood glucose level monitored for the first 72 hours following admission, and appropriate glycaemic therapy instituted to treat hyperglycaemia (glucose levels greater than 10 mmol/L), regardless of their diabetic status. (Middleton et al. 2011 *[256]*)

Practical Info

The trials in the Cochrane review (Bellolio et al. 2014 *[249]*) used tight control of blood glucose (4–7.5mmol/L), however the QASC trial (Middleton et al. 2011 *[256]*) suggested that insulin should only be used to maintain blood glucose levels of less than 11 mmol/L (euglycaemia) as part of a care bundle.

The Australian Diabetes Society Guidelines for Routine Glucose Control in Hospital recommend:
1. Patients admitted to hospital with acute thrombotic stroke who have hyperglycaemia should be treated to achieve and maintain glucose levels less than 10 mmol/L (a threshold based on expert opinion).
2. Hypoglycaemia must be avoided, and therefore it would be prudent to avoid treatment which lower the glucose below 5 mmol/L.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

The QASC trial showed that when used as part of a bundled care package, monitoring of blood glucose levels and treatment of hyperglycaemia ≥ 11 mmol/L in the first 72 hours improves outcomes at 90 days (157 fewer patients with the outcome of death or dependency per 1000 patients treated) (Middleton et al. 2011 *[256]*).

Certainty of the Evidence

Moderate

The quality of evidence is considered moderate, as the intervention was a bundled package including other elements of care.

Preference and values

No substantial variability expected

It is expected that all patients would want to receive blood glucose level monitoring and treatment of hyperglycaemia.

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 in the National Stroke Audit on the total number of patients who, in the first 72 hours of their admission, developed a finger-prick glucose level of greater or equal to 10 mmol/L. There is a further clinical indicator

collected on the provision of insulin treatment within 1 hour of the first elevated finger-prick glucose of greater or equal to 10 mmol/L. There is also an organisational indicator collected to determine whether participating hospitals have locally-agreed management protocols for glucose.

Rationale

The QASC trial showed moderate-quality evidence that when used as part of a bundled care package, monitoring of blood glucose levels and treatment of hyperglycaemia ≥ 11 mmol/L in the first 72 hours improves outcomes at 90 days (Middleton et al. 2011 *[256]*).

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Fever, Sugar, Swallow (FeSS) protocol
Comparator: No FeSS protocol

Summary

The Quality in Acute Stroke Care (QASC) trial reported by Middleton et al (2011) *[256]* was a cluster randomised trial (N = 1696) of a treatment protocol FeSS for managing fever, glycaemia, and swallowing dysfunction. The trial demonstrated that when used as part of a bundled care package, monitoring of blood glucose levels and treatment of hyperglycaemia ≥ 11 mmol/L in the first 72 hours improves outcomes at 90 days, although it is important to note the effects of individual components of the intervention cannot be separated. Therefore, the evidence for the benefits of hyperglycaemia management specifically is somewhat indirect.

Drury et al (2014) *[257]* provides evidence of current management practices in the pre-intervention cohort prospectively recruited for the QASC trial. Retrospective medical record audits of all 19 participating stroke units (n=718) revealed:

- 138 (19%) had four hourly or more temperature readings and 204 patients (29%) had a fever, with 44 (22%) receiving paracetamol.
- A quarter of patients (n = 102/412, 25%) had six hourly or more glucose readings and 23% (95/412) had hyperglycemia, with 31% (29/95) of these treated with insulin.
- The majority of patients received a swallow assessment (n = 562, 78%) by a speech pathologist in the first instance rather than a swallow screen by a nonspeech pathologist (n = 156, 22%). Of those who passed a screen (n = 108 of 156, 69%), 68% (n = 73) were reassessed by a speech pathologist and 97% (n = 71) were reconfirmed to be able to swallow safely.

Note: The statistical analysis used in Middleton et al (2011) *[256]* estimates absolute risk differences directly, and relative effects were not really reported. The absolute differences entered are those reported in the study. The raw numbers of events in the control group are used to calculate baseline risk, with the reported absolute risk difference then used to calculate risk in the intervention group. Relative effects have been left blank.

Outcome Timeframe	**Study results and measurements**	**Comparator** No FeSS protocol	**Intervention** Fever, Sugar, Swallow (FeSS) protocol	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death or dependency [1] 90 days 9 Critical	n/a Based on data from 1,007 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	577 per 1000	420 per 1000 Difference: **157 fewer** per 1000 (CI 95% 58 fewer — 254 fewer)	**Moderate** Due to serious imprecision, Due to serious indirectness [2]	Patients treated in stroke care units with FeSS protocols have improved death or dependency outcomes when compared to patients treated in stroke care units without FeSS protocols.
Functional dependency (Barthel Index >=	n/a Based on data from 955	898 per 1000	923 per 1000	**Moderate** Due to serious imprecision, Due	There is little or no difference in functional dependency as measured

Outcome Timeframe	Study results and measurements	Comparator No FeSS protocol	Intervention Fever, Sugar, Swallow (FeSS) protocol	Certainty of the Evidence (Quality of evidence)	Plain text summary
60) [3] 90 days 7 Critical	patients in 1 studies. (Randomized controlled) Follow up: 90 days.	Difference: 25 more per 1000 (CI 95% 36 fewer — 86 more)		to serious indirectness [4]	by Barthel Index >= 60 for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.
Functional dependency (Barthel Index >= 95) [5] 90 days 7 Critical	n/a Based on data from 955 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	600 per 1000	695 per 1000 Difference: 95 more per 1000 (CI 95% 50 fewer — 195 fewer)	Moderate Due to serious imprecision, Due to serious indirectness [6]	There is little or no difference in functional dependency as measured by Barthel Index >= 95 for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.
Length of stay [7] 7 Critical	Measured by: Length of Stay Lower better Based on data from: 1,086 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	13.7 days (Mean)	11.3 days (Mean) Difference: MD 1.5 lower (CI 95% 0.5 higher — 3.5 lower)	Moderate Due to serious imprecision, Due to serious indirectness [8]	There is no difference in mean length of stay for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.

1. Death or dependency as measured by mRS >= 2
2. **Inconsistency: No serious. Indirectness: Serious.** Exclusion palliative patients may have under represented severe stroke patients., Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
3. Barthel Index >= 60
4. **Inconsistency: No serious. Indirectness: Serious.** Exclusion palliative patients may have resulted in severe strokes being under represented., Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
5. Barthel Index >= 95%
6. **Inconsistency: No serious. Indirectness: Serious.** Exclusion palliative patients may have resulted in under representation severe strokes. Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** **Publication bias: No serious.**
7. Length of stay as measured by days in hospital.
8. **Inconsistency: No serious. Indirectness: Serious.** Exclusion palliative patients may have under represented severe stroke patients. Differences between the intervention/comparator of interest and those studied. **Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**

Strong recommendation against

For stroke patients, an intensive approach to the maintenance of tight glycaemic control (between 4.0–7.5 mmol/L) is not recommended. (Bellolio et al. 2014 *[249]*; Ntaios et al. 2014 *[247]*; Johnston et al. 2019 *[250]*)

Practical Info

The trials in the Cochrane review used tight control of blood glucose (4–7.5 mmol/L) whereas the QASC trial (Middleton et al. 2011

[256]) suggested that insulin should only be used to maintain blood glucose levels of less than 11 mmol/L (euglycaemia) as part of a care bundle.

The Australian Diabetes Society Guidelines for Routine Glucose Control in Hospital recommend:
1. Patients admitted to hospital with acute thrombotic stroke who have hyperglycaemia should be treated to achieve and maintain glucose levels less than 10 mmol/L.
2. Hypoglycaemia must be avoided, and therefore it would be prudent to avoid treatment which lowers the glucose below 5 mmol/L.

Evidence To Decision

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

The risk of hypoglycaemia was higher in the intervention groups treated with intravenous insulin to maintain a tight range of glycaemic level (4–7.5 mmol/L), whereas the intervention did not show any benefits in improving mortality or functional outcomes (Bellolio et al. 2014 *[249]*; Ntaios et al. 2014 *[247]*; Johnston et al. 2019 *[250]*).

Certainty of the Evidence — Moderate

The quality of evidence would be considered moderate due to a risk of bias with regard to allocation and blinding in the trials assessed in the reviews.

Preference and values — No substantial variability expected

Patients are unlikely to want to receive a treatment with no proven benefit that is potentially harmful.

Resources and other considerations — Factor not considered

Rationale

Two systematic reviews (Bellolio et al. 2014 *[249]*; Ntaios et al. 2014 *[247]*) were included. The Cochrane systematic review (Bellolio et al. 2014 *[249]*) included 11 trials (N = 1583 participants) and the other review (Ntaios et al. 2014 *[247]*) included 9 trials (N = 1491 participants). Both reviews were consistent and reported no benefits from intensive therapy with intravenous insulin, but also an increase in rate of complications (hypoglycaemia). Similar results were confirmed in the large SHINE trial (Johnston et al. 2019) which compared early, intensive IV insulin versus subcutaeous inslulin but was terminated early due to futility. Early and intense therapy via intravenous insulin is not recommended.

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Insulin for tight glycaemic control
Comparator: Usual care

Summary

Two systematic reviews (Bellolio et al 2014 *[249]*; Ntaios et al 2014 *[247]*) were included. The Cochrane systematic review (Bellolio et al 2014) included 11 trials (N=1583 participants) and the other review (Ntaios et al 2014 *[247]*) included 9 trials (N=1491 participants). Both reviews were consistent and reported no benefits from intensive therapy with IV insulin but also an increased rate of complications (hypoglycemia).

Another review by Cerecedo-Lopez et al (2020) *[248]* included 12 RCTs (n=2734) and found the same results as earlier reviews with tight glycemic control compared to conventional therapy or placebo. At 90 days follow up there was no change in mortality (OR 0.99, 95%CI 0.79 to 1.22; 6 studies, n=2424) or independence (OR, 0.95 95% CI 0.79 to1.14, 6 studies, n=2424), but there was an increase in adverse events specifically, symptomatic or severe hypoglycemia (OR 5.2 95% CI 1.7 to 15.9, 11 studies, n=2612).(Importantly this review included the major SHINE trial (Johnston et al. 2019 *[250]*) which included 1151 participants. Tighter blood blood glucose level (mean 6.6 mmol/L) compared to standard treatment (mean 9.9 mmol/L) had no effect on favorable outcome (20.5% vs 21.6 %, RR 0.97, 95% CI 0.87 to 1.08). Treatment was stopped to due adverse events or hypoglycemia in 11.2% vs 2.6%.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Insulin for glycaemic control in acute ischaemic stroke	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Dependency or death at the end of the follow-up 9 Critical	Odds Ratio 0.99 (CI 95% 0.79 — 1.23) Based on data from 1,516 patients in 9 studies. [1] (Randomized controlled) Follow up: <30 days to 90 days.	658 per 1000	656 per 1000 Difference: **2 fewer** per 1000 (CI 95% 55 fewer — 45 more)	**Moderate** Due to serious risk of bias [2]	Insulin for glycaemic control in acute ischaemic stroke probably has little or no difference on dependency or death at the end of the follow-up
Death 9 Critical	Odds Ratio 1.09 (CI 95% 0.85 — 1.41) Based on data from 1,422 patients in 9 studies. [3] (Randomized controlled) Follow up: discharge-120 days.	224 per 1000	239 per 1000 Difference: **15 more** per 1000 (CI 95% 27 fewer — 65 more)	**Moderate** Due to serious risk of bias [4]	Insulin for glycaemic control in acute ischaemic stroke probably has little or no difference on death
Independent in daily activities 8 Critical	Odds Ratio 1.03 (CI 95% 0.81 — 1.32) Based on data from 1,224 patients in 9 studies. [5] (Randomized controlled) Follow up: Discharge to 120 Days.	317 per 1000	323 per 1000 Difference: **6 more** per 1000 (CI 95% 44 fewer — 63 more)	**Moderate** Due to serious risk of bias [6]	Insulin for glycaemic control probably has little or no difference on independence in daily activities when compared to usual care
Symptomatic hypoglycaemia 6 Important	Odds Ratio 14.6 (CI 95% 6.62 — 32.21) Based on data from 1,455 patients in 10 studies. [7] (Randomized controlled) Follow up: 5 to 120 days.	4 per 1000	55 per 1000 Difference: **51 more** per 1000 (CI 95% 22 more — 111 more)	**Moderate** Due to serious risk of bias [8]	This meta-analysis showed a significant difference in the incidence of hypoglycaemia between the treatment and control groups suggesting that insulin for glycaemic control probably worsens symptomatic hypoglycaemia
Hypoglycaemia (with or without symptoms) 6 Important	Odds Ratio 18.41 (CI 95% 9.09 — 37.27) Based on data from 1,455 patients in 10 studies. [9] (Randomized controlled) Follow up: 5 to 120 days.	10 per 1000	157 per 1000 Difference: **147 more** per 1000 (CI 95% 74 more — 264 more)	**Moderate** Due to serious risk of bias [10]	This meta-analysis found a significant difference in the incidence of hypoglycaemia between the treatment and control groups suggesting that insulin for glycaemic control probably worsens hypoglycaemia (with or without symptoms).
Functional neurological outcome at the end of the follow-up - NIHSS or ESS [11] 7 Critical	Measured by: NIHSS and ESS Lower better Based on data from: 1,432 patients in 8 studies. [12] (Randomized controlled) Follow up: Discharge to 120 days.		Difference: **SMD 0.09 lower** (CI 95% 0.19 lower — 0.01 higher)	**Moderate** Due to serious risk of bias [13]	Insulin for glycaemic control probably has little or no difference on functional neurological outcome at the end of the follow-up

1. Systematic review [249] with included studies: McCormick 2010, INSULINFARCT 2012, THIS 2008, Azevedo 2009, Kreisel 2009, GIST-UK 2007, GRASP 2009, Vinychuk 2005, Staszewski 2011. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: Serious.** Most of the studies did not use blinded assessors, resulting in potential for performance bias. Inadequate concealment of allocation, in 5 studies, during randomization process, resulting in potential for selection bias, GIST-UK stopping earlier than scheduled, due to slow enrollment rate resulting in potential for overestimating benefits. 4 studies had a high risk of bias secondary to inadequate allocation. . **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.** Smaller numbers in individual trials.. **Publication bias: No serious.**
3. Systematic review [249] with included studies: Walters 2006, Azevedo 2009, McCormick 2010, Kreisel 2009, Staszewski 2011, INSULINFARCT 2012, THIS 2008, GRASP 2009, GIST-UK 2007. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: Serious.** Most of the studies did not use blinded assessors, resulting in potential for performance bias. Inadequate concealment of allocation, in 5 studies, during randomization process, resulting in potential for selection bias, GIST-UK stopping earlier than scheduled, due to slow enrollment rate resulting in potential for overestimating benefits. 4 studies had a high risk of bias . **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
5. Systematic review [249] . **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias in one study and unclear in three of the studies Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias in all studies Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias in five studies. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
7. Systematic review [249] . **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: Serious.** All trials had lack of blinding of personnel, and only THIS 2008 blinded the participants resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias in six of the 10 trials. Two trials had inadequate concealment of allocation during randomization process, and two it was unclear int he reporting resulting in potential for selection bias. Two trials had incomplete data and/or large loss to follow up. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
9. Systematic review [249] . **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias in one trial, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias in all trials accept THIS 2008 who blinded the participants. Only four trials had adequate/ of outcome assessors, resulting in potential for detection bias. Incomplete data and/or large loss to follow up for two trials and unclear in two more.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
11. Studies measured neurological deficit using National Institutes of Health Stroke Scale (NIHSS) and the European Stroke Scale (ESS)
12. Systematic review [249] . **Baseline/comparator:** Control arm of reference used for intervention.
13. **Risk of Bias: Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias in only one study Inadequate concealment of allocation during randomization process, resulting in potential for selection bias in two studies and unclear in another one study. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias in all studies Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias in five of the studies, Incomplete data and/or large loss to follow up in four studies. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

Pyrexia management

In the initial period after a stroke, temperature higher than 37·5°C (Pyrexia) occurs in 20–50% of patients (Castillo et al. 1999 *[261]*).

Pyrexia is associated with poorer outcomes after stroke (Greer et al. 2008 *[262]*) and the most common causes of pyrexia are chest or urinary infections (Langhorne et al. 2000 *[263]*). Fever in stroke patients needs to be managed proactively by the interdisciplinary team, ideally as part of a bundled care package where it has been demonstrated to reduce mortality and morbidity (Middelton et al. 2011 *[256]*).

Strong recommendation

All stroke patients should have their temperature monitored at least four times a day for 72 hours. (Middleton et al. 2011 *[256]*)

Practical Info

To reduce patient fatigue, it was considered reasonable to undertake four observations over a 24-hour period rather than strict 6-hourly protocol.

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

There were no harms reported in the patients who were treated in stroke units that had implemented the FeSS treatment protocols in the QASC study. The substantial benefits of this care package (patients are 16% more likely to be alive and independent) compared to those cared for in stroke units without FESS protocols warrant the recommendation that stroke units should follow similar protocols (Middleton et al. 2011 *[256]*).

Certainty of the Evidence — Moderate

For the comparison FeSS vs no FeSS the quality of evidence is very high, as the evidence is from a large single-blinded RCT with minimal bias (Middleton et al 2011 *[256]*).

Drury et al. (2014) *[257]* provides a systematic evaluation of records and data that documents current stroke management practices, indicating the need for urgent behaviour change.

Preference and values — No substantial variability expected

There is no perceived risks or inconvenience to having temperature recorded four times a day within the first 72 hours. The low-quality evidence available for therapeutic hypothermia does not warrant consideration at this stage due to safety concerns related to serious complication rates.

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 in the National Stroke Audit to determine the total number of patients with stroke who, in the first 48 hours of their admission, developed a fever greater than or equal to 37.5°C. There is an additional clinical indicator collected on whether paracetamol was administered for those patients within 1 hour of the recorded temperature of greater than or equal to 37.5°C.

Rationale

Fever is an important indicator of developing sepsis which requires specific investigation and treatment. The QASC trial showed high-quality evidence that monitoring and treatment of fever ≥ 37.5 °C improve outcomes at 90 days, when used as part of a bundle of care. The absolute benefits reported in this trial clearly outweigh the drawbacks/harms associated with not receiving this aspect of the care bundle (temperature recorded four times a day).

Clinical Question/ PICO

Population: Adults with stroke
Intervention: FeSS protocol (Fever, Sugar, Swallow)
Comparator: No FeSS protocol

Summary

The Quality in Acute Stroke Care (QASC) trial reported by Middleton et al (2011) *[256]* was a cluster randomised trial (N = 1696) of a treatment protocol (FeSS) for managing fever, glycaemia, and swallowing dysfunction. The trial showed high-quality evidence that monitoring and treatment of fever ≥ 37.5 ^{O}C improves outcomes at 90 days, when used as part of a bundle of care, although the effects of individual components of the intervention cannot be separated. Therefore, the evidence for the benefits of pyrexia management specifically is somewhat indirect.

Drury et al (2014) *[257]* provides a systematic evaluation of records and data that documents current stroke management practices of the pre-intervention cohort prospectively recruited for the Quality in Acute Stroke Care trial. Retrospective medical record audits of all 19 participating stroke units (n=718) revealed:

- 138 (19%) had four hourly or more temperature readings and 204 patients (29%) had a fever, with 44 (22%) receiving paracetamol.
- A quarter of patients (n = 102/412, 25%) had six hourly or more glucose readings and 23% (95/412) had hyperglycemia, with 31% (29/95) of these treated with insulin.
- The majority of patients received a swallow assessment (n = 562, 78%) by a speech pathologist in the first instance rather than a swallow screen by a nonspeech pathologist (n = 156, 22%). Of those who passed a screen (n = 108 of 156, 69%), 68% (n = 73) were reassessed by a speech pathologist and 97% (n = 71) were reconfirmed to be able to swallow safely.

Note: The statistical analysis used in Middleton et al (2011) *[256]* estimates absolute risk differences directly, and relative effects were therefore not reported. The absolute differences entered are those reported in the study. The raw numbers of events in the control group are used to calculate baseline risk, with the reported absolute risk difference then used to calculate (estimated) risk in the intervention group. Relative effects have been left blank.

Outcome Timeframe	**Study results and measurements**	**Comparator** No FeSS protocol	**Intervention** FeSS protocol (Fever, Sugar, Swallow)	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Functional dependency (Barthel Index >= 95) [1] 90 days 7 Critical	Based on data from 955 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	600 per 1000	695 per 1000 Difference: 95 more per 1000 (CI 95% 50 fewer — 195 fewer)	High [2]	There is little or no difference in functional dependency as measured by Barthel Index >= 95 for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.
Death or dependency [3] 90 days 9 Critical	n/a Based on data from 1,007 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	577 per 1000	420 per 1000 Difference: 157 fewer per 1000 (CI 95% 58 fewer — 254 fewer)	High [4]	Patients treated in stroke care units with FeSS protocols have improved death or dependency outcomes when compared to patients treated in stroke care units without FeSS protocols.
Functional dependency (Barthel Index >=	n/a Based on data from 955 patients in 1 studies.	898 per 1000	923 per 1000	High [6]	There is little or no difference in functional dependency as measured by Barthel Index >= 60

Outcome Timeframe	Study results and measurements	Comparator No FeSS protocol	Intervention FeSS protocol (Fever, Sugar, Swallow)	Certainty of the Evidence (Quality of evidence)	Plain text summary
60) [5] 90 days 7 Critical	(Randomized controlled) Follow up: 90 days.	Difference: 25 more per 1000 (CI 95% 36 fewer — 86 more)			for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.
Length of stay [7] 7 Critical	Measured by: Length of Stay Lower better Based on data from: 1,086 patients in 1 studies. (Randomized controlled) Follow up: 90 days.	13.7 days (Mean) Difference: MD 1.5 lower (CI 95% 0.5 higher — 3.5 lower)	11.3 days (Mean)	High [8]	There is no difference in mean length of stay for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.

1. Barthel Index >= 95%
2. **Inconsistency: No serious. Indirectness: No serious.** Exclusion palliative patients may have resulted in under representation severe strokes.. **Imprecision: No serious. Publication bias: No serious.**
3. Death or dependency as measured by mRS >= 2
4. **Inconsistency: No serious. Indirectness: No serious.** Exclusion palliative patients may have under represented severe stroke patients.. **Imprecision: No serious. Publication bias: No serious.**
5. Barthel Index >= 60
6. **Inconsistency: No serious. Indirectness: No serious.** Exclusion palliative patients may have resulted in severe strokes being under represented.. **Imprecision: No serious. Publication bias: No serious.**
7. Length of stay as measured by days in hospital.
8. **Inconsistency: No serious. Indirectness: No serious.** Exclusion palliative patients may have under represented severe stroke patients.. **Imprecision: No serious. Publication bias: No serious.**

Weak recommendation

Stroke patients with fever ≥ 37.5 °C may be treated with paracetamol as an antipyretic therapy. (Chen et al. 2018 *[264]*; Middleton et al. 2011 *[256]*)

Practical Info

Paracetamol is a safe medication with no serious adverse events. Normal dose is 1g. High-dose paracetamol (6 g per day x 3 days) for all patients did not lead to overall benefits.

For those with dysphagia, antipyretics can be given orally or via a nasogastric tube or suppository.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Net benefits of implementing the bundled approach to fever, sugar and swallow care including monitoring and management for those with temperature >37.5 degrees celsius in the QASC study (Middleton et al. 2011 *[256]*).

Therapeutic hypothermia probably has little or no difference on death or disability and may increase length of stay, but further research is needed. (den Hertog et al. 2009*[260]*)

Paracetamol reduces body temperature within 24 hours, reduces risk of early death and has no serious adverse events although

it seems to have no overall impact on functional outcome (Chen et al. 2018 *[264]*).

Certainty of the Evidence High

For the comparison FeSS vs no FeSS the quality of evidence is very high, as the evidence is from a large single-blinded RCT with minimal bias. The Drury et al. study provides a systematic evaluation of records and data that documents current stroke management practices, indicating the need for urgent behaviour change.

Therapeutic hypothermia is based on small pilot trials at risk of bias.

The two main trials of Paracetamol were of high quality. Four other smaller trials were of moderate quality. (Chen et al. 2018*[264]*).

Preference and values No substantial variability expected

No variability in values and preferences expected.

Resources and other considerations No important issues with the recommended alternative

Resources considerations

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

Implementation considerations

There is a clinical indicator collected in the National Stroke Audit to determine whether paracetamol was administered for patients within 1 hour of the recorded temperature of greater than or equal to 37.5°C.

Rationale

Fever is an important indicator of developing sepsis which requires specific investigation and treatment. The QASC trial showed high-quality evidence that monitoring and treatment of fever ≥ 37.5 °C improve outcomes at 90 days, when used as part of a bundle of care.

Paracetamol reduces body temperature and reduces the risk of early death. However, there was no benefits of routine paracetamol for all patients based on the PIAS trials so paracetamol should only be used where fever is identified.

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Paracetamol
Comparator: Placebo

Summary

A Cochrane review (Den Hertog et al 2009 *[260]*) included five pharmacological temperature reduction trials and three physical cooling trials (total of 423 participants). No benefits were found for either strategy in terms of reducing the risk of death or dependency (odds ratio (OR) 0.9, 95% confidence interval (CI) 0.6 to 1.4) or death (OR 0.9, 95% CI 0.5 to 1.5).

One large subsequent trial (Den Hertog et al 2009 *[259]*) including 1400 patients found no benefits for routine high dose paracetamol but some groups (such as those with fever) may benefit based on subgroup analysis.

An updated meta-analysis including this trial reported paracetamol reduces body temperature within 24 hours and reduces early risk of death but does not appear to impact overall functional outcomes within 3 months. (Chen et al. 2018 *[264]*)

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Paracetamol	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Disability: favourable outcome (mRS <= 2) [1] 9 Critical	Relative risk 1.07 (CI 95% 0.91 — 1.27) Based on data from 1,755 patients in 4 studies. (Randomized controlled) Follow up: 30 or 90 days.	367 per 1000	393 per 1000 Difference: **26 more** per 1000 (CI 95% 33 fewer — 99 more)	**High** Majority of data is from 2 large high quality studies so certainty level remains high. [2]	More patients in the paracetamol group than in the placebo group improved beyond expectation, but this was not statistically significant therefore paracetamol has little or no difference on disability (mRS) when compared with placebo
Mortality 7 or 14 days 8 Critical	Relative risk 0.62 (CI 95% 0.41 — 0.93) Based on data from 1,743 patients in 4 studies. (Randomized controlled) Follow up: 7 or 14 days.	65 per 1000	40 per 1000 Difference: **25 fewer** per 1000 (CI 95% 38 fewer — 5 fewer)	**High** Majority of data is from 2 high quality trials so certainty level remains high. [3]	Paracetamol reduces early risk of death
Serious adverse events at discharge 8 Critical	Relative risk 0.9 (CI 95% 0.66 — 1.22) Based on data from 1,654 patients in 2 studies. (Randomized controlled) Follow up: At discharge.	12 per 1000	11 per 1000 Difference: **1 fewer** per 1000 (CI 95% 4 fewer — 3 more)	**High**	Paracetamol may have little or no difference on serious adverse events

1. Reported estimates are odds of a favourable outcome - so odds ratios > 1 mean the intervention improves outcomes
2. **Risk of Bias: No serious.** Main two trials contributing majority of data are both high quality trials with no risk of bias.. **Inconsistency: No serious. Indirectness: No serious.** The analysis plan for PAIS was changed from a fixed dichotomy of the mRS to the sliding dichotomy analysis during the trial, neither showed an effect of paracetamol on functional outcome. . **Imprecision: No serious. Publication bias: No serious.**
3. **Risk of Bias: No serious.** Main two trials contributing majority of data are both high quality trials with no risk of bias.. **Inconsistency: No serious. Indirectness: No serious.** Liver disease may not be picked up within first 3 months but unlikely. **Imprecision: No serious. Publication bias: No serious.**

Acute stroke telehealth services

Acute stroke telehealth services usually focus on diagnosis and decision making for thrombolysis therapy but are also important for other treatment advice. Seventy-two percent of acute services report having access to onsite telehealth facilities which had been used for clinical decision making in the previous six months (80% of sites in an inner regional location and 100% of sites in an outer regional location) (Stroke Foundation 2019 *[28]*). Many states (e.g. Victoria, New South Wales, South Australia, Western Australia and Tasmania) have, or are in the stages of implementing acute stroke telehealth services.

Strong recommendation

New

DRAFT RECOMMENDATION FOR PUBLIC CONSULTATION JUNE 2021

In hospitals without onsite 24/7 stroke medical specialist availability, telestroke systems should be used to assist in patient assessment and decision making regarding acute thrombolytic therapy and possible transfer for endovascular therapy. This system should include the ability for stroke medical specialists to access remote brain imaging scans and preferably include the use of videoconferencing facilities or, if not possible, ensure the diagnosis and management discussions between local clinicians/family/patient occurs via a telephone consultation. (Lazarus et al 2020 *[265]*; Bladin et al 2020 *[268]*)

Practical Info

Telestroke systems incorporating videoconferencing vary in cost and complexity, and the needs of any local or state-wide system must be carefully considered in selecting the most appropriate system.

Dedicated training and resources to implement and sustain a telestroke system is crucial.

The impact of interacting with patients and their family via videoconference or simple telephone systems can be different when compared to face-to-face consultation, and clinicians may need to adapt their communication. Clearly documented treatment plans are also useful. Any interaction should occur concomitantly with clinical care.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Acute telestroke services improved timeliness of therapy and improved functional outcomes while also lowering risks of mortality compared to usual stroke care in rural and regional hospitals. Telestroke appears to also improve the rate of thrombolysis. Other benefits have been reported such as improved access to stroke medical specialists for stroke diagnosis and treatment advice. Telestroke services delivered to rural and regional hospitals may provide similar onset-to-treatment times compared to non-ambulance patients presenting to metropolitan stroke specialist centres.

Certainty of the Evidence

Low

The certainty of the evidence is low. This is due in part to the challenges of undertaking systems level studies.

Preference and values

No substantial variability expected

We believe the use of telehealth as a means of connecting to a stroke specialist doctor (when in-person care is unavailable) is likely to be preferred by all patients/family and little variation is expected.

Resources

No important issues with the recommended alternative

Few economic evaluations of telestroke have been undertaken, mainly in Europe and North America, and cost-effectiveness has been mainly determined on the basis of simulation modelling of a societal and hospital perspective. (Wechsler et al. 2017 *[270]*) Two previous economic evaluations conducted alongside historical controlled studies of stroke telemedicine in the United

States that have used patient-level data have shown evidence that telestroke is cost-effective. (Nelson et al. 2016 *[271]*; Whetten et al. 2018 *[272]*). In preliminary, simulated cost-effectiveness research undertaken within the context of Australia, acute telestroke provides benefits at an acceptable additional cost. (Moodie et al. 2018 *[273]*; Sheppard et al. 2016 *[274]*)

Equity No important issues with the recommended alternative

Acute telestroke improves equity in regional and rural settings where there is no or limited access to onsite specialist medical staff for acute stroke.

Acceptability Important issues, or potential issues not investigated

Most telestroke systems are reported to be acceptable to hub and spoke sites. However, technology solutions do require appropriate infrastructure designed for medical consultations and includes stable access to secure and high-quality internet services which, if varies, will affect user experience and acceptance. (Bagot et al 2016 *[218]*)

Feasibility Important issues, or potential issues not investigated

Telestroke systems incorporating videoconferencing vary in cost and complexity and may require dedicated training and resources to implement and ensure optimal access. However, there is sufficient published experience across multiple countries and health services to support the feasibility and maintenance of acute telestroke services.

Rationale

Telestroke systems improve access to thrombolytic therapy in non-stroke specialist services and improves workflow metrics across most studies, although the underlying evidence is weak reflecting the challenges in undertaking systems and implementation research. Greater equity was an important consideration in developing this strong recommendation.

Telehealth can be used for acute assessment as well as consultation by stroke specialists for general treatment advice (see also recommendations for telehealth in rehabilitation discussed in Chapter 5: Rehabilitation). Technology considerations along with staffing and education needs are important practical aspects in selecting and implementing the most appropriate system.

Clinical Question/ PICO

Population: People with suspected acute stroke
Intervention: Integrated telestroke program
Comparator: Usual care

Summary

Lazarus et al (2020)*[265]* undertook a review of the effects of telestroke in non-urban centres. They included 19 studies (n=28,496) of which four were RCTs (n=492), 12 non-randomised studies and three pre–post-studies. Two studies evaluated prehospital (ambulance) systems and 17 involved hub-and-spoke hospital network. 14 studies were pooled quantitatively. Ten studies were conducted in Europe (eight in Germany, one in Spain, and one in UK), seven in North America (six in the USA and one in Canada), and two in Asia-Pacific (Australia and Thailand). Videoconference was utilized in 15 studies, telephone in eight studies, and both interventions were implemented in four studies. Telestroke models increased the number of patients treated within 3 hours of onset (OR 2.15 95%CI 1.37-3.40; three studies (n=629); moderate certainty evidence reported by authors), reduced the onset-to-treatment time (MD −27.97 mins, 95% CI −35.51 to −20.42; six studies (n=8112); low certainty evidence), lowered the risk of in-hospital mortality (OR 0.67, 95% CI 0.52 to 0.87; four studies (n=6,919); very low certainty evidence), and improved functional outcomes at 3 months (OR 1.29, 95%CI 1.01 to 1.63; three studies (n=3,854); very low certainty evidence). There was no effect on sICH (OR 1.27, 95%CI 0.65 to 2.49; six studies (n=1,437); low certainty evidence). Telestroke may increase the rate of IV thrombolysis (OR 2.60 95%CI 0.89-7.57, p=0.08; four studies (n=7,665); Very low certainty evidence). In sensitivity analysis removing the most extreme result resulted in a significant effect (OR 1.56, 95% CI 1.01 to 2.41). There was no different in the rate with video versus teleconference use. When compared to walk-in patients at stroke centers (three studies, 718 patients) implementation resulted in a reduction of onset to treatment by 21.10 min (95% CI −28.30 to −13.89 min; p <0.001). Again sensitivity analysis did not alter the effect and there was no difference in type of connection used (videoconference vs telephone).

McDermott et al (2019)*[267]* included 25 studies of which 6 related to telestroke. Pooling studies only enrolling ischaemic stroke patients revealed a non-significant increase in thrombolysis rates with telestroke (RR 1.58, 95%CI 0.72 to 3.47)and heterogeneity was very high (I^2=96.2%).

Baratloo et al (2018)*[266]* included 26 studies (n=6,605), 2 RCTs, 8 prospective and 16 retrospective observational studies. There was no significant difference with in-hospital mortality (OR 1.21, 95%CI 0.98 to 1.49; 18 studies, n=4907) or mortality at 90 days (OR 1.08, 95%CI 0.85 to 1.37; 9 studies). There was no difference in sICH (OR 1.10, 95%CI 0.79 to 1.53; 21 studies, n=4022) or onset to treatment times (MD −5.90 minutes, 95%CI −13.23 to 1.42).

All reviews appear consistent with mostly similar benefits and risks with the use of telestroke.

In Australia the Victorian Stroke Telemedicine (VST) project conducted a historical controlled cohort study in which a slightly higher proportion of patients with ischaemic stroke who arrived within 4.5 hours of symptom onset received thrombolysis during the intervention than during the control period (37% v 30%, p=0.06) with some sites commencing thrombolysis for the first time. Workflow timeliness improved significantly (median door-to-CT scan time: 25 min v 34 min, p<0.001; door-to-needle time for stroke thrombolysis: 73 min v 102 min, p<0.001). In-hospital mortality and symptomatic ICH were significantly lower (6% v 20%; 4% v 16% respectively) during the intervention period. (Bladin et al. (2020)*[268]*)

Another Australian study by Kashida et al (2021)*[275]* conducted an observational study from 2017-2019 (n=433 confirmed ischaemic stroke or TIA; 243 in phase 1 and 190 in phase 2). None of the workflow metrics (e.g. door-to-imagine, door-to-call, door-to-decision) were statistically significant. The authors noted the challenges with studies of this nature including high staff turnover and work-force shortages.

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Telestroke	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
rate of IV thrombolysis 8 Critical	Odds Ratio 2.6 (CI 95% 0.89 — 7.57) Based on data from 7,665 patients in 4 studies. (Observational (non-randomized))	49 per 1000	118 per 1000 Difference: **69 more** per 1000 (CI 95% 4 fewer — 232 more)	**Very low** Due to very serious risk of bias, Due to serious inconsistency, Due to very serious imprecision [1]	We are uncertain whether telestroke increases or decreases rate of iv thrombolysis
In-hospital mortality 8 Critical	Odds Ratio 0.67 (CI 95% 0.52 — 0.87) Based on data from 8,112 patients in 6 studies. (Observational (non-randomized))	53 per 1000	36 per 1000 Difference: **17 fewer** per 1000 (CI 95% 25 fewer — 7 fewer)	**Very low** Due to serious risk of bias, Due to serious imprecision [2]	Telestroke may decrease in-hospital mortality
mRS 0-2 90 days 8 Critical	Odds Ratio 1.29 (CI 95% 1.01 — 1.63) Based on data from 3,854 patients in 3 studies. (Observational (non-randomized)) Follow up: 90 days.	446 per 1000	509 per 1000 Difference: **63 more** per 1000 (CI 95% 2 more — 122 more)	**Very low** Due to very serious inconsistency, Due to serious indirectness, Due to serious imprecision [3]	Telestroke may increase mRS 0-2 slightly
sICH 7 Critical	Odds Ratio 1.27 (CI 95% 0.65 — 2.49) Based on data from 1,437 patients in 6 studies. (Observational (non-randomized))	25 per 1000	32 per 1000 Difference: **7 more** per 1000 (CI 95% 9 fewer — 35 more)	**Low** Due to serious risk of bias, Due to very serious imprecision [4]	Telestroke may have little or no difference on sICH

Outcome Timeframe	Study results and measurements	Comparator Usual care	Intervention Telestroke	Certainty of the Evidence (Quality of evidence)	Plain text summary
Patients treated within 3 hrs 8 Critical	Odds Ratio 2.15 (CI 95% 1.37 — 3.4) Based on data from 629 patients in 3 studies. (Observational (non-randomized))	593 per 1000	758 per 1000 Difference: **165 more** per 1000 (CI 95% 73 more — 239 more)	**Moderate** Due to risk of bias, Due to imprecision [5]	Telestroke may increase patients treated within 3 hrs slightly
Onset-to-treatment time 7 Critical	Measured by: time Lower better Based on data from: 8,112 patients in 6 studies.		Difference: **MD 27.97 lower** (CI 95% 35.51 lower — 20.42 lower)	**Low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias [6]	Telestroke may decrease onset-to-treatment time slightly

1. **Risk of Bias: Very serious. Inconsistency: Serious. Indirectness: No serious. Imprecision: Very serious. Publication bias: Serious.**
2. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. Publication bias: Serious.**
3. **Inconsistency: Very serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**
4. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. Publication bias: No serious.**
5. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. Publication bias: No serious.**
6. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. Publication bias: Serious.**

Clinical Question/ PICO

Population: Adults with acute or suspected stroke
Intervention: Acute telestroke connections using video conference
Comparator: Telestroke using telephone contact alone

Summary

Lazarus et al (2020)*[265]* included 19 studies (n=28,496) of which four were RCTs (n=492), 12 non-randomised studies and three pre–post-studies. Videoconference was utilized in 15 studies, telephone in eight studies, and both interventions were implemented in four studies. There was no different in the rate of thrombolysis with videoconference versus telephone use (OR 1.27, 95%CI 0.74 to 2.17; two studies, n=275). There was also no difference in onset-to-treatment times (MD 2.62, 95%CI -13.60 to 18.83; three studies, n=319; moderate heterogenity I^2=70%).

The one major RCT (Meyer et al. 2008) included in Lazarus et al. (2020) review reported no difference between group receiving videoconferencing compared to telephone for sICH, mRS 0-1 or mortality (after was adjusted for baseline NIHSS) within 90 days or at 6 and 12 months. However, correct treatment decisions were made more often using telemedicine (98% vs. 82%, OR 10.9, 95%CI 2.7 to 44.6, p=0.0009).

Outcome Timeframe	Study results and measurements	Comparator Telestroke with telephone	Intervention Telestroke with videoconferenci ng	Certainty of the Evidence (Quality of evidence)	Plain text summary
rate of IV thrombolysis	Odds Ratio 1.27 (CI 95% 0.74 — 2.17) Based on data from 275	239	285	**Low** Due to serious risk of bias, Due to	Telestroke with videoconferencing may have little or no

Outcome Timeframe	**Study results and measurements**	**Comparator** Telestroke with telephone	**Intervention** Telestroke with videoconferencing	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
8 Critical	patients in 2 studies. (Randomized controlled)	per 1000 Difference: **46 more** per 1000 (CI 95% 50 fewer — 166 more)	per 1000	serious imprecision [1]	difference on rate of IV thrombolysis compared to phone consultation
Onset-to-treatment time 7 Critical	Measured by: time High better Based on data from: 319 patients in 3 studies.	Difference: **MD 2.62 higher** (CI 95% 13.6 lower — 18.83 higher)		**Very low** Due to serious risk of bias, Due to very serious risk of bias, Due to serious imprecision [2]	We are uncertain whether telestroke with videoconferencing increases or decreases onset-to-treatment time compared to telephone consultation

1. **Risk of Bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.**
2. **Risk of Bias: Very serious. Inconsistency: No serious.** The magnitude of statistical heterogeneity was high, with I^2:70%., Point estimates vary widely. **Indirectness: No serious. Imprecision: Serious.** Low number of patients.

Head position

Weak recommendation

New

DRAFT RECOMMENDATION FOR PUBLIC CONSULTATION JUNE 2021

Patients with acute stroke, while in bed and not receiving nasogastric feeding, may be managed in any position during the first 24 hours after hospital admission.

Practical Info

Patient comfort and preferences should be considered when offering bed rest positions in acute stroke. Patient preferences may vary dependent on activities undertaken e.g. resting in bed compared to having visitors. Communication may be easier with head raised or sitting up.

Patients should be nursed at least 30 degrees head up while receiving nasogastric tube feeds to reduce risk of aspiration.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Lying flat (0 degrees) positioning of patients with acute stroke while in bed, probably has little or no effect on degree of disability, occurrence of death or disability at 90 days, and the rate of serious adverse outcomes when compared to a head up position (Anderson et al 2017 *[276]*).

Certainty of the Evidence

Moderate

The certainty of evidence is moderate due to evidence from a single randomised control trial.

Preference and values

No substantial variability expected

We do not believe there will be significant variation in preferences given the lack of difference between positions.

Resources and other considerations

No important issues with the recommended alternative

No cost effectiveness literature was identified. Given there is no difference between positions there are no resource implications.

Rationale

Anderson et al 2017 *[276]* observed that lying-flat positioning, which is proposed to improve cerebral blood flow after acute stroke, had no effect on outcomes compared to a head up position. Patients lying-flat were slightly less likely to maintain the position for 24 hours (87% vs 95%). However, it is noted that the median stroke severity was mild (National Institutes of Health Stroke Scale score median = 4), 12% of cohort were lost to follow up or refused the intervention, demonstration of vessel occlusion was not required, and the intervention commenced a median 7 hours after arrival to hospital and 14 hours from symptom onset. Observational data suggests lying-flat may improve cerebral blood flow in patients with large vessel occlusion (Wojner-Alexander et al 2005 *[278]*) and trials in this specific patient group are ongoing. Patient comfort and preferences should be considered when offering bed rest positions in acute stroke.

Clinical Question/ PICO

Population: Adults with stroke
Intervention: Supine positioning
Comparator: Sitting up

Summary

Anderson et al (2017)*[276]* conducted a cluster-randomised study with 11,093 patients across 114 hospitals. Patients were either allocated to lying-flat or head up position soon after hospital admission (mean 7 hours) and maintained for 24 hours. No significant shift in the distribution of disability at 90 days was found (OR 1.01, 95% CI 0.92 to 1.10; n= 9748). There was no difference in death at 90 days (OR 0.98, 95% CI 0.85 to 1.114) or any other secondary outcome except scores on visual analogue scale of the EQ-5D favouring lying-flat (p=0.009). No difference was found in subgroup analysis (particularly ischaemic stroke vs intracerebral heamorrhage) or sensitivity analysis, and post-hoc analysis suggested no heterogeneity according to stroke severity or time from onset to commencing intervention. Patients lying-flat were slightly less likely to maintain the position for 24 hours (87% vs 95%). However, the median stroke severity was mild (National Institutes of Health Stroke Scale score median 4), 12% of the cohort was either lost to follow-up or refused the intervention, demonstration of vessel occlusion was not required, the study had a large percentage ofischaemic stroke patients (85.5% of the cohort with the rest intracerebral heamorrhage, stroke mimics and TIA), and the intervention commenced a median of 14 hours post-symptom onset.

A review by Hifumi et al (2021)*[277]* investigating head positioning with two studies and 11,187 participants, dominated by the large international study by Anderson et al (2017)*[276]* and another small study (n=94). The review found no difference between lying-flat and head up positions for degree of disability (RR 0.86, 95% CI 0.56 to 1.32; 2 studies, n= 9832; moderate heterogeneity I^2= 51%; low certainty evidence), 90 day mortality (RR 1.00, 95% CI 0.87 to 1.14; 2 studies, n= 10945; high certainty evidence) and recurrent ischemic stroke (RR 0.81, 95% CI 0.14 to 4.64; 1 study, n= 91; moderate certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** Sitting up	**Intervention** Supine positioning	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Distribution of disability 90 days 8 Critical	Odds Ratio 1.01 (CI 95% 0.92 — 1.1) Based on data from 9,748 patients in 1 studies. [1] (Randomized controlled)	CI 95%		**Moderate** Due to imprecision [2]	Lying flat for 24 hours after hospital admission probably has little or no difference on disability compared to head up position
Death or disability (mRS 3-6) 90 days 8 Critical	Odds Ratio 0.94 (CI 95% 0.85 — 1.05) Based on data from 9,738 patients in 1 studies. [3] (Randomized controlled)	**389** per 1000	**374** per 1000 Difference: **15 fewer** per 1000 (CI 95% 38 fewer — 12 more)	**Moderate** Due to imprecision [4]	Lying flat for 24 hours after hospital admission probably has little or no difference on death or disability compared to head up position
Serious adverse events 90 days 8 Critical	Odds Ratio 1.05 (CI 95% 0.91 — 1.2) Based on data from 11,093 patients in 1 studies. [5] (Randomized controlled)	**135** per 1000	**141** per 1000 Difference: **6 more** per 1000 (CI 95% 11 fewer — 23 more)	**Moderate** Due to imprecision [6]	Lying flat for 24 hours after hospital admission probably has little or no difference on serious adverse events compared to head up position

1. Primary study[276]. **Baseline/comparator:** Control arm of reference used for intervention.
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. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**
3. Primary study[276]. **Baseline/comparator:** Control arm of reference used for intervention[276].
4. **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. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**

5. Primary study[276]. **Baseline/comparator:** Control arm of reference used for intervention[276].
6. **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. Imprecision: Serious.** Only data from one study. **Publication bias: No serious.**

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
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
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
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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