

# **Clinical Guidelines for Stroke Management 2017**

**Chapter 3 of 8:  
Acute medical and surgical management**

**Main editor**

Stroke Foundation

**Publishing Information**

v5.0 published on 07.09.2017

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

**Contact**

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

**Sponsors/Funding**

The Stroke Foundation gratefully acknowledges the financial assistance provided by the Australian Government Department of Health. The development of the final recommendations has not been influenced by the views or interests of the funding body.

**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. The Clinical Guidelines can be viewed at [www.informme.org.au](http://www.informme.org.au) - Citation: Stroke Foundation. Clinical Guidelines for Stroke Management 2017. Melbourne Australia. © No part of this publication can be reproduced by any process without permission from the Stroke Foundation. August 2017.

# Sections

Summary of recommendations.....	4
1 - Introduction .....	13
2 - Methodology.....	16
3 - Clinical questions .....	19
4 - Acute medical and surgical management - overview.....	20
5 - Stroke unit care.....	21
6 - Assessment for rehabilitation.....	39
7 - Palliative care.....	41
8 - Reperfusion therapy .....	46
8.1 - Thrombolysis.....	46
8.2 - Neurointervention .....	58
9 - Dysphagia.....	74
10 - Antithrombotic therapy.....	93
11 - Acute blood pressure lowering therapy.....	102
12 - Surgery for ischaemic stroke and management of cerebral oedema .....	108
13 - Intracerebral haemorrhage (ICH) management .....	116
13.1 - Medical interventions .....	116
13.2 - Surgical interventions .....	123
14 - Oxygen therapy.....	131
15 - Neuroprotection.....	137
16 - Glycaemic therapy .....	138
17 - Pyrexia management .....	146
18 - Glossary and abbreviations.....	154
References .....	160

# Summary of recommendations

## 1 - Introduction

## 2 - Methodology

## 3 - Clinical questions

## 4 - Acute medical and surgical management - overview

## 5 - Stroke unit care

### Strong Recommendation

All stroke patients should be admitted to hospital and be treated in a stroke unit with an interdisciplinary team. (SUTC 2013 [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 [157])

## 6 - Assessment for rehabilitation

### Info Box

#### 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 [22]).
- 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.

## 7 - 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 [28])

### 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.

## 8 - Reperfusion therapy

### 8.1 - Thrombolysis

### Strong Recommendation

- For patients with potentially disabling ischaemic stroke who meet specific eligibility criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) should be administered. (Wardlaw et al. 2014 [37]; Emberson et al. 2014 [38])
- Thrombolysis should commence as early as possible (within the first few hours) after stroke onset but may be used up to 4.5 hours after onset. (Wardlaw et al. 2014 [37]; Anderson et al. 2016 [40])

### 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.

## 8.2 - Neurointervention

### Strong Recommendation

For patients with ischaemic stroke caused by a large vessel occlusion in the internal carotid artery, proximal cerebral artery (M1 segment), or with tandem occlusion of both the cervical carotid and intracranial arteries, endovascular thrombectomy should be undertaken when the procedure can be commenced within six hours of stroke onset. (Goyal et al. 2016 [55])

### Strong Recommendation

Eligible stroke patients should receive intravenous thrombolysis while concurrently arranging endovascular thrombectomy, with neither treatment delaying the other. (Goyal et al. 2016 [55])

### Strong Recommendation

In selected stroke patients with occlusion of the basilar artery, endovascular thrombectomy should be undertaken. (Kumar et al. 2015 [65])

### Practice Statement

#### **Consensus-based recommendations**

For stroke patients, endovascular thrombectomy may be considered in the following situations based on individual patient and advanced imaging factors:

- commencement of procedure beyond 6 hours (but within 24 hours) from stroke onset
- occlusion in more distal middle cerebral artery branches (M2 segment).

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](http://CCINR.org.au)).

## 9 - Dysphagia

### Practice Statement

#### **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 [93])

Weak Recommendation

People with acute stroke should have their swallowing screened, using a validated screening tool, by a trained healthcare professional. (Poorjavad et al. 2014 [82])

Weak 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 [85]; O'Horo et al. 2015 [87])

Strong Recommendation

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 [77])

Weak Recommendation

AGAINST

For stroke survivors with dysphagia, non-invasive brain stimulation should only be provided within a research framework. (Pisegna et al. 2016 [79])

Weak Recommendation

AGAINST

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 [76])

Weak Recommendation

AGAINST

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 [71])

Weak Recommendation

AGAINST

For stroke survivors with dysphagia, pharyngeal electrical stimulation is not routinely recommended. (Bath et al. 2016 [73]; Scutt et al. 2015 [74])

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](#).

## 10 - 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 [100])

Strong Recommendation

AGAINST

Acute antiplatelet therapy should not be given within 24 hours of alteplase administration. (Zinkstok et al. 2012 [104])

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 [97]; Whiteley et al. 2013 [103])

Weak Recommendation

Aspirin plus clopidogrel may be used in the short term (first three weeks) in high-risk patients with minor ischaemic stroke or TIA to prevent stroke recurrence. (Wong et al. 2013 [102])

## 11 - 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 [108])

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 [111]; Qureshi et al. 2016 [109])

Weak Recommendation

Pre-existing antihypertensive medication may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 [108])

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.

## 12 - Surgery for ischaemic stroke and management of cerebral oedema

Strong 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 [114])

Weak 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. (Back et al. 2015 [112]; Jüttler et al. 2014 [113])

Weak Recommendation

**AGAINST**

Corticosteroids are not recommended for management of stroke patients with brain oedema and raised intracranial pressure. (Sandercock et al. 2011 [115])

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.

Practice Statement

**Consensus-based recommendation**

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

## 13 - Intracerebral haemorrhage (ICH) management

### 13.1 - 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 [121])
- 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 [121])

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 [124]; Connolly 2016 [125])

Strong Recommendation

**AGAINST**

For stroke patients with intracerebral haemorrhage previously receiving antiplatelet therapy, platelet transfusion should not be administered. (Baharoglu et al. 2016 [122])

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](#)).

## 13.2 - Surgical interventions

Weak Recommendation **AGAINST**

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 [126]; Gregson et al. 2012 [129])

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 [129]; Naff et al. 2011 [130])

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.

## 14 - Oxygen therapy

Weak Recommendation **AGAINST**

For acute stroke patients who are not hypoxic, the routine use of supplemental oxygen is not recommended. (Ali et al. 2014 [134]; Roffe et al. 2011 [135])

Weak Recommendation **AGAINST**

For acute ischaemic stroke patients, hyperbaric oxygen therapy is not recommended. (Bennett et al. 2014 [133])

Practice Statement

### Consensus-based recommendation

Stroke patients who are hypoxic (i.e. < 95% oxygen saturation) should be given supplemental oxygen.

## 15 - 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.

## 16 - 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 [157])

### 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 [151]; Ntaios et al. 2014 [150])

## 17 - 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 [157])

### Weak Recommendation

Stroke patients with fever  $\geq 37.5$  °C may be treated with paracetamol as an antipyretic therapy. (den Hertog et al. 2009 [160]; Middleton et al. 2011 [157])

## 18 - Glossary and abbreviations

## 1 - 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. The existing Clinical Guidelines for Stroke Management 2010 were approved by the National Health and Medical Research Council (NHMRC) in September 2010.

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 5-years. As a result, the Stroke Foundation was contracted by the Australian Government Department of Health to update the Clinical Guidelines for Stroke Management 2010, commencing July 2015.

The *Clinical Guidelines for Stroke Management 2017* updates and supersedes the Clinical Guidelines for Stroke Management 2010. 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 (Grading of Recommendations Assessment, Development and Evaluation), and an innovative guideline development and publishing platform, known as MAGICapp (Making Grade the Irresistible Choice). 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 2017* 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, 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 management, 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); or
- Primary prevention of stroke. (Refer to *Guidelines for the management of absolute cardiovascular disease risk 2012* (National Vascular Disease Prevention Alliance [5]) - <https://informme.org.au/en/Guidelines/Guidelines-for-the-assessment-and-management-of-absolute-CVD-risk>, and *Guideline for the diagnosis and management of hypertension in adults 2016* (Heart Foundation [6]) - <https://www.heartfoundation.org.au/for-professionals/clinical-information/hypertension>).

### Target audience

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

### Development

The Guidelines are published in eight separate chapters:

[Pre-hospital care](#)

[Early assessment and diagnosis](#)

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

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

### Use

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

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

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

Refer to the document on [InformMe](#) that summarises all the Clinical Guidelines recommendations.

### Aboriginal and Torres Strait Islander People

Refer to the document on [InformMe](#) for information regarding Aboriginal and Torres Strait Islander people.

### Decision-making

Stroke survivors should be treated in accordance with the principles of shared decision-making contained within the *Acute Stroke Care Clinical Standard*, *Acute Stroke Services Framework 2015* 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 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 guidelines recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 25 July 2017, 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.

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. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

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.

#### Funding

The Stroke Foundation gratefully acknowledges the financial assistance provided by the Australian Government Department of Health. The development of the final recommendations has not been influenced by the views or interests of the funding body.

#### Citation

Stroke Foundation. Clinical Guidelines for Stroke Management 2017. Melbourne Australia.

© No part of this publication can be reproduced by any process without permission from the Stroke Foundation. August 2017.

## 2 - Methodology

### Brief summary of GRADE

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

GRADE methodology includes four factors to guide the development of a recommendation and determine the strength of that recommendation:

1. The balance between desirable and undesirable consequences.
2. Confidence in the estimates of effect (quality of evidence).
3. Confidence in values and preferences and their variability (clinical and consumer preferences).
4. Resource use (cost and implementation considerations).

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

### Strength of recommendations

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

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

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

The implications of a strong or weak recommendation for a particular treatment are summarised in the GRADE handbook as follows:

*Table 1: Implications of GRADE recommendation categories (for a positive recommendation) for patients, clinicians and policy makers. Source: GRADE Handbook (<http://gdt.guidelinedevelopment.org/app/handbook/handbook.html>)*

	Strong Recommendation	Weak Recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this 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 his values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences. Clinicians may expect to spend more time with patients who are uncertain 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 debate and involvement of many stakeholders. Policies are more likely to vary between regions. Performance indicators would have to focus on the fact that there is a need for deliberation about the management options in 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.

### 3 - 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 Does the use of antithrombotic therapy within first 48 hours improve outcomes in acute stroke?
- 3.6 Does the use of acute blood pressure lowering therapy improve outcomes for people with stroke?
- 3.7 Does the use of surgical interventions improve the outcomes for people with acute ischemic stroke?
- 3.8 What interventions improve outcomes in acute stroke patients with raised intracranial pressure?
- 3.9 Does the administration of medical interventions improve outcomes after acute haemorrhagic stroke?
- 3.10 Do surgical interventions improve outcomes after acute haemorrhagic stroke?
- 3.11 Does oxygen therapy improve outcomes in stroke patients who are not hypoxic?
- 3.12 Does glycaemic therapy improve outcomes in stroke patients with hyperglycaemia?
- 3.13 Does the use of neuroprotective agents improve outcomes for people with acute stroke?
- 3.14 What interventions improve outcomes in stroke survivors with pyrexia?

## 4 - 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*).

## 5 - 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 2016, the percentage of patients receiving stroke unit care has not increased (Stroke Foundation 2014 [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 (SUTC 2013 [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 87 stroke units managing acute stroke patients (a small number of these also managing rehabilitation) but only 12 stroke rehabilitation units (units reporting co-location of stroke beds) as reported in the National Stroke Audits in 2015 and 2016.

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

- location in a geographically discrete unit;
- 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 Acute 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. (SUTC 2013 [7])

### Practical Info

Further details about the definition of a stroke unit can be found in the [National Acute Stroke Services Framework 2015 \[8\]](#) available from the Stroke Foundation website.

## Key Info

### 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: 44 fewer deaths, 54 fewer deaths or being dependent, and 64 fewer deaths or being under institutional care, with every 1000 stroke patients (SUTC 2013 [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 (SUTC 2013 [7]).

### Quality of evidence

High

The overall quality of evidence is high (SUTC 2013 [7]).

### 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

#### Resources considerations

Two economic evaluations of stroke unit care have been 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 DALY avoided when compared to care provided on a general ward (cost reference year 1997) (Mihalopoulos et al. 2005 [105]).

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]).

There is evidence that the costs of stroke unit care can be equivalent to conventional care and can be cost-effective for prevention of adverse health events. In one 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]). In a study conducted in the UK, it was found that stroke unit care was cost-effective per death and nursing home admission avoided (ICER £496, reference year 1997/1998), but was not cost-effective (given a willingness to pay of £30,000 per QALY gained) when compared to domiciliary care, costing an additional £64,097 per QALY gained (cost reference year 1997/1998) (Patel et al. 2004 [20]).

#### Implementation considerations

The Australian National Acute Stroke Services Framework clearly defines the services, infrastructure and staff found in a stroke unit (Stroke Foundation 2015 [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 2013 Cochrane review based on 28 trials and 5855 patients (SUTC 2013 [7]). Stroke unit care must comprise at least four minimum criteria as outlined in the [Acute 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**

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

**Summary**

A Cochrane review conducted by the Stroke Unit Trialists' Collaboration (2013) [7] compared organised stroke unit care to alternative services. The review included 28 RCTs with 5855 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 mortality compared to conventional care (OR 0.76, 95% CI 0.66 to 0.88), and significantly reduced the odds of death or institutionalisation and death or dependency. Comparisons between different kinds of stroke wards generally did not provide strong evidence for particular forms of stroke unit organisation.

Sun et al. (2013) [8] also carried out a systematic review and meta-analysis comparing acute stroke unit care to conventional care in general medical wards. The 8 trials included in the main analysis were a subset of those included in the Cochrane review for the comprehensive stroke ward subgroup, excluding unpublished data and trials with short observation periods. Analysis of these 8 trials revealed a borderline significant effect on mortality (OR 0.84, 95% CI 0.70 to 1.00). This is a weaker finding than was seen in the Cochrane review. It may be explained by the inclusion of newer and unpublished studies in the 2013 Cochrane review. However, Sun et al. also mention an error in an earlier version of the Cochrane review that appears to be uncorrected in the 2013 review, where the number of deaths in the control group was incorrectly recorded for one trial. This error does raise some questions about the effect reported in the 2013 Cochrane review, suggesting the true effect may be slightly weaker.

Chan et al. (2013) [9] conducted a systematic review of comparisons between different forms of stroke unit care, i.e. comparisons of acute stroke units, rehabilitation units and comprehensive units which provide both acute care and rehabilitation. There were no randomised controlled trials that directly compared comprehensive stroke units to other forms of stroke unit, so the review included a meta-analysis which used indirect comparisons, a cross-sectional comparison and a 'before-and-after' study. The review found that comprehensive stroke units were associated with decreased death and dependency and shorter length of stay. However, the indirect nature of the evidence means that there is substantial uncertainty about these benefits.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Alternative services    Organised stroke unit care		Certainty in effect estimates (Quality of evidence)	Plain text summary
<b>Death by the end of scheduled follow-up</b> Up to 12 months  7 Critical	Odds Ratio 0.76 (CI 95% 0.66 - 0.88) Based on data from 5,855 patients in 28 studies. (Randomized controlled) Follow up 6 weeks to 12 months, median 12 months	<b>221</b> per 1000	<b>177</b> per 1000	<b>High</b> Sensitivity analysis based only on those trials with a low risk of bias: Stroke unit care was associated with a statistically non-significant reduction in the odds of death (OR 0.82, 95% CI 0.64	The people receiving organised inpatient (stroke unit) care were more likely to survive than those receiving less organised care.
		Difference: <b>44 fewer</b> per 1000 (CI 95% 63 fewer - 21 fewer)			

to 1.05; P = 0.12)<sup>1</sup>

**Death or institutional care by the end of scheduled follow-up**

Up to 12 months

7 Critical

Odds Ratio 0.76  
(CI 95% 0.67 - 0.86)  
Based on data from 4,840 patients in 23 studies.  
(Randomized controlled)  
Follow up Median follow-up of 1 year

**406**  
per 1000

**342**  
per 1000

Difference: **64 fewer** per 1000  
( CI 95% 92 fewer - 36 fewer )

**High**  
The sensitivity analysis based on those trials that used an unequivocally blinded assessment suggested that such bias has not seriously influenced the results.<sup>2</sup>

The people receiving organised inpatient (stroke unit) care were more likely to survive and return home than those receiving less organised care.

**Death or dependency by the end of scheduled follow-up**

up to 12 months

7 Critical

Odds Ratio 0.8  
(CI 95% 0.67 - 0.97)  
Based on data from 4,807 patients in 23 studies.  
(Randomized controlled)  
Follow up Median of 1 year

**611**  
per 1000

**557**  
per 1000

Difference: **54 fewer** per 1000  
( CI 95% 98 fewer - 7 fewer )

**High**  
The main methodological difficulty when using dependency as an outcome was the degree of blinding at final assessment and the potential for bias if the assessor was aware of the treatment allocation. The results were unchanged (OR 0.74, 95% CI 0.61 to 0.90; P = 0.002) when restricted to those trials in which an unequivocally blinded final assessment for all participants was undertaken<sup>3</sup>

The people receiving organised inpatient (stroke unit) care were more likely to survive and regain independence than those receiving less organised care.

**Death or dependency at 5-year follow-up**

Five year follow up

9 Critical

Odds Ratio 0.54  
(CI 95% 0.22 - 1.34)  
Based on data from 535 patients in 2 studies.<sup>4</sup>  
(Randomized controlled)  
Follow up 5 years

**859**  
per 1000

**767**  
per 1000

Difference: **92 fewer** per 1000  
( CI 95% 286 fewer - 32 more )

**Moderate**  
There is sustained benefit among stroke unit patients.<sup>5</sup>

There is probably sustained benefit among stroke unit patients.

**Death or dependency at**

Odds Ratio 0.7  
(CI 95% 0.27 - 1.8)

**900**

**863**

**Low**  
The summary

There is probably sustained benefit among

<p><b>10-year follow-up</b> 10 years 9 Critical</p>	<p>Based on data from 535 patients in 2 studies.<sup>6</sup> (Randomized controlled) Follow up 10 years</p>	<p>per 1000                      per 1000 Difference: <b>37 fewer</b> per 1000 ( CI 95% 192 fewer - 42 more )</p>	<p>results continue to favour stroke unit care but with increased heterogeneity and loss of statistical significance for the outcomes of death or dependency<sup>7</sup></p>	<p>stroke unit patients.</p>
<p><b>Length of stay in a hospital or institution or both</b> Until discharge 7 Critical</p>	<p>Based on data from: 4,115 patients in 18 studies. (Randomized controlled)</p>	<p>Difference: <b>SMD 0.15 fewer</b> ( CI 95% 0.32 fewer - 0.02 more )</p>	<p><b>Very Low</b> The calculation of a summary result for length of stay was subject to major methodological limitations.<sup>8</sup></p>	<p>More research is required in this area.</p>

- Risk of bias: No serious** . 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** .
- 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. ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: No serious** . **Publication bias: No serious** .
- 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. ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: No serious** . **Publication bias: No serious** .
- Systematic review [7] with included studies: Nottingham 1996, Trondheim 1991. **Baseline/comparator::** Control arm of reference used for intervention .
- Risk of bias: No serious** . There is unclear bias regarding concealment, blinding of outcome assesment and incomplete outcome data in the two trials included. ; **Inconsistency: Serious** . The magnitude of statistical heterogeneity was high, with I<sup>2</sup>: 72% . ; **Indirectness: No serious** . **Imprecision: No serious** . **Publication bias: No serious** .
- Systematic review [7] with included studies: Nottingham 1996, Trondheim 1991. **Baseline/comparator::** Control arm of reference used for intervention .
- Risk of bias: No serious** . There is unclear bias regarding concealment, blinding of outcome assesment and incomplete outcome data in the two trials included. ; **Inconsistency: Serious** . The magnitude of statistical heterogeneity was substantial, with I<sup>2</sup>: 62% . ; **Indirectness: No serious** . **Imprecision: Serious** . Wide confidence intervals ; **Publication bias: No serious** .
- Risk of bias: No serious** . Inadequate/lack of blinding of outcome assessors, resulting in potential for detection 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<sup>2</sup>:86-88 % . ; **Indirectness: No serious** . **Imprecision: No serious** . **Publication bias: No serious** .

## References

[7] Stroke Unit Trialists' Collaboration : Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 2013;(9): [Journal](#)

[8] Sun Y, Paulus D, Eyssen M, Maervoet J, Saka O : A systematic review and meta-analysis of acute stroke unit care: what's beyond the statistical significance?. BMC medical research methodology 2013;13 132 [Pubmed Journal](#)

[9] Chan DK, Cordato D., O'Rourke F., Chan DL, Pollack M., Middleton S., Levi C. : Comprehensive stroke units: a review of comparative evidence and experience. International Journal of Stroke 2013;8(4):260-4 [Journal](#)

### Clinical Question/ PICO

**Population:** Adults with stroke  
**Intervention:** Organised stroke unit care  
**Comparator:** General medical wards

Outcome Timeframe	Study results and measurements	Absolute effect estimates General medical wards    Organised stroke unit care		Certainty in effect estimates (Quality of evidence)	Plain text summary
<p><b>Death by the end of scheduled follow-up</b>                      Median follow-up of 12 months</p> <p>9 Critical</p>	<p>Odds Ratio 0.81                      (CI 95% 0.69 - 0.94)                      Based on data from 4,591 patients in 23 studies.                      (Randomized controlled)                      Follow up Median follow-up of 12 months</p>	<p><b>233</b>                      per 1000</p>	<p><b>197</b>                      per 1000</p> <p>Difference: <b>36 fewer</b> per 1000                      ( CI 95% 60 fewer - 11 fewer )</p>	<p><b>High</b>                      Two different models of care (comprehensive stroke ward, mixed assessment or rehabilitation ward) tended to be more effective than general medical ward care. However, for the comparison of rehabilitation stroke wards or mobile team care (peripatetic service) versus general medical wards there were no statistically significant differences. <sup>1</sup></p>	<p>The people receiving organised inpatient (stroke unit) care were more likely to survive than those receiving care in general medical wards.</p>
<p><b>Death or institutional care by the end of scheduled follow-up</b>                      Median follow-up of 12 months</p> <p>9 Critical</p>	<p>Odds Ratio 0.78                      (CI 95% 0.68 - 0.89)                      Based on data from 3,940 patients in 20 studies.                      (Randomized controlled)                      Follow up Median follow-up of 12 months</p>	<p><b>404</b>                      per 1000</p>	<p><b>346</b>                      per 1000</p> <p>Difference: <b>58 fewer</b> per 1000                      ( CI 95% 88 fewer - 28 fewer )</p>	<p><b>High</b>                      Two different models of care (comprehensive stroke ward, mixed assessment or rehabilitation ward) tended to be more effective than general</p>	<p>The people receiving organised inpatient (stroke unit) care were more likely to survive and return home than those receiving care in general medical wards.</p>

<p><b>Death or dependency by the end of scheduled follow-up</b> Median follow-up 12 months 9 Critical</p>	<p>Odds Ratio 0.79 (CI 95% 0.68 - 0.9) Based on data from 3,510 patients in 19 studies. (Randomized controlled) Follow up Median follow-up of 12 months</p>	<p><b>615</b> per 1000</p> <p><b>558</b> per 1000</p> <p>Difference: <b>57 fewer</b> per 1000 (CI 95% 94 fewer - 25 fewer)</p>	<p>medical ward care. However, for the comparison of rehabilitation stroke wards or mobile team care (peripatetic service) versus general medical wards there were no statistically significant differences.<sup>2</sup></p> <p><b>High</b> Two different models of care (comprehensive stroke ward, mixed assessment or rehabilitation ward) tended to be more effective than general medical ward care. However, for the comparison of rehabilitation stroke wards or mobile team care (peripatetic service) versus general medical wards there were no statistically significant differences.<sup>3</sup></p> <p>The people receiving organised inpatient (stroke unit) care were more likely to survive and regain independence than those receiving care in general medical wards.</p>
<p><b>Length of stay (days) in a hospital or institution</b> Median follow-up 12 months 7 Critical</p>	<p>Based on data from: 2,934 patients in 13 studies. (Randomized controlled) Follow up Median follow-up of 12 months</p>	<p>Difference: <b>SMD 0.08 fewer</b> (CI 95% 0.23 fewer - 0.06 more)</p>	<p><b>Low</b> Interpretation of length of stay data was complicated by substantial heterogeneity.<sup>4</sup></p> <p>There was no evidence of a systematic increase in length of stay.</p>

1. **Risk of bias: No serious** . 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 ; **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 ; **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 ;

**Inconsistency: Serious** . The magnitude of statistical heterogeneity was high, with  $I^2:70\%$  . ; **Indirectness: No serious** . **Imprecision: No serious** . **Publication bias: No serious** .

### References

[7] Stroke Unit Trialists' Collaboration : Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 2013;(9): [Journal](#)

### Clinical Question/ PICO

**Population:** Adults with stroke  
**Intervention:** Different systems of organised care: acute stroke ward  
**Comparator:** Alternative service

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Alternative service	Different systems of organised care: acute stroke ward		
<b>Death by the end of scheduled follow-up</b> 3 months - 1 year  9 Critical	Odds Ratio 0.49 (CI 95% 0.04 - 5.92) Based on data from 265 patients in 2 studies. (Randomized controlled) Follow up 3 months - 1 year	<b>243</b> per 1000	<b>136</b> per 1000	<b>Low</b> Overall, acute (monitoring) units did not have statistically significant different odds of death when compared with acute (non-intensive) units. <sup>1</sup>	There is probably little or no difference in survival between patients cared in acute stroke ward and those cared in alternative service.
<b>Death or institutional care by the end of scheduled follow-up</b> 3 months - 1 year  9 Critical	Odds Ratio 0.88 (CI 95% 0.32 - 2.39) Based on data from 265 patients in 2 studies. (Randomized controlled) Follow up 3 months - 1 year	<b>429</b> per 1000	<b>398</b> per 1000	<b>Low</b> Overall, acute (monitoring) units did not have statistically significant different odds of death or requiring institutional care when compared with acute (non-intensive) units. <sup>2</sup>	There is probably little or no difference in survival or institutional care between patients cared in acute stroke ward and those cared in alternative service.

<p><b>Death or dependency by the end of scheduled follow up</b> 3 months - 1 year 9 Critical</p>	<p>Odds Ratio 0.76 (CI 95% 0.24 - 2.41) Based on data from 265 patients in 2 studies. (Randomized controlled) Follow up 3 months - 1 year</p>	<p><b>486</b> per 1000</p> <p><b>418</b> per 1000</p> <p>Difference: <b>68 fewer</b> per 1000 ( CI 95% 301 fewer - 209 more )</p>	<p><b>Low</b> Overall, acute (monitoring) units did not have statistically significant different odds of death or dependency when compared with acute (non-intensive) units.<sup>3</sup></p> <p>There is probably little or no difference in survival or dependency between patients cared in acute stroke ward and those cared in alternative service.</p>
<p><b>Length of stay (days) in a hospital or institution</b> 3 months - 1 year 7 Critical</p>	<p>Based on data from: 265 patients in 2 studies. (Randomized controlled) Follow up 3 months - 1 year</p>	<p>Difference: <b>SMD 0.89 fewer</b> ( CI 95% 2.58 fewer - 0.79 more )</p>	<p><b>Very Low</b> Interpretation of length of stay was complicated by substantial heterogeneity.<sup>4</sup></p> <p>There was no evidence of a systematic increase in the length of stay.</p>

1. **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<sup>2</sup>:80% . ; **Indirectness: No serious** . **Imprecision: Serious** . Wide confidence intervals, Low number of patients ; **Publication bias: No serious** .
2. **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<sup>2</sup>:64% . ; **Indirectness: No serious** . **Imprecision: Serious** . Low number of patients, Wide confidence intervals, Wide confidence intervals ; **Publication bias: No serious** .
3. **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<sup>2</sup>:71% . ; **Indirectness: No serious** . **Imprecision: Serious** . Wide confidence intervals, Low number of patients ; **Publication bias: No serious** .
4. **Risk of bias: No serious** . Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: Very Serious** . The magnitude of statistical heterogeneity was high, with I<sup>2</sup>:92% . ; **Indirectness: No serious** . **Imprecision: Serious** . Wide confidence intervals, Low number of patients ; **Publication bias: No serious** .

## References

[7] Stroke Unit Trialists' Collaboration : Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 2013;(9): [Journal](#)

## Clinical Question/ PICO

**Population:** Adults with stroke  
**Intervention:** Different systems of organised care: comprehensive stroke ward  
**Comparator:** Alternative service (mobile stroke team)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Alternative service	Different systems of organised care: comprehensive stroke ward		
<p><b>Death by the end of scheduled follow-up</b> 12 months</p> <p>9 Critical</p>	<p>Odds Ratio 0.35 (CI 95% 0.19 - 0.65) Based on data from 304 patients in 1 studies.<sup>1</sup> (Randomized controlled) Follow up 12 months</p>	<p><b>224</b> per 1000</p>	<p><b>92</b> per 1000</p>	<p><b>Low</b> Orpington 2000 is the only trial in this analysis and these results require further confirmation.</p>	<p>Stroke unit care in comprehensive stroke ward (providing acute care and rehabilitation) may reduce death as compared to admission to general wards where care was provided by mobile stroke team.</p>
<p><b>Death or institutional care by the end of scheduled follow-up</b> 12 months</p> <p>9 Critical</p>	<p>Odds Ratio 0.4 (CI 95% 0.23 - 0.68) Based on data from 304 patients in 1 studies.<sup>2</sup> (Randomized controlled) Follow up 12 months</p>	<p><b>296</b> per 1000</p>	<p><b>144</b> per 1000</p>	<p><b>Low</b> Orpington 2000 is the only trial in this analysis and these results require further confirmation.</p>	<p>Patients who receive organised stroke unit care in comprehensive stroke ward (providing acute care and rehabilitation) may be more likely to survive and return home as compared to admission to general wards where care was provided by mobile stroke team.</p>
<p><b>Death or dependency by the end of scheduled follow-up</b> 12 months</p> <p>9 Critical</p>	<p>Odds Ratio 0.73 (CI 95% 0.46 - 1.14) Based on data from 304 patients in 1 studies.<sup>3</sup> (Randomized controlled) Follow up 12 months</p>	<p><b>480</b> per 1000</p>	<p><b>403</b> per 1000</p>	<p><b>Low</b> Orpington 2000 is the only trial in this analysis and these results require further confirmation.</p>	<p>Patients who receive organised stroke unit care in comprehensive stroke ward (providing acute care and rehabilitation) may be more likely to survive and regain independence as compared to admission to general wards where care was provided by mobile stroke team.</p>
<p><b>Length of stay (days) in a hospital or institution</b> 12 months</p> <p>7 Critical</p>	<p>Based on data from: 301 patients in 1 studies.<sup>4</sup> (Randomized controlled) Follow up 12 months</p>	<p><b>29.5</b> days (Mean)</p>	<p><b>32</b> days (Mean)</p>	<p><b>Low</b> Orpington 2000 is the only trial in this analysis and these results require further confirmation.</p>	<p>More research is required in this area.</p>

1. Systematic review [7] with included studies: Orpington 2000. **Baseline/comparator**:: Control arm of reference used for intervention .

2. Systematic review [7] with included studies: Orpington 2000. **Baseline/comparator**:: Control arm of reference used for

intervention .

3. Systematic review [7] with included studies: Orpington 2000. **Baseline/comparator::** Control arm of reference used for intervention .

4. Systematic review [7] with included studies: Orpington 2000. **Baseline/comparator::** Control arm of reference used for intervention .

## References

[7] Stroke Unit Trialists' Collaboration : Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 2013;(9): [Journal](#)

## Clinical Question/ PICO

**Population:** Organised inpatient (stroke unit) care for stroke  
**Intervention:** Different systems of organised care: rehabilitation stroke ward  
**Comparator:** Alternative service (mixed rehabilitation ward)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Alternative service (mixed rehabilitation ward)	Different systems of organised care: rehabilitation stroke ward		
<b>Death by the end of scheduled follow-up</b> Up to 1 year  9 Critical	Odds Ratio 0.51 (CI 95% 0.29 - 0.9) Based on data from 331 patients in 3 studies. <sup>1</sup> (Randomized controlled) Follow up 12 months	<b>238</b> per 1000	<b>137</b> per 1000	<b>Low</b> The numbers were small and no definite conclusions could be drawn. <sup>2</sup>	There was a pattern of improved outcomes in the stroke rehabilitation ward with statistically significant fewer deaths.
<b>Death or institutional care by the end of scheduled follow-up</b> Up to 1 year  9 Critical	Odds Ratio 0.71 (CI 95% 0.46 - 1.09) Based on data from 331 patients in 3 studies. <sup>3</sup> (Randomized controlled) Follow up 12 months	<b>506</b> per 1000	<b>421</b> per 1000	<b>Low</b> The numbers were small and no definite conclusions could be drawn. <sup>4</sup>	There was a pattern of improved outcomes in the stroke rehabilitation ward with non-significant trend for fewer patients with the composite end points of death or requiring institutional care
<b>Death or dependency by the end of scheduled</b>	Odds Ratio 0.8 (CI 95% 0.45 - 1.42) Based on data from 331 patients in 3 studies. <sup>5</sup>	<b>829</b> per 1000	<b>795</b> per 1000	<b>Low</b> The numbers were small and no definite	There was a pattern of improved outcomes in the stroke rehabilitation ward with a statistically non-significant trend for

<p><b>follow-up</b> Up to 1 year</p> <p>9 Critical</p>	<p>(Randomized controlled) Follow up 12 months</p>	<p>( CI 95% 143 fewer - 44 more )</p>	<p>conclusions could be drawn. <sup>6</sup></p>	<p>fewer patients with the composite end points of death or dependency.</p>
<p><b>Length of stay (days) in a hospital or institution</b> 12 months</p> <p>7 Critical</p>	<p>Based on data from: 331 patients in 3 studies. <sup>7</sup> (Randomized controlled) Follow up 12 months</p>	<p>Difference: <b>SMD 0.22 more</b> ( CI 95% 0.61 fewer - 1.05 more )</p>	<p><b>Very Low</b> Interpretation of length of stay data was complicated by substantial heterogeneity. <sup>8</sup></p>	<p>There was no evidence of systematic increase in length of stay.</p>

1. Systematic review [7] with included studies: Dover 1984 (MRW), Nottingham 1996 (MRW), Orpington 1993 (MRW). **Baseline/comparator::** Control arm of reference used for intervention .
2. **Risk of bias: No serious** . Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** . ; **Indirectness: No serious** . **Imprecision: No serious** . Low number of patients ; **Publication bias: No serious** .
3. Systematic review [7] with included studies: Nottingham 1996 (MRW), Orpington 1993 (MRW), Dover 1984 (MRW). **Baseline/comparator::** Control arm of reference used for intervention .
4. **Risk of bias: No serious** . Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: No serious** . Low number of patients ; **Publication bias: No serious** .
5. Systematic review [7] with included studies: Orpington 1993 (MRW), Dover 1984 (MRW), Nottingham 1996 (MRW). **Baseline/comparator::** Control arm of reference used for intervention .
6. **Risk of bias: No serious** . Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: No serious** . Low number of patients ; **Publication bias: No serious** .
7. Systematic review [7] with included studies: Dover 1984 (MRW), Nottingham 1996 (MRW), Orpington 1993 (MRW). **Baseline/comparator::** Control arm of reference used for intervention .
8. **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<sup>2</sup>:92 % . ; **Indirectness: No serious** . **Imprecision: No serious** . **Publication bias: No serious** .

## References

[7] Stroke Unit Trialists' Collaboration : Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 2013;(9): [Journal](#)

## 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Intermittent monitoring of physiological variables	Continuous monitoring		
<p><b>Death or dependency by the end of scheduled follow up</b> Discharge to 3 months</p> <p>9 Critical</p>	<p>Odds Ratio 0.27 (CI 95% 0.13 - 0.56) Based on data from 354 patients in 3 studies.<sup>1</sup> (Randomized controlled) Follow up Discharge to 3 months</p>	<p><b>469</b> per 1000</p>	<p><b>193</b> per 1000</p>	<p><b>Low</b> 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 (I<sup>2</sup> = 67%, 95% CI 93% to 44%).<sup>2</sup></p>	<p>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.</p>
		<p>Difference: <b>276 fewer</b> per 1000 ( CI 95% 366 fewer - 138 fewer )</p>			

<p><b>Cardiac complications</b> Discharge to three months</p> <p>7 Critical</p>	<p>Odds Ratio 8.65 (CI 95% 2.52 - 29.66) Based on data from 354 patients in 3 studies.<sup>3</sup> (Randomized controlled) Follow up Discharge to three months</p>	<p><b>17</b> per 1000</p> <p><b>130</b> per 1000</p> <p>Difference: <b>113 more</b> per 1000 (CI 95% 25 more - 322 more)</p>	<p><b>Low</b> 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.<sup>4</sup></p> <p>Continuous monitoring was associated with a significant increase in the detection of cardiac complications (arrhythmias, heart failure, myocardial infarction)</p>
<p><b>Fever</b><sup>5</sup> Discharge to three months</p> <p>7 Critical</p>	<p>Odds Ratio 2.17 (CI 95% 1.27 - 3.7) Based on data from 354 patients in 3 studies.<sup>6</sup> (Randomized controlled) Follow up Discharge to three months</p>	<p><b>158</b> per 1000</p> <p><b>289</b> per 1000</p> <p>Difference: <b>131 more</b> per 1000 (CI 95% 34 more - 252 more)</p>	<p><b>Low</b> 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.<sup>7</sup></p> <p>Continuous monitoring was associated with a significant increase in the detection of fever.</p>
<p><b>Length of stay (days)</b> Discharge to three months</p> <p>7 Critical</p>	<p>Based on data from: 354 patients in 3 studies.<sup>8</sup> (Randomized controlled) Follow up Discharge to three months</p>	<p>Difference: <b>MD 5.24 fewer</b> (CI 95% 10.51 fewer - 0.03 more)</p>	<p><b>Very Low</b> There are a small number of studies and small samples sizes. There was substantial heterogeneity across trials for this outcome (<math>I^2 = 83%</math>, 95% CI 94% to 49%; <math>P = 0.003</math>) 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)</p> <p>Continuous monitoring was associated with a non-significant reduction in the number of days of hospital stay.</p>

-8.15 days, 95% CI  
-9.85 to -6.44)  
without significant  
inconsistency ( $I^2 =$   
0%,  $P = 0.54$ ).<sup>9</sup>

1. Systematic review [10] with included studies: VERITAS 2007, Cavallini 2003, Sulter 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.
6. Systematic review [10] with included studies: Sulter 2003, VERITAS 2007, Cavallini 2003. **Baseline/comparator::** Control arm of reference used for intervention .
7. **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** .
8. Systematic review [10] with included studies: Cavallini 2003, Sulter 2003, VERITAS 2007. **Baseline/comparator::** Control arm of reference used for intervention .
9. **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** .

## References

[10] Ciccone A, Celani MG, Chiaramonte R, Rossi C, Righetti E : Continuous versus intermittent physiological monitoring for acute stroke. Cochrane Database of Systematic Reviews 2013;(2): [Journal](#)

## 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.

## Key Info

### 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.

### Strong Recommendation

All acute stroke services should implement standardised protocols to manage fever, glucose and swallowing difficulties in stroke patients. (Middleton et al. 2011 [157])

## 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.

## Key Info

### 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 [157]) 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.

### Quality of 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

Factors 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 [157]). 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:** Adults with stroke  
**Intervention:** Acute nursing intervention  
**Comparator:** Control

**Summary**

The Quality in Acute Stroke Care (QASC) study conducted by Middleton et al. (2011) [157] 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  $\geq 2$ ), 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  $\geq 60$  or  $\geq 95$ , 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Acute nursing intervention		
<b>Death or dependency</b> <sup>1</sup> 90 days after admission  9 Critical	n/a  Based on data from 1,007 patients in 1 studies. <sup>2</sup> (Randomized controlled) Follow up 90 days	<b>577</b> per 1000  Difference: <b>157 fewer</b> per 1000 ( CI 95% 58 fewer - 254 fewer )	<b>420</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>3</sup>	The FeSS protocol for acute stroke care probably decreases death or dependency
<b>Functional independence (Barthel Index <math>\geq 95</math>)</b>  8 Critical	n/a  Based on data from 955 patients in 1 studies. <sup>4</sup> (Randomized controlled) Follow up 90 days	<b>600</b> per 1000  Difference: <b>95 more</b> per 1000 ( CI 95% 5 fewer - 195 more )	<b>695</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>5</sup>	The FeSS protocol for acute stroke care probably has little or no difference on functional independence (Barthel Index $\geq 95$ )
<b>Functional Independence (Barthel Index <math>\geq 60</math>)</b>  8 Critical	n/a  Based on data from 955 patients in 1 studies. <sup>6</sup> (Randomized controlled) Follow up 90 days	<b>898</b> per 1000  Difference: <b>25 more</b> per 1000 ( CI 95% 36 fewer - 86 more )	<b>923</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>7</sup>	The FeSS protocol for acute stroke care has little or no difference on functional independence (Barthel Index $\geq 60$ )
<b>Physical health</b> <sup>8</sup>	Measured by: SF-36			<b>Moderate</b>	The FeSS protocol for

90 days after admission	Physical health score High better Based on data from: 1,009 patients in 1 studies. <sup>9</sup> (Randomized controlled) Follow up 90 days	Difference: <b>MD 3.4 more</b> ( CI 95% 1.2 more - 5.5 more )	Due to serious imprecision <sup>10</sup>	acute stroke care improves physical health
7 Critical				
<b>Mental health</b> 90 days after admission	Measured by: SF-36 Mental health score High better Based on data from: 1,009 patients in 1 studies. <sup>11</sup> (Randomized controlled) Follow up 90 days	Difference: <b>MD 0.5 more</b> ( CI 95% 1.9 fewer - 2.8 more )	<b>Moderate</b> Due to serious imprecision <sup>12</sup>	The FeSS protocol for acute stroke care has little or no difference on mental health
7 Critical				

1. Dependency categorised as modified Rankin Scale scores  $\geq 2$ . 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 [157]. **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 [157]. **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 [157]. **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 [157]. **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 review with included studies: [157]. **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 .**

## References

[157] Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, Evans M, Cadilhac D, Levi C : Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial.. *Lancet* (London, England) 2011;378(9804):1699-706  
[Pubmed Journal](#)

## 6 - 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 [21]). Similarly there is evidence that rehabilitation needs of patients with severe stroke are inconsistently documented (Lynch et al. 2015 [23]), 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 [25]). 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 [22]). 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 [27]) 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 [24], Stroke Foundation 2015 [26]).

### Info Box

#### 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 [22]).
- 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 [22] 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.

### Key Info

#### 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).

## 7 - Palliative care

11% of acute stroke patients die in hospital during acute care (Stroke Foundation 2015 [26]) and approximately 20% die as a result of the stroke in the first 30 days (Thrift et al. 2000 [36]).

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.

### 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 [28])

### Key Info

#### Benefits and harms

Substantial net benefits of the recommended alternative

Gade et al. (2008) [28] (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.

#### Quality of 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) [31]; Burton and Payne (2012) [30] and de Boer et al. (2015) [32] 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 be 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.

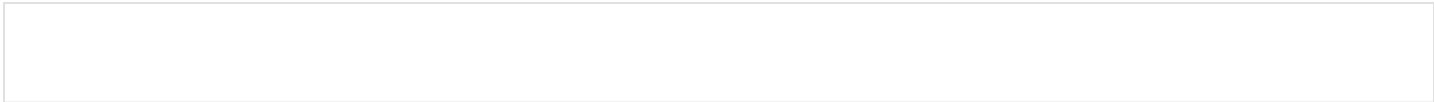
Although these studies were undertaken mainly in the UK they would have direct applicability to the stroke unit care model in Australia and the needs of patients and their families/carers in relation to palliative care.

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.

Blacquiére et al. (2013) [33], 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) [28] 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) [28] 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) [28] 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.

Creutzfeld et al. (2012) [29] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Usual care	Palliative care		
<b>Advance directives</b> <sup>1</sup> At discharge	n/a Based on data from 512 patients in 1 studies. (Randomized controlled) Follow up At discharge	<b>778</b> per 1000	<b>911</b> per 1000	<b>Moderate</b> The difference was significant (chi-squared test) but confidence intervals were not reported. Due to serious imprecision <sup>2</sup>	Interdisciplinary palliative care probably increases completion of advance directives
<b>ICU admissions</b>	n/a Based on data from 448 patients in 1 studies. (Randomized controlled)	<b>96</b> per 1000	<b>52</b> per 1000	<b>Moderate</b> The difference was significant according to a chi-squared test, but	Interdisciplinary palliative care probably decreases ICU admissions

<p><b>Patient satisfaction - care environment</b> 2 weeks after discharge</p>	<p>Measured by: MCOHPQ Place of Care environment scale Scale: 0-10 High better Based on data from: 295 patients in 1 studies. (Randomized controlled) Follow up Within 2 weeks of discharge</p>	<p><b>6.4</b> (Mean)</p> <p><b>6.8</b> (Mean)</p> <p>Difference: <b>MD 0.4 more</b> CI 95%</p>	<p>confidence intervals were not reported. Due to serious imprecision <sup>3</sup></p> <p><b>Moderate</b> The difference was significant but no confidence intervals were reported. Due to serious imprecision <sup>4</sup></p>	<p>Interdisciplinary palliative care probably improves patient satisfaction with the care environment slightly</p>
<p><b>Patient satisfaction - communication with providers</b> 2 weeks after discharge</p>	<p>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</p>	<p><b>7.4</b> (Mean)</p> <p><b>8</b> (Mean)</p> <p>Difference: <b>MD 0.6 more</b> CI 95%</p>	<p><b>Moderate</b> The difference was significant but no confidence intervals were reported. Due to serious imprecision <sup>5</sup></p>	<p>Interdisciplinary palliative care probably improves patient satisfaction regarding communication with providers slightly</p>
<p><b>Hospice length of stay</b></p>	<p>Measured by: Days in hospice Based on data from: 512 patients in 1 studies. (Randomized controlled)</p>	<p><b>12</b> days (Median)</p> <p><b>24</b> days (Median)</p> <p>Difference: <b>12 more</b> CI 95%</p>	<p><b>Moderate</b> The difference was significant but no confidence intervals were reported. Due to serious imprecision <sup>6</sup></p>	<p>Interdisciplinary palliative care probably increases hospice length of stay</p>

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 .**

## References

[28] Gade G, Venohr I, Conner D, McGrady K, Beane J, Richardson RH, Williams MP, Liberson M, Blum M, Della Penna R : Impact of an inpatient palliative care team: a randomized control trial.. *Journal of palliative medicine* 2008;11(2):180-90 [Pubmed Journal](#)

[29] Creutzfeldt CJ, Holloway RG, Walker M. : Symptomatic and palliative care for stroke survivors. *Journal of General Internal Medicine* 2012;27(7):853-860 [Journal](#)

## 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.

## 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 [34]).

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 [35]).

## 8 - Reperfusion therapy

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

### 8.1 - 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 [37]). Thrombolytic drugs can also, however, cause serious bleeding in the brain, which can be fatal (Wardlaw et al. 2014 [37]). 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 low in Australia. In the National Stroke Audit in 2015, the overall thrombolysis rate had stalled at 7% for the last four years, despite 76% of hospitals reporting provision of thrombolysis (Stroke Foundation 2015 [26]). Only 24% of patients arriving within 4.5 hours of stroke onset received thrombolysis (Stroke Foundation 2015 [26]). Only 26% 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 who meet specific eligibility criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) should be administered. (Wardlaw et al. 2014 [37]; Emberson et al. 2014 [38])
- Thrombolysis should commence as early as possible (within the first few hours) after stroke onset but may be used up to 4.5 hours after onset. (Wardlaw et al. 2014 [37]; Anderson et al. 2016 [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 [38]). 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 [50]).

Benefit from thrombolysis is strongly time-dependent and so treatment should be commenced as early as possible within the 4.5 hour period after stroke onset. Commencing treatment beyond 4.5 hours has not been shown to be of net benefit. Ongoing trials using imaging selection are evaluating thrombolysis in this group of patients.

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 a meta-analysis of all alteplase trials has clearly demonstrated a treatment benefit of at least as great a magnitude in patients aged >80 compared to younger patients. The trial data did not demonstrate an increase in symptomatic intracerebral haemorrhage in the elderly compared to younger patients. The patient's pre-morbid level of function rather than chronological age should be considered when deciding whether to treat.

Scenarios that have potentially mimicked stroke and therefore been regarded as exclusions from some trials include seizure at onset, hypoglycaemia and hyperglycaemia. 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<sup>3</sup> (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 (including prophylactic doses) with abnormal anti-factor Xa activity
  - direct oral anticoagulant use (e.g. apixaban, dabigatran, rivaroxaban) 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)

**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:**

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

Thoracic aortic dissection – alteplase is contraindicated due to a high risk of death.

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, andexanet alfa for rivaroxaban or apixaban) 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.

## Key Info

### 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 [38]). 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 [38]). However, at 90 days there was no significant difference in mortality.

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 [40].

### Quality of 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 indicate 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 [52]).

### 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 [45]). 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 [45]). 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 [105])

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 [46]; Boudreau et al. 2014 [47]; Tung et al. 2011 [48]; Boudreau et al. 2013 [49]).

In a systematic review of cost-effectiveness data, Demaerschalk et al. (2010) [44] 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 [37]; Emberson et al. 2014 [38]). However, benefits have not been established beyond 4.5 hours.

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 [37]; Anderson et al. 2016 [40]).

## **Clinical Question/ PICO**

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

### **Summary**

Anderson et al. (2016) [40] 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 doses of 0.9 mg per kilogram body weight provide 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. [41], 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.

<b>Outcome Timeframe</b>	<b>Study results and measurements</b>	<b>Absolute effect estimates</b> Standard-dose intravenous alteplase	<b>Low-dose intravenous alteplase</b>	<b>Certainty in effect estimates</b> (Quality of evidence)	<b>Plain text summary</b>
------------------------------	---	--	---	--	---------------------------

<p><b>Death or disability</b><sup>1</sup> 90 days 9 Critical</p>	<p>Odds Ratio 1.09 (CI 95% 0.95 - 1.25) Based on data from 3,206 patients in 1 studies. (Randomized controlled)</p>	<p><b>511</b> per 1000</p>	<p><b>533</b> per 1000</p>	<p><b>Low</b> Due to serious imprecision, Due to serious indirectness<sup>2</sup></p>	<p>Low-dose intravenous alteplase may slightly increase death or disability</p>
<p><b>Death</b> 90 days 9 Critical</p>	<p>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</p>	<p><b>103</b> per 1000</p>	<p><b>84</b> per 1000</p>	<p><b>Low</b> Due to serious imprecision, Due to serious indirectness<sup>3</sup></p>	<p>Low-dose intravenous alteplase may slightly decrease death</p>
<p><b>Improved functional outcome</b><sup>4</sup> 90 days 8 Critical</p>	<p>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</p>			<p><b>Low</b> Due to serious imprecision, Due to serious indirectness<sup>5</sup></p>	<p>Low-dose intravenous alteplase may have little or no effect on functional outcome</p>
<p><b>Symptomatic ICH</b><sup>6</sup> 90 days 8 Critical</p>	<p>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</p>	<p><b>21</b> per 1000</p>	<p><b>10</b> per 1000</p>	<p><b>Low</b> Due to serious imprecision, Due to serious indirectness<sup>7</sup></p>	<p>Low-dose intravenous alteplase may decrease symptomatic ICH</p>

1. Disability classified as Modified Rankin Scale 2-6
2. **Inconsistency: No serious . Indirectness: Serious .** Mostly Asian population ; **Imprecision: Serious .** Only data from one study ; **Publication bias: No serious .**
3. **Inconsistency: No serious . Indirectness: Serious .** Mostly Asian population ; **Imprecision: Serious .** Only data from one study ; **Publication bias: No serious .**
4. Ordinal analysis of improvement on modified Rankin Scale
5. **Inconsistency: No serious . Indirectness: Serious .** Mostly Asian population ; **Imprecision: Serious .** Only data from one study ; **Publication bias: No serious .**
6. 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
7. **Inconsistency: No serious . Indirectness: Serious .** Mostly Asian population ; **Imprecision: Serious .** Only data from one study ; **Publication bias: No serious .**

## References

[38] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N,

Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W : Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials.. *Lancet* (London, England) 2014;384(9958):1929-35 [Pubmed Journal](#)

[40] Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee T-H, Broderick JP, Chen X, Chen G, Sharma VK, Kim JS, Thang NH, Cao Y, Parsons MW, Levi C, Huang Y, Olavarria VV, Demchuk AM, Bath PM, Donnan GA, Martins S, Pontes-Neto OM, Silva F, Ricci S, Roffe C, Pandian J, Billot L, Woodward M, Li Q, Wang X, Wang J, Chalmers J : Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. *N Engl J Med* 2016; [Journal Website](#)

[41] Wardlaw JM, Koumellis P, Liu M : Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke.. *The Cochrane database of systematic reviews* 2013;(5):CD000514 [Pubmed Journal](#)

## Clinical Question/ PICO

**Population:** Adults with acute stroke treated within 6 hours  
**Intervention:** Intravenous alteplase  
**Comparator:** Control

### Summary

A Cochrane review by Wardlaw et al. (2014) [37] included 27 RCTs of thrombolytic agents for 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 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 is more limited. The IST-3 collaborative group (2013) [39] 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% CI 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Intravenous alteplase		

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

1. Dependency defined as Modified Rankin Scale 3-6

2. Systematic review [37] with included studies: NINDS 1995, ECASS 1995, ECASS 3 2008, EPITHET 2008, IST3 2012, ECASS II 1998, ATLANTIS B 1999, ATLANTIS A 2000, Wang 2003, Mori 1992. **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 [37] with included studies: EPITHET 2008, Mori 1992, ECASS 3 2008, Wang 2003, ECASS II 1998, Haley 1993, ECASS 1995, IST3 2012. **Baseline/comparator::** Control arm of reference used for intervention .

5. Systematic review [37] with included studies: EPITHET 2008, ECASS 3 2008, IST3 2012, ECASS II 1998, ATLANTIS B 1999,

- ATLANTIS A 2000, Wang 2003, NINDS 1995, Mori 1992, Haley 1993, 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 [37] with included studies: ATLANTIS A 2000, ECASS 3 2008, IST3 2012, NINDS 1995, ECASS 1995, ECASS II 1998, ATLANTIS B 1999, Haley 1993. **Baseline/comparator::** Control arm of reference used for intervention .
8. Includes fatal symptomatic ICH
9. Systematic review [37] with included studies: ECASS II 1998, ATLANTIS B 1999, ATLANTIS A 2000, Wang 2003, NINDS 1995, Mori 1992, Haley 1993, ECASS 1995, JTSG 1993, EPITHET 2008, ECASS 3 2008, IST3 2012. **Baseline/comparator::** Control arm of reference used for intervention .

## References

[37] Wardlaw JM : Thrombolysis for acute ischaemic stroke. Cochrane Database of Systematic Review 2014; [Pubmed](#)

## Clinical Question/ PICO

**Population:** Adults with acute stroke treated within 3 hours  
**Intervention:** Intravenous alteplase  
**Comparator:** Control

## Summary

An individual patient data meta-analysis conducted by Emberson et al. (2014) [38] included subgroup analyses for patients treated  $\leq 3$  hours after stroke,  $> 3$  and  $\leq 4.5$  hours, and  $> 4.5$  hours. 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) [37] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Intravenous alteplase		

<p><b>Excellent outcome (modified Rankin Scale 0-1)</b><sup>1</sup></p> <p>3-6 months</p> <p>8 Critical</p>	<p>Odds Ratio 1.75 (CI 95% 1.35 - 2.27)</p> <p>Based on data from 1,549 patients in 9 studies. (Randomized controlled)</p> <p>Follow up 3 to 6 months</p>	<p><b>231</b> per 1000</p> <p><b>345</b> per 1000</p> <p>Difference: <b>114 more</b> per 1000 (CI 95% 58 more - 174 more)</p>	<p><b>High</b> 2</p>	<p>Intravenous alteplase within 3 hours increases favourable outcome</p>
<p><b>Death</b></p> <p>90 days</p> <p>9 Critical</p>	<p>Hazard Ratio 1 (CI 95% 0.81 - 1.24)</p> <p>Based on data from 1,549 patients in 9 studies. (Randomized controlled)</p>		<p><b>High</b> 3</p>	<p>Intravenous alteplase within 3 hours has little or no difference on death</p>
<p><b>Fatal intracranial haemorrhage</b></p> <p>7 days</p> <p>9 Critical</p>	<p>Odds Ratio 10.86 (CI 95% 2.54 - 46.41)</p> <p>Based on data from 1,549 patients in 9 studies. (Randomized controlled)</p>	<p><b>3</b> per 1000</p> <p><b>32</b> per 1000</p> <p>Difference: <b>29 more</b> per 1000 (CI 95% 5 more - 120 more)</p>	<p><b>High</b> 4</p>	<p>Intravenous alteplase within 3 hours increases fatal intracranial haemorrhage</p>

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** .

## References

[37] Wardlaw JM : Thrombolysis for acute ischaemic stroke. Cochrane Database of Systematic Review 2014; [Pubmed](#)

[38] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W : Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials.. *Lancet (London, England)* 2014;384(9958):1929-35 [Pubmed Journal](#)

## Clinical Question/ PICO

**Population:** Adults with acute stroke treated at 3-4.5 hours

**Intervention:** Intravenous alteplase  
**Comparator:** Control

### Summary

An individual patient data meta-analysis conducted by Emberson et al. (2014) [38] included subgroup analyses for patients treated  $\leq 3$  hours after stroke,  $> 3$  and  $\leq 4.5$  hours, and  $> 4.5$  hours. 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Intravenous alteplase		
<b>Death</b> 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)			<b>High</b> 1	Intravenous alteplase between 3 and 4.5 hours has little or no difference on death
<b>Excellent outcome (modified Rankin Scale 0-1)<sup>2</sup></b> 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)	<b>301</b> per 1000	<b>352</b> per 1000	<b>High</b> 3	Intravenous alteplase between 3 and 4.5 hours increases favourable outcome
<b>Fatal intracranial haemorrhage</b> 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)	<b>5</b> per 1000	<b>28</b> per 1000	<b>High</b> 4	Intravenous alteplase between 3 and 4.5 hours increases fatal intracranial haemorrhage

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

## References

[38] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W : Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials.. *Lancet* (London, England) 2014;384(9958):1929-35 [PubMed Journal](#)

## Clinical Question/ PICO

**Population:** Adults with acute stroke treated at 4.5-6 hours  
**Intervention:** Intravenous alteplase  
**Comparator:** Control

## Summary

An individual patient data meta-analysis conducted by Emberson et al. (2014) [38] included subgroup analyses for patients treated  $\leq 3$  hours after stroke,  $> 3$  and  $\leq 4.5$  hours, and 4.5 - 6 hours. 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Intravenous alteplase		
<b>Death</b> 90 days  9 Critical	Hazard Ratio 1.22 (CI 95% 0.99 - 1.5) Based on data from 2,395 patients in 9 studies. (Randomized controlled) Follow up 90 days			<b>High</b> 1	Intravenous alteplase after 4.5 hours slightly increases death
<b>Excellent outcome (modified Rankin Scale 0-1)<sup>2</sup></b> 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)	<b>306</b> per 1000	<b>336</b> per 1000	<b>High</b> 3	Intravenous alteplase after 4.5 hours slightly increases favourable outcome
		Difference: <b>30 more</b> per 1000 (CI 95% 11 fewer - 76 more)			

<b>Fatal intracranial haemorrhage</b> 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)	<b>3</b> per 1000  Difference: <b>21 more</b> per 1000 ( CI 95% 6 more - 62 more )	<b>24</b> per 1000	<b>High</b> 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** .

## References

[38] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W : Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials.. Lancet (London, England) 2014;384(9958):1929-35 [Pubmed Journal](#)

## 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.

## Key Info

### 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.

## 8.2 - 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 [53]). 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 few were able to provide a truly continuous 24/7 service (Stroke Foundation 2015 [26]). 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.

### Strong Recommendation

For patients with ischaemic stroke caused by a large vessel occlusion in the internal carotid artery, proximal cerebral artery (M1 segment), or with tandem occlusion of both the cervical carotid and intracranial arteries, endovascular thrombectomy should be undertaken when the procedure can be commenced within six hours of stroke onset. (Goyal et al. 2016 [55])

## 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 [62]), 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 [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). These trials have been stopped for positive results but are not yet published.

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, which may be 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. Treatment benefit in more **distal "M2" middle cerebral artery occlusions** was not significant in its own right, but there was no statistical heterogeneity in treatment effect compared to ICA and M1 occlusions. Some observational studies have indicated equivalent safety of M2 thrombectomy and the anatomy and clinical impact of M2 occlusions can be quite varied. Treatment can therefore 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 [64]) 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 [65]). 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 [63]). 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 [61]). 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.

Performing the procedure under general anaesthetic has repeatedly been associated with worse outcome than performing thrombectomy with the patient awake in observational studies. This may relate to hypotension, which is very frequent during induction of general anaesthesia, and treatment delays. Three single centre randomised trials (SIESTA, ANSTROKE and GOLIATH) recently showed no

difference, or even slight benefit, of GA versus conscious sedation using the same anaesthetic agents. These trials achieved 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. (Refer to references 68, 69, and 70 for further details).

### 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.

## Key Info

### 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 [55]).

### Quality of 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]).

### 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

#### Resources considerations

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 [58]; Lobotesis et al. 2016 [60]) or cost-effective (Ganesalingam et al. 2016 [59]) 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 [55]). 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 [62]).

### Clinical Question/ PICO

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

#### Summary

Goyal et al. (2016) [55] 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) [53] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Standard medical care	Endovascular mechanical thrombectomy		
<p><b>Improved functional outcome</b><sup>1</sup> 3 months</p> <p>8 Critical</p>	<p>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</p>	<p>Difference: <b>385 more</b> CI 95%</p>		<p><b>High</b> Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomized controlled trials with consistent effects.<sup>2</sup></p>	<p>Endovascular mechanical thrombectomy improves functional outcome</p>

<p><b>Functional independence</b><sup>3</sup> 3 months</p> <p>8 Critical</p>	<p>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</p>	<p><b>265</b> per 1000</p>	<p><b>494</b> per 1000</p>	<p><b>High</b> Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomized controlled trials with consistent effects.<sup>4</sup></p>	<p>Endovascular mechanical thrombectomy improves functional independence</p>
<p><b>Mortality</b> 3 months</p> <p>9 Critical</p>	<p>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</p>	<p><b>189</b> per 1000</p>	<p><b>145</b> per 1000</p>	<p><b>High</b> Overall mortality did not differ with endovascular mechanical thrombectomy. However the subgroup aged &gt;80 years did have a significant reduction in mortality.<sup>5</sup></p>	<p>Endovascular mechanical thrombectomy has little or no effect on mortality overall with a significant reduction in patients aged &gt; 80 years</p>
<p><b>Symptomatic intracranial haemorrhage</b><sup>6</sup> within 36 hours of treatment</p> <p>8 Critical</p>	<p>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</p>	<p><b>43</b> per 1000</p>	<p><b>46</b> per 1000</p>	<p><b>High</b> No difference in the rate of symptomatic haemorrhage<sup>7</sup></p>	<p>Endovascular mechanical thrombectomy has little or no effect on symptomatic intracranial haemorrhage</p>

- improvement by at least 1 level of the modified Rankin score
- 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. ;
- modified Rankin Scale 0-2
- 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. ;
- 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. ;
- 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. ;

## References

[53] Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J, Kulkarni AV, Singh S, Alqahtani A, Rochweg B, Alshahrani M, Murty NK, Alhazzani A, Yarascavitch B, Reddy K, Zaidat OO, Almenawer SA : Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis.. JAMA 2015;314(17):1832-43 [Pubmed Journal](#)

[55] Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos YBWEM, Bonafe A, Jahan R, Diener H-C, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG : Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.. Lancet (London, England) 2016;387(10029):1723-31 [Pubmed Journal](#)

## Strong Recommendation

Eligible stroke patients should receive intravenous thrombolysis while concurrently arranging endovascular thrombectomy, with neither treatment delaying the other. (Goyal et al. 2016 [55])

## Key Info

### 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 [55]). 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 [55]). Hence alteplase must not delay thrombectomy. However, in a proportion of cases thrombectomy will fail and these patients may still derive benefit from alteplase.

### Quality of 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]).

### 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 [58]; Lobotesis et al. 2016 [60]) or cost-effective (Ganesalingam et al. 2016 [59]) 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 [55]). However, endovascular thrombectomy is effective in patients with contraindications to intravenous thrombolysis (Goyal et al. 2016 [55]).

## Clinical Question/ PICO

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

## Summary

Goyal et al. (2016) [55] 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) [56] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Intravenous thrombolysis alone	Endovascular mechanical thrombectomy + intravenous thrombolysis		
<b>Functional independence</b> <sup>1</sup> 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	<b>270</b> per 1000  Difference: <b>112 more</b> per 1000 (CI 95% 161 more - 66 more)	<b>382</b> per 1000	<b>High</b> Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomised controlled trials	Endovascular mechanical thrombectomy improves functional independence

<p><b>Mortality</b> 3 months</p> <p>9 Critical</p>	<p>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</p>	<p><b>184</b> per 1000</p> <p><b>145</b> per 1000</p> <p>Difference: <b>39 fewer</b> per 1000 ( CI 95% 18 more - 83 fewer )</p>	<p>with consistent effects.<sup>2</sup></p> <p><b>High</b> Overall mortality did not differ with endovascular mechanical thrombectomy. However the subgroup aged &gt;80 years did have a significant reduction in mortality.<sup>3</sup></p> <p>Endovascular mechanical thrombectomy has little or no effect on mortality overall with a significant reduction in patients aged &gt; 80 years</p>
<p><b>Improved functional outcome<sup>4</sup></b> 3 months</p> <p>8 Critical</p>	<p>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</p>	<p>CI 95%</p>	<p><b>High</b> Endovascular thrombectomy in addition to alteplase improves functional outcome<sup>5</sup></p> <p>Endovascular mechanical thrombectomy + intravenous thrombolysis improves functional outcome</p>

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. ;

### References

[55] Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos YBWEM, Bonafe A, Jahan R, Diener H-C, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG : Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.. Lancet (London, England) 2016;387(10029):1723-31 [PubMed Journal](#)

[56] Palesch YY, Yeatts SD, Tomsick TA, Foster LD, Demchuk AM, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, von Kummer R, Molina CA, Goyal M, Schonewille WJ, Mazighi M, Engelter ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Simpson A, Simpson KN, Broderick JP : Twelve-Month Clinical and Quality-of-Life Outcomes in the Interventional Management of Stroke III Trial.. Stroke; a journal of cerebral circulation 2015;46(5):1321-7 [PubMed Journal](#)

### Clinical Question/ PICO

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

### Summary

Goyal et al. (2016) [55] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Standard care	Endovascular mechanical thrombectomy		
<b>Improved functional outcome</b> <sup>1</sup> 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			<b>High</b> Endovascular thrombectomy improves outcome in patients ineligible for alteplase <sup>2</sup>	Endovascular mechanical thrombectomy improves functional outcome in patients ineligible for intravenous thrombolysis
<b>Functional independence</b> <sup>3</sup> 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	<b>223</b> per 1000	<b>370</b> per 1000	<b>High</b> Robust statistical significance and no evidence of effect heterogeneity. <sup>4</sup>	Endovascular mechanical thrombectomy improves functional independence in patients ineligible for intravenous thrombolysis
<b>Mortality</b> 3 months	Odds Ratio 1.11 (CI 95% 0.6 - 2.07) Based on data from 188	<b>225</b> per 1000	<b>231</b> per 1000	<b>High</b> <sup>5</sup>	Endovascular mechanical thrombectomy in patients ineligible for

9 Critical	patients in 5 studies. (Randomized controlled) Follow up 3 months	Difference: <b>6 more</b> per 1000 ( CI 95% 150 more - 77 fewer )	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. ;

## References

[55] Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos YBWEM, Bonafe A, Jahan R, Diener H-C, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG : Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.. *Lancet* (London, England) 2016;387(10029):1723-31 [PubMed Journal](#)

## Clinical Question/ PICO

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

## Summary

Goyal et al. (2016) [55] 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) [53] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Standard medical care	Endovascular mechanical thrombectomy		
<b>Improved functional outcome</b> <sup>1</sup> 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: <b>385 more</b> CI 95%		<b>High</b> Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomized controlled trials with consistent effects. <sup>2</sup>	Endovascular mechanical thrombectomy improves functional outcome
<b>Functional independence</b> <sup>3</sup> 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	<b>265</b> per 1000	<b>494</b> per 1000	<b>High</b> Endovascular stent thrombectomy reduces disability with high confidence based on 5 high quality randomized controlled trials with consistent effects. <sup>4</sup>	Endovascular mechanical thrombectomy improves functional independence
<b>Mortality</b> 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	<b>189</b> per 1000	<b>145</b> per 1000	<b>High</b> Overall mortality did not differ with endovascular mechanical thrombectomy. However the subgroup aged	Endovascular mechanical thrombectomy has little or no effect on mortality overall with a significant reduction in patients aged > 80 years

<p><b>Symptomatic intracranial haemorrhage</b><sup>6</sup> within 36 hours of treatment</p> <p>8 Critical</p>	<p>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</p>	<p><b>43</b> per 1000</p> <p><b>46</b> per 1000</p> <p>Difference: <b>3 more</b> per 1000 ( CI 95% 33 more - 16 fewer )</p>	<p>&gt;80 years did have a significant reduction in mortality.<sup>5</sup></p> <p><b>High</b> No difference in the rate of symptomatic haemorrhage<sup>7</sup></p> <p>Endovascular mechanical thrombectomy has little or no effect on symptomatic intracranial haemorrhage</p>
---	--	---	--

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. ;

**References**

[53] Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhlyar F, Spears J, Kulkarni AV, Singh S, Alqahtani A, Rochweg B, Alshahrani M, Murty NK, Alhazzani A, Yarascavitch B, Reddy K, Zaidat OO, Almenawer SA : Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis.. JAMA 2015;314(17):1832-43 [Pubmed Journal](#)

[55] Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos YBWEM, Bonafe A, Jahan R, Diener H-C, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG : Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.. Lancet (London, England) 2016;387(10029):1723-31 [Pubmed Journal](#)

**Strong Recommendation**

In selected stroke patients with occlusion of the basilar artery, endovascular thrombectomy should be undertaken. (Kumar et al. 2015 [65])

**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 [64]) 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 [65]). 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 [63]). 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.

**Key Info**

**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 [65]). Safety was acceptable.

**Quality of 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**

Factors 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 [65]). Safety was acceptable (Kumar et al. 2015 [65]). 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 [63]) 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) [65] 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 [64]), 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).

### References

- [63] Schonewille WJ, Wijman CAC, Michel P, Rueckert CM, Weimar C, Mattle HP, Engelter ST, Tanne D, Muir KW, Molina CA, Thijs V, Audebert H, Pfefferkorn T, Szabo K, Lindsberg PJ, de Freitas G, Kappelle LJ, Algra A : Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study.. *The Lancet. Neurology* 2009;8(8):724-30 [Pubmed](#) [Journal](#)
- [64] Macleod MR, Davis SM, Mitchell PJ, Gerraty RP, Fitt G, Hankey GJ, Stewart-Wynne EG, Rosen D, McNeil JJ, Bladin CF, Chambers BR, Herkes GK, Young D, Donnan GA : Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke.. *Cerebrovascular diseases (Basel, Switzerland)* 2005;20(1):12-7 [Pubmed](#)
- [65] Kumar G, Shahripour RB, Alexandrov AV : Recanalization of acute basilar artery occlusion improves outcomes: a meta-analysis.. *Journal of neurointerventional surgery* 2015;7(12):868-74 [Pubmed](#) [Journal](#)

### Practice Statement

#### **Consensus-based recommendations**

For stroke patients, endovascular thrombectomy may be considered in the following situations based on individual patient and advanced imaging factors:

- commencement of procedure beyond 6 hours (but within 24 hours) from stroke onset
- occlusion in more distal middle cerebral artery branches (M2 segment).

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](http://CCINR.org.au)).

### Practical Info

### Key Info

#### **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.

### Rationale

There is clear and high-quality evidence of improved functional outcome and no evidence of increased risk of symptomatic intracerebral haemorrhage when the procedure is commenced 0–6 hours after stroke onset. Few patients were treated beyond 6 hours in the randomised trials published in 2015–2016. The benefit of endovascular thrombectomy extended to 7 hr 18 min in the HERMES meta-analysis (Saver et al. 2016 [62]). Non-randomised data from the DEFUSE-2 study suggested benefit of reperfusion in patients with favourable perfusion-diffusion imaging up to 12 hours after onset. The DAWN and DEFUSE 3 randomised trials examined treatment of anterior circulation ischaemic stroke in an extended time window (up to 24 hours from stroke onset) using imaging selection – predominantly CT perfusion processed using RAPID software (iSchemaView, Menlo Park). These trials have been stopped at interim analyses due to positive results, but are not yet published.

DAWN used clinical-core mismatch criteria which combined age, NIHSS and estimated ischaemic core volume using CT perfusion (relative cerebral blood flow < 30% of normal brain) or diffusion MRI processed using RAPID software for patients with intracranial ICA and M1 occlusion (excluding tandem extracranial carotid and intracranial lesions) 6–24 hrs after the time they were last known to be well:

Age < 80, NIHSS ≥ 20, core < 51 mL, or

Age < 80, NIHSS 10–19, core < 31 mL, or

Age > 80, NIHSS ≥ 10, core < 21 mL.

DEFUSE 3 used more inclusive criteria based on perfusion mismatch (approximately 50% also met clinical-core mismatch criteria) for patients with ICA and M1 occlusion (including tandem extracranial carotid and intracranial lesions) 6–16 hrs after the time they were last known to be well:

core < 70mL with mismatch ratio > 1.8 and absolute mismatch volume > 15 mL. DEFUSE 3 also required age ≤ 90, NIHSS ≥ 6 and calculated estimated ischaemic core volume using CT perfusion (relative cerebral blood flow < 30% of normal brain) or diffusion MRI processed with RAPID software.

In oral presentation of the DAWN results at the 2017 European Stroke Organisation Conference, the proportion of patients achieving functional independence at 3 months was 48.6% in the intervention group versus 13.1% in the control group (p<0.0001). The number needed to treat to improve at least one modified Rankin Scale category was 2.0. The proportion of patients achieving successful endovascular reperfusion was 84%, comparable to 0–6 hr treatment. Symptomatic intracerebral haemorrhage occurred in 4.8%

intervention versus 3.2% control patients ( $p=0.3$ ) and there were no safety concerns. Over half the patients had wake-up stroke.

The time window for effective treatment of basilar artery occlusion is uncertain but may be attempted up to 24 hours (particularly when there has been a stuttering onset of milder symptoms prior to onset of coma).

The randomised trials included relatively few patients with distal middle cerebral artery (M2) occlusions. Although there was no significant heterogeneity in treatment effect, this subgroup was not significant in its own right. M2 occlusions are quite variable in anatomy and the territory of brain at risk. Observational data has suggested the safety profile and outcomes after M2 treatment are similar to M1 occlusions.

## 9 - Dysphagia

Dysphagia (problems with swallowing) is a common consequence of acute stroke, with a reported incidence of 27% to 64% (Geeganage et al. 2012 [77]). Dysphagia is associated with an increased risk of complications, such as aspiration pneumonia, dehydration and malnutrition (Geeganage et al. 2012 [77]). 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 (Geeganage et al. 2012 [77]).

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 55% of stroke patients received formal swallow screening and 58% were screened before oral diet was given (Stroke Foundation 2015 [26]). Around 80% of patients received formal assessment from speech pathologists within 48 hours (Stroke Foundation 2015 [26]). A total of 104 hospitals out of 108 surveyed indicated that they had locally agreed management protocols for swallow dysfunction (Stroke Foundation 2015 [26]).

### Practice Statement

#### **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 [93])

### 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 [93]). 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 [93]). 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,  $\geq 345$  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).

### References

[93] Bray BD, Smith CJ, Cloud GC, Enderby P, James M, Paley L, Tyrrell PJ, Wolfe CDA, Rudd AG : The association between delays in screening for and assessing dysphagia after acute stroke, and the risk of stroke-associated pneumonia.. *Journal of neurology, neurosurgery, and psychiatry* 2017;88(1):25-30 [Pubmed Journal](#)

### Weak Recommendation

People with acute stroke should have their swallowing screened, using a validated screening tool, by a trained healthcare professional. (Poorjavad et al. 2014 [82])

## 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.

## Key Info

### Benefits and harms

Substantial net benefits of the recommended alternative

Swallowing screening tools (SSTs) include a range of tasks including demographics, medical history, global assessment of function, oral mechanism examination, and direct swallowing assessment. It was suggested that a direct observation of swallowing is a compulsory item within an SST. 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 SSTs outweigh any harm as an early indicator of aspiration and/or dysphagia risk. 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 that better outcomes with respect to pneumonia risk occur the earlier the swallow screening is conducted.

As dysphagia can occur without aspiration, the review by Daniels et al. 2012 [84] 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.

### Quality of 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 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 (Crary et al. 2013 [81]; Poorjavad et al. 2014 [82]; Schepp et al. 2012

[83]; Daniels et al. 2012 [84]; Leder et al. 2012 [91]; Martino et al. 2014 [94]).

## 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) [82] in a recent 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.

Schep et al. (2012) [83] 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 recent 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) [84] 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) [91] 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 [94] reported a high diagnostic performance of using water intake of 10 teaspoons and a lingual motor test.

A recent cohort study by Cray et al. (2013) [81] 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  $\leq$  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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Reference standard Swallow screen test (FEES or VF)	Certainty in effect estimates (Quality of evidence)	Plain text summary
Performance in identifying dysphagia <sup>1</sup>	Based on data from 392 patients in 6 studies.	Screening tests' sensitivities ranged from 47 to 100%, while their specificity ranged from about 63 to 100%. Four screening tools that	<b>Moderate</b> Due to serious imprecision <sup>2</sup>	Oral Pharyngeal and Clinical Swallowing Examination, Bedside

7 Critical	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)	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** .

### References

- [81] Crary MA, Carnaby GD, Sia I, Khanna A, Waters MF : Spontaneous swallowing frequency has potential to identify dysphagia in acute stroke.. Stroke; a journal of cerebral circulation 2013;44(12):3452-7 [Pubmed Journal](#)
- [82] Poorjavad M, Jalaie S : Systemic review on highly qualified screening tests for swallowing disorders following stroke: Validity and reliability issues.. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2014;19(8):776-85 [Pubmed](#)
- [83] Schepp SK, Tirschwell DL, Miller RM, Longstreth WT : Swallowing screens after acute stroke: a systematic review.. Stroke; a journal of cerebral circulation 2012;43(3):869-71 [Pubmed Journal](#)
- [84] Daniels SK, Anderson JA, Willson PC : Valid items for screening dysphagia risk in patients with stroke: a systematic review.. Stroke; a journal of cerebral circulation 2012;43(3):892-7 [Pubmed Journal](#)
- [91] Leder SB, Suiter DM, Warner HL, Acton LM, Swainson BA : Success of recommending oral diets in acute stroke patients based on passing a 90-cc water swallow challenge protocol.. Topics in stroke rehabilitation 19(1):40-4 [Pubmed Journal](#)
- [94] Martino R, Maki E, Diamant N : Identification of dysphagia using the Toronto Bedside Swallowing Screening Test (TOR-BSST®): are 10 teaspoons of water necessary?. International journal of speech-language pathology 2014;16(3):193-8 [Pubmed Journal](#)

### Weak 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 [85]; O'Horo et al. 2015 [87])

### 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.

## Key Info

### Benefits and harms

Small net benefit, or little difference between alternatives

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 [85]; O'Horo et al. 2015 [87]; Mortenson et al. 2016 [86]; Kjaersgaard et al. 2014 [88]; Kjaersgaard et al. 2015 [89]). 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.

### Quality of evidence

Low

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 bedside assessments or instrumental assessments are effective in predicting the outcomes of pneumonia or return to oral intake 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 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 intake.

## Rationale

Systematic reviews reveal that research into the effectiveness of bedside assessments is becoming more robust and in return can report with more confidence their sensitivity and specificity in detecting aspiration risk. A meta-analysis of the findings from the collective studies is still not possible, however, due to heterogeneity in study designs, populations, and study endpoints. Therefore, the recommendation remains weak as to whether bedside assessments are as effective in detecting aspiration risk as instrumental assessment. There are too few studies of high quality that explore the endpoint of pneumonia or return to oral intake to suggest bedside assessments are as effective as instrumental assessments in predicting these outcomes. Overall, consensus is that patients should be referred to a speech pathologist so appropriate assessments can be made within 24 hours.

## Clinical Question/ PICO

**Population:** Adults with stroke  
**Intervention:** Clinical bedside swallow exam  
**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 (FEES) and videofluoroscopy (VFS) (Kertscher et al 2014 [85]; O'Horo et al 2015 [87]). 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) [88] 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) [89] 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) [86] reported on the diagnostic performance of the Swallowing Assessment of Saliva (SAS) based on FOTT approach. Comparison with FEES 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.

With respect to the timing of a comprehensive swallowing assessment by a speech-language pathologist, Brady et al (2016) [93] demonstrated that there was a strong dose-response relationship between a comprehensive dysphagia 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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Instrumental swallow exam	Clinical bedside swallow exam		
<p><b>Pneumonia</b> until discharge</p> <p>8 Critical</p>	<p>n/a</p> <p>Based on data from 559 patients in 2 studies. (Randomized controlled)</p>	<p><b>65</b> per 1000</p>	<p><b>105</b> per 1000</p>	<p><b>Very Low</b> Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision <sup>1</sup></p>	<p>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</p>
		<p>Difference: <b>40 more</b> per 1000 CI 95%</p>			

<b>Performance in diagnosing dysphagia/aspiration</b>	Based on data from 10,850 patients in 53 studies.	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.	<b>Moderate</b> Due to serious imprecision <sup>2</sup>	Very few bedside assessments can allow detection of dysphagia/aspiration compared with gold standard.
7 Critical				

- 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 ;

## References

- [85] Kertscher B, Speyer R, Palmieri M, Plant C : Bedside screening to detect oropharyngeal dysphagia in patients with neurological disorders: an updated systematic review.. *Dysphagia* 2014;29(2):204-12 [Pubmed Journal](#)
- [86] Mortensen J, Jensen D, Kjaersgaard A : A validation study of the Facial-Oral Tract Therapy Swallowing Assessment of Saliva.. *Clinical rehabilitation* 2016;30(4):410-5 [Pubmed Journal](#)
- [87] O'Horo JC, Rogus-Pulia N, Garcia-Arguello L, Robbins J, Safdar N : Bedside diagnosis of dysphagia: a systematic review.. *Journal of hospital medicine* 2015;10(4):256-65 [Pubmed Journal](#)
- [88] Kjaersgaard A, Nielsen LH, Sjölund BH : Randomized trial of two swallowing assessment approaches in patients with acquired brain injury: Facial-Oral Tract Therapy versus Fiberoptic Endoscopic Evaluation of Swallowing.. *Clinical rehabilitation* 2014;28(3):243-53 [Pubmed Journal](#)
- [89] Kjaersgaard A, Nielsen LH, Sjölund BH : Factors affecting return to oral intake in inpatient rehabilitation after acquired brain injury.. *Brain injury* 2015;29(9):1094-104 [Pubmed Journal](#)
- [93] Bray BD, Smith CJ, Cloud GC, Enderby P, James M, Paley L, Tyrrell PJ, Wolfe CDA, Rudd AG : The association between delays in screening for and assessing dysphagia after acute stroke, and the risk of stroke-associated pneumonia.. *Journal of neurology, neurosurgery, and psychiatry* 2017;88(1):25-30 [Pubmed Journal](#)

## Strong Recommendation

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 [77])

## Practical Info

Where stroke patients require modified texture foods and thickened fluids, these should be prescribed using nationally agreed descriptors (Cichero et al. 2017 [95]).

## Key Info

### 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 [77]). 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 [78]).

### Quality of 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

Factors 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:** Behavioural intervention  
**Comparator:** Control

### Summary

Geeganage et al (2012) [77] undertook a systematic review exploring the impact of a range of interventions seeking to address dysphagia and nutritional support in acute and subacute stroke. Within the range of interventions investigated only 5 were reported to have been focused on randomised controlled trials of behavioural interventions such as swallowing exercises, environmental modifications, safe swallowing advice, and appropriate dietary modifications. Three of the studies compared high and low intensity with or without usual care behavioural interventions, while the remaining 2 studies investigated differing modes of delivering interventions. Overall, behavioural interventions were found to significantly reduce dysphagia at the end of the trials.

Bakhtiyari et al (2015) [78] 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 behavioural interventions can reduce dysphagia, and that earlier intervention is preferable to delayed intervention.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Behavioural intervention		
<b>Presence of dysphagia</b> At end of trial  7 Critical	Odds Ratio 0.52 (CI 95% 0.3 - 0.88) Based on data from 423 patients in 5 studies. (Randomized controlled) Follow up End of trial: 1 - 6 months	<b>495</b> per 1000	<b>338</b> per 1000	<b>Low</b> Due to serious risk of bias, Due to serious publication bias <sup>1</sup>	behavioural intervention may decrease presence of dysphagia
<b>Institutionalisation</b>  At end of trial  8 Critical	Odds Ratio 0.76 (CI 95% 0.39 - 1.48) Based on data from 306 patients in 2 studies. (Randomized controlled) Follow up 6 months	<b>229</b> per 1000	<b>184</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>2</sup>	behavioural intervention probably has little or no difference on institutionalisation
<b>Death</b> At end of trial  9 Critical	Odds Ratio 0.83 (CI 95% 0.46 - 1.51) Based on data from 306 patients in 2 studies. (Randomized controlled) Follow up 6 months	<b>216</b> per 1000	<b>186</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>3</sup>	behavioural intervention probably has little or no difference on death
<b>Chest infection or pneumonia</b> At end of trial  8 Critical	Odds Ratio 0.5 (CI 95% 0.24 - 1.04) Based on data from 423 patients in 5 studies. (Randomized controlled) Follow up End of trial: 1 - 6 months	<b>354</b> per 1000	<b>215</b> per 1000	<b>Low</b> Due to serious risk of bias, Due to serious publication bias <sup>4</sup>	behavioural intervention may decrease chest infection or pneumonia

- Risk of bias: Serious** . Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to a number of studies were written and published in Mandarin and it was not possible for all aspects relative to risk of bias to be examined. ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: No serious** . **Publication bias: Serious** . Publication of studies in a language other than English meant that not all aspects of the studies could be evaluated in systematic review. ;
- Risk of bias: No serious** . Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias -

less impact on subjective outcomes ; **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Due to the 2 studies reporting this outcome being drawn from the same cohort of patients ; **Publication bias: No serious .**

3. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Both studies were drawn from the same cohort of patients, so while 2 reported studies only 1 cohort of participants ; **Publication bias: No serious .**

4. **Risk of bias: Serious .** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to a number of studies were written and published in Mandarin and it was not possible for all aspects relative to risk of bias to be examined. ; **Inconsistency: No serious . Indirectness: No serious . Imprecision: No serious . Publication bias: Serious .** Publication of studies in a language other than English meant that not all aspects of the studies could be evaluated in systematic review. ;

## References

[77] Geeganage C, Beavan J, Ellender S, Bath PMW : Interventions for dysphagia and nutritional support in acute and subacute stroke.. The Cochrane database of systematic reviews 2012;10 CD000323 [Pubmed Journal](#)

[78] Bakhtiyari J, Sarraf P, Nakhostin-Ansari N, Tafakhori A, Logemann J, Faghihzadeh S, Harirchian MH : Effects of early intervention of swallowing therapy on recovery from dysphagia following stroke.. Iranian journal of neurology 2015;14(3):119-24 [Pubmed](#)

Weak Recommendation **AGAINST**

For stroke survivors with dysphagia, non-invasive brain stimulation should only be provided within a research framework. (Pisegna et al. 2016 [79])

## Key Info

### 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 [79]). 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.

### Quality of evidence

Low

The quality of the systematic review itself was high (Pisegna et al. 2016 [79]). 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:** Brain stimulation
- Comparator:** Sham

**Summary**

A systematic review and meta-analysis conducted by Piseigna et al (2016) [79] looked at evidence to support 2 forms of brain stimulation (tDCS and rTMS) as a treatment for dysphagia post-stroke. The review required studies to have used RCT methodology. They were able to identify 7 studies investigating whether dysphagia could be significantly improved by either rTMS (n=4) or tDCS (n=3). The methods used in each of the studies was quite variable in terms of:

- When treatment was instigated (24 hours to 40 months post-stroke)
- The primary outcome measure
- Stimulation parameters.

Overall the meta-analysis indicated that there was a significant, moderate effect size indicating that transcranial neurostimulation was a beneficial treatment for dysphagia as compared to sham. When each of the techniques was analysed separately, there was non-significant benefit from tDCS and a significant benefit from rTMS as compared to sham. However, due to the heterogeneity in methods used (e.g. hemisphere stimulated and stimulation duration) it is difficult to provide a therapeutic guideline at this stage. The long-terms effects are also not clear.

Du et al (2016) [80] reported on a double-blind RCT with 57 participants treated within 2 months of dysphagia onset. There were 3 arms to the RCT - high frequency, low frequency and sham - using rTMS. The assessor was blinded to treatment group. Findings suggested dysphagia was reduced after 5 days for both active treatment groups, which was maintained at 3 months. It should be noted that dysphagia severity reduced for all groups over the course of the study. The level of disability (mRS and Barthel Index) improved in all patients, but there was also an interaction effect for the Barthel Index.

Overall, studies to date suggest that transcranial neurostimulation may significantly improve dysphagia. However, the best treatment parameters are yet to be determined.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Sham	Brain stimulation		
<p><b>Swallowing function</b> End of treatment to 3 months</p>	<p>Measured by: PAS, functional dysphagia scale, DOSS High better</p>	<p>Difference: <b>SMD 0.55 more</b> ( CI 95% 0.17 fewer - 0.93 fewer )</p>		<p><b>Low</b> Due to serious inconsistency, Due to serious</p>	<p>brain stimulation may improve swallowing function</p>

7 Critical	Based on data from: 146 patients in 8 studies. (Randomized controlled)		indirectness <sup>1</sup>
------------	--	--	---------------------------

1. **Inconsistency: Serious** . Point estimates vary widely - differences in length of intervention and follow-up periods ; **Indirectness: Serious** . Differences between the intervention/comparator of interest and those studied - two types of brain stimulation - tDCS and rTMS, and there are differences in the comparators used as well as dosage / method of stimulation., Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important) - 3 studies use the PAS while 5 studies use functional measures of dysphagia. ; **Imprecision: No serious** . **Publication bias: No serious** .

### References

[79] Pisegna JM, Kaneoka A, Pearson WG, Kumar S, Langmore SE : Effects of non-invasive brain stimulation on post-stroke dysphagia: A systematic review and meta-analysis of randomized controlled trials.. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 2016;127(1):956-68 [Pubmed Journal](#)

[80] Du J, Yang F, Liu L, Hu J, Cai B, Liu W, Xu G, Liu X : Repetitive transcranial magnetic stimulation for rehabilitation of poststroke dysphagia: A randomized, double-blind clinical trial.. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 2016;127(3):1907-13 [Pubmed Journal](#)

Weak Recommendation

AGAINST

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 [76])

### Key Info

#### 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 [76]). No information about harm from the acupuncture treatment was reported

#### Quality of 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 [76]). 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

Factors 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) [76] 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 rigour 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.

The evidence to-date is still emerging in regards to the effectiveness of acupuncture as a treatment for dysphagia, but studies to-date say that it may be a useful treatment to reduce dysphagia.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		No acupuncture	Acupuncture		
Improved swallowing function  7 Critical	Odds Ratio 5.17 (CI 95% 4.18 - 6.38) Based on data from 6,134 patients in 72 studies. (Randomized controlled) Follow up unclear		CI 95%	<b>Very Low</b> Due to very serious risk of bias, Due to serious indirectness, Due to serious publication bias <sup>1</sup>	We are uncertain whether acupuncture improves or worsen swallowing function

1. **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, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** . **Indirectness: Serious** . lack of clear information in terms of range of follow-up times for each of the studies ; **Imprecision: No serious** . **Publication bias: Serious** . Many of the studies were not published in English and the quality of information provided was brief in many. ;

## References

[76] Long Y-B, Wu X-P : A meta-analysis of the efficacy of acupuncture in treating dysphagia in patients with a stroke..  
Acupuncture in medicine : journal of the British Medical Acupuncture Society 2012;30(4):291-7 [Pubmed Journal](#)

Weak Recommendation **AGAINST**

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 [71])

## Key Info

### 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) [71], 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) [72] 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.

### Quality of evidence

Low

There was significant heterogeneity in the studies included in the systematic review (Chen et al, 2016 [71]). 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 plus swallow therapy  
**Comparator:** Swallow therapy only

#### Summary

Chen et al (2016) [71] 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, the meta-analysis of swallowing function measures 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). There was significant heterogeneity, and excluding one study with the largest effect size yielded a significant but smaller pooled effect 0.93 with non-significant heterogeneity. 3 included studies that compared NMES alone to swallowing therapy showed no significant differences (SMD 0.25, 95% CI -0.16 to 0.65). NMES appears to be an effective addition to swallowing therapy but may not be more effective when used alone.

Huang et al (2014) [72] conducted a small randomised trial comparing NMES plus swallowing therapy to NMES alone and swallowing therapy alone in 3 treatment arms. It appears that the trial was not included in the Chen et al meta-analysis because the review authors could not obtain the required data. Between-group comparisons showed no post-treatment differences on the Functional Oral Intake Scale or the Penetration-Aspiration Scale, but on the Functional Dysphagia scale there were significant differences on cookies and thick liquids, with the combined NMES and swallowing therapy group showing the greatest performance.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Swallow therapy only	Surface neuromuscular electrical stimulation		
<b>Swallowing function</b> 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. <sup>1</sup> (Randomized controlled) Follow up 2-4 weeks of treatment	Difference: <b>SMD 1.27 more</b> ( CI 95% 0.51 more - 2.02 more )		<b>Low</b> Due to serious inconsistency, Due to serious risk of bias <sup>2</sup>	Surface neuromuscular electrical stimulation (plus swallow therapy) may improve swallowing function

1. Systematic review [71]. **Baseline/comparator:** Control arm of reference used for intervention .
2. **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<sup>2</sup>: 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** .

## References

[71] Chen Y-W, Chang K-H, Chen H-C, Liang W-M, Wang Y-H, Lin Y-N : The effects of surface neuromuscular electrical stimulation on post-stroke dysphagia: a systemic review and meta-analysis.. *Clinical rehabilitation* 2016;30(1):24-35 [PubMed Journal](#)

[72] Huang K-L, Liu T-Y, Huang Y-C, Leong C-P, Lin W-C, Pong Y-P : Functional outcome in acute stroke patients with oropharyngeal Dysphagia after swallowing therapy.. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2014;23(10):2547-53 [PubMed Journal](#)

Weak Recommendation

AGAINST

For stroke survivors with dysphagia, pharyngeal electrical stimulation is not routinely recommended. (Bath et al. 2016 [73]; Scutt et al. 2015 [74])

## Key Info

### 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 [73]) 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 [74]). No adverse events were reported in any studies investigating PES as a treatment for dysphagia.

### Quality of 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 [74]). 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 [74]). 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 [73]). 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

Factors 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. 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 [73]).

The meta-analysis by Scutt et al (2015) [74] based on 3 studies suggested that at 2 weeks post treatment there was a reduction in the severity of penetration-aspiration and clinical dysphagia presentation, with perhaps more benefit for those with more severe dysphagia. This was supported by the findings reported by Suntrup et al (2015) [75]. Therefore, there is no clear evidence to support the clinical use of PES as an intervention for dysphagia in all stroke populations, with further research required to determine if there is a subgroup of stroke survivors with dysphagia for whom it may be an effective treatment.

Suntrup et al (2015) [75] reported the descriptive findings of a small RCT (n=26 with 2:1 randomisation) of stroke survivors with severe dysphagia that required tracheostomy insertion. Their primary outcome was successful decannulation at the completion of the intervention due to increased swallow function, and had secondary outcomes of length of stay (LOS) and swallowing function at discharge as measured by the Functional Oral Intake Scale (FOIS). Results indicated that those who received PES were more likely to be decannulated at the end of the intervention period than those who received the sham intervention, but there was no impact on LOS or swallowing function at discharge as measured by the FOIS.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Sham	Pharyngeal electrical stimulation		
<b>Death</b> <sup>1</sup> 12 week follow-up period  9 Critical	Hazard Ratio 1.11 (CI 95% 0.34 - 3.59) Based on data from 141 patients in 1 studies. (Randomized controlled) Follow up 12 weeks		CI 95%	<b>Very Low</b> Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision <sup>2</sup>	pharyngeal electrical stimulation may have little or no difference on death

<p><b>Respiratory tract infection</b> Up to 12 weeks post treatment</p> <p>7 Critical</p>	<p>Odds Ratio 1.33 (CI 95% 0.31 - 5.79) Based on data from 152 patients in 1 studies. (Randomized controlled) Follow up 12 weeks post treatment</p>	<p><b>45</b> per 1000</p> <p><b>59</b> per 1000</p> <p>Difference: <b>14 more</b> per 1000 (CI 95% 31 fewer - 169 more)</p>	<p><b>Very Low</b> Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision<sup>3</sup></p>	<p>pharyngeal electrical stimulation may have little or no difference on respiratory tract infection</p>
<p><b>Severity of stroke</b><sup>4</sup> 2 weeks post treatment</p> <p>8 Critical</p>	<p>Odds Ratio 0.53 (CI 95% 0.23 - 1.22) Based on data from 134 patients in 1 studies. (Randomized controlled) Follow up 2 weeks post treatment</p>	<p>CI 95%</p>	<p><b>Very Low</b> Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision<sup>5</sup></p>	<p>We are uncertain whether pharyngeal electrical stimulation improves or worsen severity of stroke</p>
<p><b>Swallowing function</b><sup>6</sup> 2 weeks post treatment</p> <p>7 Critical</p>	<p>Measured by: Dysphagia Severity Rating Scale Scale: 0-12 Lower better Based on data from: 133 patients in 1 studies. (Randomized controlled) Follow up 2 weeks</p>	<p><b>4.9</b> (Mean)</p> <p><b>5.2</b> (Mean)</p> <p>Difference: <b>MD 0.31 more</b> (CI 95% 0.56 fewer - 1.18 more)</p>	<p><b>Very Low</b> Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness<sup>7</sup></p>	<p>We are uncertain whether pharyngeal electrical stimulation improves or worsen swallowing function</p>

- All-cause death during follow-up was recorded and compared between intervention groups.
- Risk of bias: Serious**. Missing intention-to-treat analysis, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to incomplete / unclear description of the comparator and details relating to what activities (therapeutic or not) that were conducted during the 10 minute "active intervention", Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: No serious**. **Indirectness: Serious**. Differences between the population of interest and those studied - there are many individuals seen in the clinical stroke population who were excluded from the study. ; **Imprecision: Serious**. Only data from one study ;
- Risk of bias: Serious**. Missing intention-to-treat analysis, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to incomplete / unclear description of the comparator and details relating to what activities (therapeutic or not) that were conducted during the 10 minute "active intervention", Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: No serious**. **Indirectness: Serious**. Differences between the population of interest and those studied - there are many individuals seen in the clinical stroke population who were excluded from the study. ; **Imprecision: Serious**. Only data from one study, Wide confidence intervals ;
- covariate adjusted odds ratio from an ordinal logistic regression comparing modified Rankin scores, where odds ratios < 1 mean that the PES group had lower odds of a worse outcome.
- Risk of bias: Serious**. where odds ratios < 1 mean that the PES group had lower odds of a worse outcome. ; **Inconsistency: No serious**. **Indirectness: Serious**. Differences between the population of interest and those studied - there are many individuals seen in the clinical stroke population who were excluded from the study. ; **Imprecision: Serious**. Only data from one study ;
- Swallowing function measured by DSRS was a secondary outcome as opposed to the pen-asp scale which was a primary outcome measure assessing swallowing safety.
- Risk of bias: Serious**. Missing intention-to-treat analysis, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, due to incomplete / unclear description of the comparator and details relating to what activities (therapeutic or not) that were conducted during the 10 minute "active intervention". ; **Inconsistency: No serious**. **Indirectness: Serious**. Differences between the population of interest and those studied - there are many individuals seen in the clinical stroke population who were excluded from the study. ; **Imprecision: Serious**. Only data from one study ; **Publication bias: No serious**.

## References

[73] Bath PM, Scutt P, Love JO, Clavé P, Cohen D, Dziewas R, Iversen HK, Ledl C, Ragab S, Soda H, Warusevitane A, Woisard V, Hamdy S : Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke: A Randomized Controlled Trial.. Stroke; a journal of cerebral circulation 2016;47(6):1562-70 [Pubmed Journal](#)

[74] Scutt P, Lee HS, Hamdy S, Bath PM : Pharyngeal Electrical Stimulation for Treatment of Poststroke Dysphagia: Individual Patient Data Meta-Analysis of Randomised Controlled Trials.. Stroke research and treatment 2015;2015 429053 [Pubmed Journal](#)

[75] Suntrup S, Marian T, Schröder JB, Suttrup I, Muhle P, Oelenberg S, Hamacher C, Minnerup J, Warnecke T, Dziewas R : Electrical pharyngeal stimulation for dysphagia treatment in tracheotomized stroke patients: a randomized controlled trial.. Intensive care medicine 2015;41(9):1629-37 [Pubmed Journal](#)

## 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 [92]). Therefore, the hydration and nutrition status should be regularly monitored and managed.

## 10 - 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 [100]; Sandercock et al. 2015 [97]). 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 [100]; Sandercock et al. 2015 [97]).

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 71% of stroke patients received hyperacute aspirin therapy and 90% of ischaemic stroke patients received aspirin within 48 hours of admission (Stroke Foundation 2014 [26]).

### 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 [100])

### Key Info

#### 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 [100]). It was shown to increase symptomatic intracranial haemorrhage but the effect was small (2 more per 1000 patients) (Sandercock et al. 2014 [100]).

#### Quality of 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

##### Resources considerations

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 [105]).

##### Implementation consideration

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) [100] 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) [96] 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 aspirin 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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo or no treatment	Aspirin		
<b>Death or dependence</b> 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	<b>462</b> per 1000	<b>449</b> per 1000	<b>High</b>	Aspirin decreases death or dependence
Difference: <b>13 fewer</b> per 1000 ( CI 95% 23 fewer - 2 fewer )					
<b>Death</b> 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	<b>129</b> per 1000	<b>120</b> per 1000		
Difference: <b>9 fewer</b> per 1000 ( CI 95% 15 fewer - 2 fewer )					
<b>Recurrent stroke<sup>1</sup></b> During treatment	Odds Ratio 0.77 (CI 95% 0.69 - 0.87) Based on data from 40,850 patients in 3 studies. (Randomized controlled)	<b>31</b> per 1000	<b>24</b> per 1000	<b>High</b>	Aspirin decreases recurrent stroke
Difference: <b>7 fewer</b> per 1000 ( CI 95% 9 fewer - 4 fewer )					

8 Critical	Follow up 5 days to 3 months of treatment				
<b>Symptomatic intracranial haemorrhage</b> During treatment	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	<b>8</b> per 1000	<b>10</b> per 1000	<b>High</b>	Aspirin slightly increases symptomatic intracranial haemorrhage
8 Critical	Follow up 5 days to 3 months of treatment	Difference: <b>2 more</b> per 1000 (CI 95% 0 fewer - 4 more)			

1. Recurrent ischaemic/unknown stroke during treatment period

**References**

[96] Rothwell PM, Algra A, Chen Z, Diener H-C, Norrving BO, Mehta Z : Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. The Lancet 2016; [Journal Website](#)

[100] Sandercock PAG, Counsell C, Tseng M-C, Cecconi E : Oral antiplatelet therapy for acute ischaemic stroke.. The Cochrane database of systematic reviews 2014;3 CD000029 [Pubmed Journal](#)

Strong Recommendation

AGAINST

Acute antiplatelet therapy should not be given within 24 hours of alteplase administration. (Zinkstok et al. 2012 [104])

**Key Info**

**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 [104]).

**Quality of 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

Factors 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 alteplase is given.

## 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 [104]) 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		No additional therapy	Early antiplatelet therapy		
<b>Death</b> 3 months  9 Critical	n/a  Based on data from 564 patients in 1 studies. (Randomized controlled) Follow up 3 months	<b>97</b> per 1000	<b>112</b> per 1000  CI 95%	<b>Low</b> Due to very serious imprecision <sup>1</sup>	early antiplatelet therapy (within 24h) may increase death
<b>Favourable outcome<sup>2</sup></b> 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	<b>572</b> per 1000	<b>549</b> per 1000  Difference: <b>23 fewer</b> per 1000 ( CI 95% 103 fewer - 55 more )	<b>Moderate</b> Due to serious imprecision <sup>3</sup>	early antiplatelet therapy (within 24h) probably has little or no difference on favourable outcome
<b>Symptomatic intracranial haemorrhage<sup>4</sup></b>  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	<b>16</b> per 1000	<b>44</b> per 1000  Difference: <b>28 more</b> per 1000 ( CI 95% 106 more - 0 fewer )	<b>Moderate</b> Due to serious imprecision <sup>5</sup>	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 .**

## References

[104] Zinkstok SM, Roos YB : Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial.. Lancet (London, England) 2012;380(9843):731-7 [Pubmed](#) [Journal](#)

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 [97]; Whiteley et al. 2013 [103])

## Key Info

### 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 [97]). These effects appeared to produce a neutral effect on death and dependency at follow-up of greater than a month (Sandercock et al. 2015 [97]).

### Quality of 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

Factors 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 [97]; Whiteley et al. 2013 [103]). 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) [97] 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) [103] 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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo or no treatment	Anticoagulant		
<b>Death or dependence</b> 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	<b>599</b> per 1000	<b>597</b> per 1000	<b>Moderate</b> Due to serious inconsistency <sup>1</sup>	Anticoagulant probably has little or no difference on death or dependence
<b>Death</b> 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	<b>205</b> per 1000	<b>213</b> per 1000	<b>High</b>	Anticoagulant has little or no difference on death
<b>Recurrent stroke<sup>2</sup></b> 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	<b>36</b> per 1000	<b>28</b> per 1000	<b>High</b>	Anticoagulant decreases recurrent stroke

<p><b>Symptomatic intracranial haemorrhage</b> During treatment</p> <p>8 Critical</p>	<p>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</p>	<p><b>5</b> per 1000</p> <p><b>13</b> per 1000</p> <p>Difference: <b>8 more</b> per 1000 ( CI 95% 5 more - 11 more )</p>	<p><b>High</b></p> <p>Anticoagulant increases symptomatic intracranial haemorrhage</p>
---	---	--	--

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

### References

[97] Sandercock PAG, Counsell C, Kane EJ : Anticoagulants for acute ischaemic stroke.. The Cochrane database of systematic reviews 2015;3 CD000024 [Pubmed Journal](#)

[103] Whiteley WN, Adams HP, Bath PMW, Berge E, Sandset PM, Dennis M, Murray GD, Wong K-SL, Sandercock PAG : Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials.. The Lancet. Neurology 2013;12(6):539-45 [Pubmed Journal](#)

### Weak Recommendation

Aspirin plus clopidogrel may be used in the short term (first three weeks) in high-risk patients with minor ischaemic stroke or TIA to prevent stroke recurrence. (Wong et al. 2013 [102])

### Key Info

#### Benefits and harms

Small net benefit, or little difference between alternatives

A systematic review with the majority of data coming from the comparison of clopidogrel plus aspirin versus aspirin alone in the CHANCE trial showed significant reduction in recurrent stroke (28 fewer per 1000 patients) and the composite outcome of stroke, TIA, ACS and all deaths (35 fewer per 1000 patients), with no increase in major bleeding (Wong et al. 2013 [102]). Sub-group analysis found that the majority of benefit in absolute terms was in patients with intracranial atherosclerosis (a high-risk group that is less common in the Australian population) (Liu et al. 2015 [106]).

#### Quality of evidence

Moderate

Quality of evidence is moderate because the majority of population was Asian with a high prevalence of intracranial atherosclerosis – the applicability to Asian and non-Asian patients in Australia is uncertain.

#### Preference and values

No substantial variability expected

Patients are likely to prefer to receive this treatment due to significant benefits and little harm, despite uncertainty in the transferability of evidence.

**Resources and other considerations**

No important issues with the recommended alternative

**Resources considerations**

In an economic evaluation of patients with acute TIA or minor stroke with a high risk of recurrence, it was found that clopidogrel plus aspirin, compared to aspirin alone, was cost-effective at an additional cost of US\$5,200 per QALY gained (cost reference year 2011), and was cost-saving when the cost of the generic clopidogrel drug was used (Pan et al. 2014 [101]). 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**

Evidence, predominantly from the CHANCE trial, shows that the combination of aspirin and clopidogrel significantly improved patients outcomes without an increase in harms. However, as the majority of participants were Asian and most benefit occurred in those with intra-cranial atherosclerosis, it is unclear if these conclusions can be directly applied to stroke patients in Australia.

**Clinical Question/ PICO**

**Population:** Adults with acute stroke  
**Intervention:** Dual antiplatelet therapy  
**Comparator:** Mono antiplatelet therapy

**Summary**

A systematic review (Wong et al 2013 [102]) of trials investigating dual antiplatelet therapy compared to mono antiplatelet included 14 studies with 9012 patients, including the recent CHANCE 2012 study that was substantially larger than all previous trials. Dual antiplatelet therapies included aspirin + clopidogrel, aspirin + dipyridamole and cilostazol + aspirin. Dual antiplatelet therapy produced significant reductions in the risk of recurrent stroke (RR 0.69, 95% CI 0.60 to 0.80) and the composite outcome of stroke, TIA, ACS, and all deaths, with no significant increase in major bleeding. Sensitivity analyses that included only the 7 trials that were double-blinded showed similar results. While there was no significant heterogeneity across different dual and mono antiplatelet treatment regimens, the majority of data came from the aspirin + clopidogrel versus aspirin alone comparison investigated in the CHANCE trial.

Two subsequent randomised controlled trials (He et al 2015 [98]; Yi et al 2014 [99]) compared combined clopidogrel and aspirin treatment to aspirin alone. Both had short follow-up periods, of 14 or 30 days. In both trials, neurological deterioration and recurrent stroke occurred less often in the combined therapy groups, although only one of the studies reported that these differences were statistically significant.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Mono antiplatelet therapy	Dual antiplatelet therapy		
<b>Recurrent stroke</b> 7 days to 18+ months of follow- up	Relative risk 0.69 (CI 95% 0.6 - 0.8) Based on data from 8,796 patients in 14 studies. (Randomized controlled) Follow up 7 days to 18+ months	<b>90</b> per 1000	<b>62</b> per 1000	<b>Moderate</b> Due to serious indirectness <sup>1</sup>	Dual antiplatelet therapy probably decreases recurrent stroke
		Difference: <b>28 fewer</b> per 1000 (CI 95% 18 fewer - 36 fewer)			

8 Critical					
<b>Composite outcome of stroke, TIA, ACS, and all deaths</b> 7 days to 18+ months of follow-up	Relative risk 0.71 (CI 95% 0.63 - 0.81) Based on data from 8,174 patients in 8 studies. (Randomized controlled) Follow up 7 days-18 months	<b>121</b> per 1000	<b>86</b> per 1000	<b>Moderate</b> Due to serious indirectness <sup>2</sup>	Dual antiplatelet therapy probably decreases composite outcome of stroke, TIA, ACS, and all deaths
8 Critical					
<b>Major bleeding</b> 7 days to 18+ months of follow-up	Relative risk 1.35 (CI 95% 0.7 - 2.59) Based on data from 8,466 patients in 10 studies. (Randomized controlled) Follow up 7 days to 18+ months	<b>4</b> per 1000	<b>5</b> per 1000	<b>Moderate</b> Due to serious indirectness <sup>3</sup>	Dual antiplatelet therapy probably has little or no effect on major bleeding
8 Critical					

1. **Inconsistency: No serious . Indirectness: Serious .** Differences between the population of interest and those studied - predominantly Asian population ; **Imprecision: No serious . Publication bias: No serious .**
2. **Inconsistency: No serious . Indirectness: Serious .** Differences between the population of interest and those studied - predominantly Asian population ; **Imprecision: No serious . Publication bias: No serious .**
3. **Inconsistency: No serious . Indirectness: Serious .** Differences between the population of interest and those studied - predominantly Asian population ; **Imprecision: No serious . Publication bias: No serious .**

## References

- [98] He F, Xia C, Zhang J-H, Li X-Q, Zhou Z-H, Li F-P, Li W, Lv Y, Chen H-S : Clopidogrel plus aspirin versus aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke.. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2015;22(1):83-6 [PubMed Journal](#)
- [99] Yi X, Lin J, Wang C, Zhang B, Chi W : A comparative study of dual versus monoantiplatelet therapy in patients with acute large-artery atherosclerosis stroke.. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2014;23(7):1975-81 [PubMed Journal](#)
- [102] Wong KSL, Wang Y, Leng X, Mao C, Tang J, Bath PMW, Markus HS, Gorelick PB, Liu L, Lin W, Wang Y : Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis.. Circulation 2013;128(15):1656-66 [PubMed Journal](#)

## 11 - Acute blood pressure lowering therapy

Acute stroke, whether due to infarction or haemorrhage, is associated with high blood pressure (Bath et al 2014 [108]), and 70% of stroke patients have a history of high blood pressure on admission (Stroke Foundation 2015 [26]). In acute ischaemic stroke, high blood pressure appears to adversely affect outcomes through increasing the risk of cerebral oedema (Bath et al 2014 [108]). In acute intracerebral haemorrhage, the blood pressure often becomes elevated and may be associated with haematoma expansion (Bath et al 2014 [108]). 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 [108]). 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 [108])

### Key Info

#### Benefits and harms

Small net benefit, or little difference between alternatives

No benefits were found in a robust Cochrane systematic review of acute blood pressure lowering to SBP < 140 mmHg (Bath and Krishnan 2014 [108]) and in the ATACH-2 trial there was no benefit of lowering to < 140 mmHg and increased renal adverse effects (Qureshi 2016 [105]).

#### Quality of evidence

High

The evidence has multiple high-quality randomised controlled trials (Bath and Krishnan 2014 [108]).

#### Preference and values

No substantial variability expected

No substantial variability was identified or expected.

#### Resources and other considerations

Factors 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 ischaemic stroke  
**Intervention:** Blood pressure lowering  
**Comparator:** Control

#### Summary

Two systematic reviews from Lee et al (2015) [107] and Bath et al (2014) [108] showed that there was no overall effect of treatment on death as an outcome in the studies analysed. No differences were observed when analysed by the subgroup of ischaemic stroke either.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Blood pressure lowering		
<b>Death and dependency</b> <sup>1</sup>  9 Critical	Odds Ratio 1 (CI 95% 0.92 - 1.08) Based on data from 11,015 patients in 8 studies. <sup>2</sup> (Randomized controlled)	<b>409</b> per 1000  Difference: <b>0 fewer</b> per 1000 ( CI 95% 19 more - 20 fewer )	<b>409</b> per 1000	<b>High</b>	Blood pressure lowering has little or no difference on death and dependency

- mRS > 1 or > 2 depending on definition in individual trials
- Systematic review [108] with included studies: Eveson 2007, PRoFESS 2009, RIGHT 2013, CATIS 2013, CHHIPS 2009, SCAST 2011, VENTURE 2013, ENOS 2014. **Baseline/comparator::** Control arm of reference used for intervention .

### References

[107] Lee M, Ovbiagele B, Hong K-S, Wu Y-L, Lee J-E, Rao NM, Feng W, Saver JL : Effect of Blood Pressure Lowering in Early Ischemic Stroke: Meta-Analysis . Stroke 2015/05/28 ; [Website](#)

[108] Bath PM, Krishnan K : Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database of Systematic Reviews 2014; [Journal](#)

### Clinical Question/ PICO

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

### Summary

Systematic review by Tsivgoulis et al 2016 [111], 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 [109]).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Blood pressure lowering		

<b>Death and dependency</b> <sup>1</sup>  9 Critical	Odds Ratio 0.87 (CI 95% 0.76 - 1) Based on data from 3,315 patients in 4 studies. <sup>2</sup> (Randomized controlled)	<b>543</b> per 1000  Difference: <b>2 more</b> per 1000 ( CI 95% 47 more - 43 fewer )	<b>545</b> per 1000	<b>High</b>	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 [108] with included studies: SCAST 2011, ENOS 2014, INTERACT pilot 2008, INTERACT-2 2013, Koch 2008, CHHIPS 2009, RIGHT 2013. **Baseline/comparator::** Control arm of reference used for intervention .

### References

[108] Bath PM, Krishnan K : Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database of Systematic Reviews 2014; [Journal](#)

[109] Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, Toyoda K, Wang Y, Yamamoto H, Yoon B-W : Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage.. The New England journal of medicine 2016; [Pubmed](#)

[111] Tsivgoulis G, Katsanos AH : Intensive blood pressure reduction in acute intracerebral hemorrhage: A meta-analysis.. Neurology 2015;84(24):2464 [Pubmed](#) [Journal](#)

### 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 [111]; Qureshi et al. 2016 [109])

## Key Info

### 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. [111], 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 [110]). 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 [110]). 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 [109]).

### Quality of evidence

Multiple high-quality randomised controlled trials.

High

### 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 (Tsvigoulis et al. 2016 [111]), together with results from ATACH-2 (Qureshi et al. 2016 [109]), 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

Systematic review by Tsvigoulis et al 2016 [111], 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 [109]).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Control	Blood pressure lowering		
Death and dependency <sup>1</sup>  9 Critical	Odds Ratio 0.87 (CI 95% 0.76 - 1) Based on data from 3,315 patients in 4 studies. <sup>2</sup> (Randomized controlled)	<b>543</b> per 1000	<b>545</b> per 1000	<b>High</b>	In patients with mild to moderate size ICH, a treatment target of SBP 140 has little or no difference on death and dependency.
		Difference: <b>2 more</b> per 1000 ( CI 95% 47 more - 43 fewer )			

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

2. Systematic review [108] with included studies: SCAST 2011, ENOS 2014, INTERACT pilot 2008, INTERACT-2 2013, Koch 2008, CHHIPS 2009, RIGHT 2013. **Baseline/comparator::** Control arm of reference used for intervention .

### References

[108] Bath PM, Krishnan K : Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database of Systematic Reviews 2014; [Journal](#)

[109] Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, Toyoda K, Wang Y, Yamamoto H, Yoon B-W : Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage.. The New England journal of medicine 2016; [Pubmed](#)

[111] Tsvigoulis G, Katsanos AH : Intensive blood pressure reduction in acute intracerebral hemorrhage: A meta-analysis.. Neurology 2015;84(24):2464 [Pubmed Journal](#)

#### Weak Recommendation

Pre-existing antihypertensive medication may be withheld until patients are neurologically stable and treatment can be given safely. (Bath and Krishnan 2014 [108])

### Key Info

#### Benefits and harms

Small net benefit, or little difference between alternatives

In the meta-analysis incorporating the ENOS study, continuing pre-stroke anti-hypertensives did not affect the primary outcome but was associated with worse Barthel Index at 90 days (Bath and Krishnan 2014 [108]). The exact reason for this is uncertain.

#### Quality of 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) [108] conducted a systematic review of the effectiveness of altering blood pressure in acute stroke patients. In a total of 2860 patients, they did not find a significant difference of death or dependency between patients who continued pre-stroke anti-hypertensive treatment and those who stopped. However, better functional outcomes measured by Barthel Index were associated with discontinuation of antihypertensives.

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

- mRS > 1 or > 2 depending on definition in individual trials
- Systematic review [108] with included studies: COSSACS 2010, ENOS 2014. **Baseline/comparator**:: Control arm of reference used for intervention.

## References

[108] Bath PM, Krishnan K : Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database of Systematic Reviews 2014; [Journal](#)

## 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.

## 12 - Surgery for ischaemic stroke and management of cerebral oedema

Patients with a large cerebral infarction generally have a poor prognosis (Cruz-Flores et al. 2012 [114]). 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 [113]). Conservative management of brain oedema is not supported by clinical trials (Juttler et al. 2014 [113]).

### Strong 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 [114])

### Key Info

#### Benefits and harms

Substantial net benefits of the recommended alternative

There is a clear benefit in terms of survival for those aged 60 years and under (386 fewer deaths per 1000 patients treated) (Cruz-Flores et al. 2012 [114]). For those that survived there was a non-significant trend toward moderate to severe disability (Cruz-Flores et al. 2012 [114]).

#### Quality of evidence

Moderate

The overall quality of evidence is moderate, with a meta-analysis of three randomised controlled trials in which numbers are small and the confidence intervals are wide (Cruz-Flores et al. 2012 [114]). An individual patient pooled analysis of patients treated within 48 hours also supports most of the findings.

#### 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

##### Resources considerations

In a study conducted in the Netherlands, Hofmeijer et al. (2013) [116] 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. No similar studies have been conducted in Australia.

### Rationale

There is a clear benefit in terms of survival. For those that survived there was a non-significant trend toward moderate to severe disability. The overall quality of evidence is moderate, with a meta-analysis of three randomised controlled trials in which numbers are small and confidence intervals are wide. An individual patient pooled analysis of patients treated within 48 hours also supports most of the findings.

### 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 [114] 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.

A systematic review of trials investigating hemicraniectomy for middle cerebral artery infarction by Back et al (2015) [112] found 6 studies meeting inclusion criteria. This included the 3 trials in the Cruz-Flores et al review as well as 3 more recent trials that did not restrict inclusion to patients < 60 years of age. The meta-analysis found similar reductions in mortality but also provided further evidence that surviving patients experience at least moderately severe disability.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Medical treatment	Hemicraniectomy		
<b>Death at end of follow-up</b> 12 months of follow-up  9 Critical	Odds Ratio 0.19 (CI 95% 0.09 - 0.37) Based on data from 134 patients in 3 studies. <sup>1</sup> (Randomized controlled) Follow up 12 months	<b>631</b> per 1000  Difference: <b>386 fewer</b> per 1000 ( CI 95% 498 fewer - 243 fewer )	<b>245</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>2</sup>	Hemicraniectomy probably decreases death at end of follow-up
<b>Death or disability defined as mRS &gt; 3 at end of follow-up</b> 12 months of follow-up  9 Critical	Odds Ratio 0.56 (CI 95% 0.27 - 1.15) Based on data from 134 patients in 3 studies. <sup>3</sup> (Randomized controlled) Follow up 12 months	<b>754</b> per 1000  Difference: <b>122 fewer</b> per 1000 ( CI 95% 301 fewer - 25 more )	<b>632</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>4</sup>	Hemicraniectomy probably slightly decreases death or disability defined as mRS >3 at end of follow-up
<b>Death or severe disability defined as mRS &gt; 4 at 12 months</b> 12 months of follow-up	Odds Ratio 0.26 (CI 95% 0.13 - 0.51) Based on data from 134 patients in 3 studies. <sup>5</sup> (Randomized controlled) Follow up 12 months	<b>662</b> per 1000  Difference: <b>325 fewer</b> per 1000 ( CI 95% 459 fewer - 162 fewer )	<b>337</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>6</sup>	Hemicraniectomy probably decreases death or severe disability defined as mRS >4 at end of follow-up

9 Critical					
<b>Severe disability among survivors defined as mRS 4 to 5 at 12 months</b>	Odds Ratio 2.45 (CI 95% 0.92 - 6.55) Based on data from 78 patients in 3 studies. <sup>7</sup> (Randomized controlled) Follow up 12 months	<b>333</b> per 1000	<b>550</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>8</sup>	Hemicraniectomy probably increases severe disability among survivors defined as mRS 4 to 5 at 12 months
9 Critical		Difference: <b>217 more</b> per 1000 (CI 95% 18 fewer - 433 more)			

1. Systematic review [114] with included studies: DECIMAL 2007, DESTINY 2007, HAMLET 2009. **Baseline/comparator::** Control arm of reference used for intervention .
2. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Low number of patients ; **Publication bias: No serious** .
3. Systematic review [114] with included studies: DECIMAL 2007, DESTINY 2007, HAMLET 2009. **Baseline/comparator::** Control arm of reference used for intervention .
4. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Low number of patients ; **Publication bias: No serious** .
5. Systematic review [114] with included studies: DESTINY 2007, HAMLET 2009, DECIMAL 2007. **Baseline/comparator::** Control arm of reference used for intervention .
6. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Low number of patients ; **Publication bias: No serious** .
7. Systematic review [114] with included studies: DECIMAL 2007, DESTINY 2007, HAMLET 2009. **Baseline/comparator::** Control arm of reference used for intervention .
8. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Low number of patients ; **Publication bias: No serious** .

## References

[112] Back L, Nagaraja V, Kapur A, Eslick GD : Role of decompressive hemicraniectomy in extensive middle cerebral artery strokes: a meta-analysis of randomised trials.. Internal medicine journal 2015;45(7):711-7 [Pubmed Journal](#)

[114] Cruz-Flores S, Berge E, Whittle IR : Surgical decompression for cerebral oedema in acute ischaemic stroke. Cochrane Database of Systematic Reviews 2012; [Pubmed Journal](#)

## Weak 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. (Back et al. 2015 [112]; Jüttler et al. 2014 [113])

## Key Info

### Benefits and harms

Small net benefit, or little difference between alternatives

There is evidence from a single randomised controlled trial that hemicraniectomy in patients over the age of 60 with malignant middle cerebral artery territory infarction improves the odds of survival with moderately severe disability.

### Quality of evidence

Moderate

The evidence is based on a single randomised controlled trial (Jüttler et al. 2014 [113]).

### 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.

## Rationale

There is evidence from a single randomised controlled trial that hemicraniectomy in patients over the age of 60 with malignant middle cerebral artery territory infarction improves the odds of survival with moderately severe disability, although the evidence is based on a single randomised controlled trial.

## Clinical Question/ PICO

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

### Summary

Jüttler et al (2014) [113] conducted a randomised trial (N = 112) of hemicraniectomy for patients with malignant middle-cerebral-artery infarction, which was stopped early when significant benefits were seen at 6-month follow-up. The trial included patients 61 years of age or older (up to 80) as benefits of hemicraniectomy have previously been demonstrated for people 60 years or younger. The control group received conservative treatment in an intensive care unit. Hemicraniectomy significantly increased the proportion of patients surviving without severe disability at 6 months (OR 2.91, 95% CI 1.06 to 7.49) and 12 months, although all patients in both groups had at least moderate disability (modified Rankin scores  $\geq 3$ ). Substantially fewer patients in the hemicraniectomy group had died by 12-month follow-up.

A systematic review of trials investigating hemicraniectomy for middle cerebral artery infarction by Back et al (2015) [112] found 6 studies meeting inclusion criteria. This included the trial by Jüttler et al as well as earlier trials that had only included younger patients (18 to 60 years) and two other recent trials that also included older patients (up to 75 or 80 years). The meta-analysis showed that hemicraniectomy significantly reduced the odds of death at 6 and 12 months, as well as the odds of having a modified Rankin score of 2 at 12 months. The benefits of hemicraniectomy that had been reported in earlier reviews including patients 60 years or younger appear to apply equally to patients older than 60 years, although only the trial by Jüttler et al provides direct evidence for this specific subgroup.

**Note:** Jüttler et al (2014) [113] did not report relative effect estimates for the outcomes at 12 months. The estimates reported here were manually calculated based on the reported raw numbers of events.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Medical treatment	Hemicraniectomy		
<b>Survival without severe disability at 6 months</b> <sup>1</sup> 6 months  9 Critical	Odds Ratio 2.91 (CI 95% 1.06 - 7.49) Based on data from 112 patients in 1 studies. (Randomized controlled)	<b>159</b> per 1000  Difference: <b>196 more</b> per 1000 (CI 95% 8 more - 427 more)	<b>355</b> per 1000	<b>Moderate</b> Due to serious imprecision - single study <sup>2</sup>	Hemicraniectomy probably increases survival without severe disability at 6 months
<b>Survival at 12 months</b> 12 months  9 Critical	Odds Ratio 4.23 (CI 95% 1.86 - 9.6) Based on data from 109 patients in 1 studies. (Randomized controlled)	<b>242</b> per 1000  Difference: <b>333 more</b> per 1000 (CI 95% 131 more - 512 more)	<b>575</b> per 1000	<b>Moderate</b> Due to serious imprecision - single study <sup>3</sup>	Hemicraniectomy probably increases survival at 12 months
<b>Survival without severe disability at 12 months</b> <sup>4</sup> 12 months  9 Critical	Odds Ratio 3.23 (CI 95% 1.32 - 7.91) Based on data from 109 patients in 1 studies. (Randomized controlled)	<b>161</b> per 1000  Difference: <b>222 more</b> per 1000 (CI 95% 41 more - 442 more)	<b>383</b> per 1000	<b>Moderate</b> Due to serious imprecision - single study <sup>5</sup>	Hemicraniectomy probably increases survival without severe disability at 12 months
<b>Neurological Outcome at 12 Months</b> <sup>6</sup> 12 months  9 Critical	Measured by: NIHSS Scale: 0-42 Lower better Based on data from: 112 patients in 1 studies. (Randomized controlled)	<b>42</b> points (Median)  Difference: <b>20 fewer</b> CI 95%	<b>22</b> points (Median)	<b>Moderate</b> The difference was significant according to a Wilcoxon test. Due to serious imprecision - single study <sup>7</sup>	Hemicraniectomy probably improves neurological outcome at 12 months

1. mRS 0-4 at 6 months

2. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Only data from one study, Low number of patients ; **Publication bias: No serious .**

3. **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 .**

4. mRS 0-4 at 12 months

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 .**

6. All patients (includes deaths imputed as NIHSS=42)

7. **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 .**

## References

[112] Back L, Nagaraja V, Kapur A, Eslick GD : Role of decompressive hemicraniectomy in extensive middle cerebral artery strokes: a meta-analysis of randomised trials.. Internal medicine journal 2015;45(7):711-7 [Pubmed Journal](#)

[113] Jüttler E, Unterberg A, Woitzik J, Bösel J, Amiri H, Sakowitz OW, Gondan M, Schiller P, Limprecht R, Luntz S, Schneider H, Pinzer T, Hobohm C, Meixensberger J, Hacke W : Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke.. The New England journal of medicine 2014;370(12):1091-100 [Pubmed Journal](#)

[114] Cruz-Flores S, Berge E, Whittle IR : Surgical decompression for cerebral oedema in acute ischaemic stroke. Cochrane Database of Systematic Reviews 2012; [Pubmed Journal](#)

Weak Recommendation

AGAINST

Corticosteroids are not recommended for management of stroke patients with brain oedema and raised intracranial pressure. (Sandercock et al. 2011 [115])

## Key Info

### 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.

### Quality of 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

Factors 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) [115] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo	Corticosteroids		
<b>Death</b> 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. <sup>1</sup> (Randomized controlled) Follow up 2 weeks to 12 months	<b>379</b> per 1000	<b>347</b> per 1000	<b>High</b>	Corticosteroids have little or no effect on death
Difference: <b>32 fewer</b> per 1000 ( CI 95% 121 fewer - 71 more )					
<b>Death within one month</b> 1 month  9 Critical	Odds Ratio 0.97 (CI 95% 0.63 - 1.47) Based on data from 466 patients in 8 studies. <sup>2</sup> (Randomized controlled)	<b>281</b> per 1000	<b>275</b> per 1000	<b>High</b>	Corticosteroids have little or no effect on death within one month
Difference: <b>6 fewer</b> per 1000 ( CI 95% 83 fewer - 84 more )					

1. Systematic review [115] with included studies: McQueen 1978, Mulley 1978, Norris 1976, Norris 1986, Ogun 2001, Patten 1972, Bauer 1973, Gupta 1978. **Baseline/comparator::** Control arm of reference used for intervention .

2. Systematic review [115] with included studies: Norris 1986, Ogun 2001, Patten 1972, Bauer 1973, Gupta 1978, McQueen 1978, Mulley 1978, Norris 1976. **Baseline/comparator::** Control arm of reference used for intervention .

## References

[115] Sandercock PA, Soane T : Corticosteroids for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2011; [Pubmed Journal](#)

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.

Practice Statement

**Consensus-based recommendation**

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

## 13 - Intracerebral haemorrhage (ICH) management

ICH accounts for 11% to 22% of incident strokes and half of all stroke deaths (Feigin et al. 2009 [117]). 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.

### 13.1 - 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 [123]). 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 [118]; Bajenaru et al. 2010 [119]; Sprigg et al. 2014 [120]).

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 [121])
- 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 [121])

### Key Info

#### Benefits and harms

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 [121]).

Small net benefit, or little difference between alternatives

#### Quality of evidence

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.

Moderate

#### Preference and values

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

No substantial variability expected

#### Resources and other considerations

##### Resources considerations

Important issues, or potential issues not investigated

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 [121]). 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 [121]). 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) [121] 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) [121] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Fresh frozen plasma	Prothrombin complex concentrate		
INR $\leq 1.2$ 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	<b>87</b> per 1000	<b>745</b> per 1000	<b>Moderate</b> Due to serious risk of bias, Due to serious imprecision, Upgraded due to Large magnitude	Prothrombin complex concentrate may improve the chances of INR reduction to $\leq 1.2$ within 3 h in patients with warfarin related ICH
		Difference: <b>658 more</b> per 1000 (CI 95% 222 more - 863 more)			

<b>Death</b> 90 days	Relative risk 0.53 (CI 95% 0.2 - 1.4) Based on data from 50 patients in 1 studies. <sup>2</sup> (Randomized controlled) Follow up 90 days	<b>348</b> per 1000	<b>184</b> per 1000	of effect and reasons for bias limited <sup>1</sup>	<b>Low</b> Due to serious risk of bias, Due to serious imprecision <sup>3</sup>	Prothrombin complex concentrate may decrease death in patients with warfarin related ICH, compared with standard FFP
<b>Functional independence</b> <sup>4</sup> 90 days	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	<b>391</b> per 1000	<b>522</b> per 1000	<b>Low</b> Due to serious risk of bias, Due to serious imprecision <sup>5</sup>	Prothrombin complex concentrate may increase functional independence	
<b>Haematoma expansion</b> <sup>6</sup> 24 hours	Measured by: blood in brain (mL) Lower better Based on data from: 50 patients in 1 studies. (Randomized controlled) Follow up 24 hours	Difference: <b>MD 16.4 fewer</b> ( CI 95% 2.9 fewer - 29.9 fewer )		<b>Low</b> Due to serious risk of bias, Due to serious imprecision <sup>7</sup>	Prothrombin complex concentrate may decrease haematoma expansion	

- 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** .
- Primary study [121]. **Baseline/comparator::** Control arm of reference used for intervention .
- 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** .
- mRS score of 0-3
- 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** . Low number of patients, Only data from one study, Wide confidence intervals ; **Publication bias: No serious** .
- Haematomata expansion commonly occurs in warfarin related ICH, and is a well-recognised surrogate marker for increased risk of death and poor outcome
- 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** .

## References

[121] Steiner T, Poli S, Griebel M, Hüsing J, Hajda J, Freiberger A, Bendszus M, Bösel J, Christensen H, Dohmen C, Hennerici M, Kollmer J, Stetefeld H, Wartenberg KE, Weimar C, Hacke W, Veltkamp R : Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *The Lancet Neurology* 15(6):566-573 [Journal Website](#)

## 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 [124]; Connolly 2016 [125])

## 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.

A study of andexanet alfa has been published showing effective reversal of apixaban and rivaroxaban, but it is not yet available in Australia.

## Key Info

### 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 [124]; Connolly 2016 [125]).

### Quality of evidence

Low

Evidence is from two single-group prospective cohort studies (Pollack et al. 2016 [124]; Connolly 2016 [125]). 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 [124]; Connolly 2016 [125]). 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) [124] 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 normalised 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 ( $\leq 72$  hours) after idarucizumab administration.

In the ANNEXA-4 trial, Connolly et al (2016) [125] 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 hemostasis. 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.

### References

[124] Pollack CV : Evidence Supporting Idarucizumab for the Reversal of Dabigatran.. The American journal of medicine 2016; [Pubmed Journal](#)

[125] Connolly SJ, Milling TJ, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Goodman S, Leeds J, Wiens BL, Siegal DM, Zotova E, Meeks B, Nakamya J, Lim WT, Crowther M : Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors.. The New England journal of medicine 2016;375(12):1131-41 [Pubmed Journal](#)

Strong Recommendation

AGAINST

For stroke patients with intracerebral haemorrhage previously receiving antiplatelet therapy, platelet transfusion should not be administered. (Baharoglu et al. 2016 [122])

## Key Info

### 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 [122]).

### Quality of evidence

Moderate

One large randomised controlled trial of low risk of bias (downgraded due to only one study available) (Baharoglu et al. 2016 [122]).

### 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

Factors 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 [122]). 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) [122] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Standard care	Platelet transfusion		
<b>Death or dependence</b> <sup>1</sup> 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	<b>559</b> per 1000  Difference: <b>162 more</b> per 1000 ( CI 95% 28 more - 267 more )	<b>721</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>2</sup>	Platelet transfusion probably increases death or dependence following intracerebral haemorrhage in patients previously taking antiplatelet therapy
<b>Survival</b> <sup>3</sup> 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	<b>774</b> per 1000  Difference: <b>94 fewer</b> per 1000 ( CI 95% 243 fewer - 29 more )	<b>680</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>4</sup>	Platelet transfusion may decrease survival following intracerebral haemorrhage in patients previously taking antiplatelet therapy
<b>Serious adverse events</b> <sup>5</sup> 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	<b>295</b> per 1000  Difference: <b>126 more</b> per 1000 ( CI 95% 8 fewer - 275 more )	<b>421</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>6</sup>	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** .

## References

[122] Baharoglu MI, Cordonnier C, Salman RA-S, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, Nederkoorn PJ, de Haan RJ, Roos YB : Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial.. Lancet (London, England) 2016; [Pubmed Journal](#)

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](#)).

## 13.2 - 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 [129]). 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 [130]).

Weak Recommendation

AGAINST

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 [126]; Gregson et al. 2012 [129])

### 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.

### Key Info

#### 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 [126]; Xiao et al. 2012 [127]; Gregson et al. 2012 [129]). Crossover from medical to surgical treatment is a frequent confounding factor in interpretation.

#### Quality of 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 [126]). Furthermore, another meta-analysis found no statistically significant difference in outcomes (Gregson et al. 2012 [129]).

#### 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

Factors not considered

### Rationale

Although a meta-analysis suggested net benefit from surgery for lobar haematomas (Mendelow et al. 2013 [126]), 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 [129]). This therapy should therefore be carefully considered in each situation.

**Clinical Question/ PICO**

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

**Summary**

A meta-analysis by Mendelow et al (2013) [126] 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) [127], 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Conservative treatment	Surgery		
<b>Unfavourable outcome</b> <sup>1</sup> 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	<b>665</b> per 1000  Difference: <b>70 fewer</b> per 1000 ( CI 95% 34 fewer - 105 fewer )	<b>595</b> per 1000	<b>Low</b> Due to serious inconsistency, Due to serious indirectness <sup>2</sup>	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<sup>2</sup>: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**.

## References

[126] Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM : Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial.. *Lancet* (London, England) 2013;382(9890):397-408 [Pubmed Journal](#)

[127] Xiao BO, Wu F-F, Zhang H, Ma Y-B : A randomized study of urgent computed tomography-based hematoma puncture and aspiration in the emergency department and subsequent evacuation using craniectomy versus craniectomy only.. *Journal of neurosurgery* 2012;117(3):566-73 [Pubmed Journal](#)

## 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) [129] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Conservative treatment	Surgery		
<b>Unfavourable outcome<sup>1</sup></b> 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	<b>782</b> per 1000  Difference: <b>31 fewer</b> per 1000 ( CI 95% 16 more - 82 fewer )	<b>751</b> per 1000	<b>Moderate</b> Due to serious inconsistency <sup>2</sup>	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  $\geq 3$  or Barthel index  $\leq 90$ .

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 than 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. ;

## References

[129] Gregson BA, Broderick JP, Auer LM, Batjer H, Chen X-C, Juvela S, Morgenstern LB, Pantazis GC, Teernstra OPM, Wang W-Z, Zuccarello M, Mendelow AD : Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage.. Stroke; a journal of cerebral circulation 2012;43(6):1496-504 [Pubmed Journal](#)

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 [129]; Naff et al. 2011 [130])

## Key Info

### 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 [128]; Naff et al. 2011 [130]). 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 [129]; Chen et al. 2011 [131]).

### Quality of 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

Factors not considered

## Rationale

There are few studies assessing intraventricular thrombolysis or endoscopic surgery for ventricular haemorrhage (King et al. 2012 [128]; Gregson et al. 2012 [129]; Naff et al. 2011 [130]; Chen et al. 2011 [131]). 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) [129] showed that surgery probably reduces the rate of an unfavourable outcome. A small randomised controlled trial (N = 48) by Chen et al (2010) [131] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Conservative treatment	Surgery		
<b>Unfavourable outcome</b> <sup>1</sup> 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	<b>888</b> per 1000  Difference: <b>204 fewer</b> per 1000 ( CI 95% 488 fewer - 275 more )	<b>684</b> per 1000	<b>Moderate</b> Due to serious imprecision (statistically nonsignificant outcome) <sup>2</sup>	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<sup>2</sup>=0 ; **Indirectness: No serious** . **Imprecision: Serious** . Wide confidence intervals ; **Publication bias: No serious** .

**References**

[129] Gregson BA, Broderick JP, Auer LM, Batjer H, Chen X-C, Juvela S, Morgenstern LB, Pantazis GC, Teernstra OPM, Wang W-Z, Zuccarello M, Mendelow AD : Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage.. Stroke; a journal of cerebral circulation 2012;43(6):1496-504 [Pubmed Journal](#)

[131] Chen C-C, Liu C-L, Tung Y-N, Lee H-C, Chuang H-C, Lin S-Z, Cho D-Y : Endoscopic surgery for intraventricular hemorrhage (IVH) caused by thalamic hemorrhage: comparisons of endoscopic surgery and external ventricular drainage (EVD) surgery.. World neurosurgery 2011;75(2):264-8 [Pubmed Journal](#)

**Clinical Question/ PICO**

**Population:** Adults with intraventricular haemorrhage complicating parenchymal haemorrhage  
**Intervention:** Intraventricular thrombolysis  
**Comparator:** Placebo

**Summary**

Naff et al (2011) [130] 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) [128] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo	Intraventricular thrombolysis		
<b>Death</b> 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	<b>227</b> per 1000	<b>193</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>1</sup>	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.
<b>Adverse events - Ventriculitis</b> 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	<b>91</b> per 1000	<b>77</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>2</sup>	intraventricular thrombolysis probably has little or no difference on adverse events - ventriculitis
<b>Adverse events - Symptomatic bleeding</b> 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	<b>45</b> per 1000	<b>229</b> per 1000	<b>Moderate</b> Due to serious imprecision <sup>3</sup>	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 .**

### References

[128] King NKK, Lai JL, Tan LB, Lee KK, Pang BC, Ng I, Wang E : A randomized, placebo-controlled pilot study of patients with spontaneous intraventricular haemorrhage treated with intraventricular thrombolysis.. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* 2012;19(7):961-4 [Pubmed Journal](#)

[130] Naff N, Williams MA, Keyl PM, Tuhim S, Bullock MR, Mayer SA, Coplin W, Narayan R, Haines S, Cruz-Flores S, Zuccarello M, Brock D, Awad I, Ziai WC, Marmarou A, Rhoney D, McBee N, Lane K, Hanley DF : Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial.. *Stroke; a journal of cerebral circulation* 2011;42(11):3009-16 [Pubmed Journal](#)

### 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 [126]; Mendelow et al. 2005 [132]). 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 [132]). 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.

## 14 - 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 [135]). 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 [135]). 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. It also impedes early mobilisation and poses an infection risk (Roffe et al. 2011 [135]).

The majority of recommendations on the use of oxygen after acute stroke are based on consensus (Poutine et al. 2012 [137]). A survey of UK physicians showed that just over half would start oxygen supplementation after stroke (Poutine et al. 2012 [137]). Therefore, it is crucial to determine the balance between benefits and harms of oxygen therapy.

There have been a number of small randomised controlled trials on this topic and the biggest trial to date, SO2S, is awaiting publication.

Weak Recommendation

AGAINST

For acute stroke patients who are not hypoxic, the routine use of supplemental oxygen is not recommended. (Ali et al. 2014 [134]; Roffe et al. 2011 [135])

### Key Info

#### Benefits and harms

Small net benefit, or little difference between alternatives

Routine oxygen supplementation was shown to improve neurological outcome measured on NIHSS but not critical outcomes of death and disability (Ali et al. 2014 [134]; Roffe et al. 2011 [135]).

#### Quality of evidence

Low

The overall quality is low due to high risk of bias and imprecision (data were from a single randomised controlled trial).

#### 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

Factors not considered

### Rationale

Low-quality evidence shows ambivalent results for routine use of oxygen supplementation for acute stroke patients (Ali et al. 2014 [134]; Roffe et al. 2011 [135]; Ronning et al. 1999 [136]). Considering the extra cost incurred and uncertainty in the benefit, routine use of supplemental oxygen cannot be recommended.

### Clinical Question/ PICO

**Population:** Adults with acute ischaemic stroke  
**Intervention:** Early routine oxygen supplementation  
**Comparator:** Room air

### Summary

A pilot RCT with 289 participants showed no benefits in death or disability, but improvement in neurological outcomes at one week (Ali et al 2014 [134]; Roffe et al 2011 [135]). The full trial of this pilot study (N=8003) has only been published in abstract version and concluded that routine oxygen therapy does not improve functional outcome at 90 days in any of the predefined subgroups including stroke type or severity. A previous quasi-RCT with 550 patients also did not find routine supplemental oxygen to be beneficial in nonhypoxic stroke patients (Ronning et al 1999 [136]). Overall, the current evidence does not support the use of routine oxygen supplementation.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Room air	Early routine oxygen supplementation		
<b>Death</b> 1 week  9 Critical	Odds Ratio 1.2 (CI 95% 0.32 - 4.55) Based on data from 289 patients in 1 studies. (Randomized controlled)	<b>28</b> per 1000	<b>33</b> per 1000	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>1</sup>	Early routine oxygen supplementation may have little or no difference on death
<b>Death at 6 months</b> 6 months  9 Critical	Hazard Ratio 1.1 (CI 95% 0.59 - 2.07) Based on data from 289 patients in 1 studies. (Randomized controlled) Follow up 6 months			<b>Low</b> Due to serious imprecision and serious risk of bias <sup>2</sup>	Early routine oxygen supplementation may have little or no difference on death at 6 months
<b>Improvement in neurological outcome <sup>3</sup></b> 1 week  7 Critical	Odds Ratio 2.9 (CI 95% 1.59 - 5.4) Based on data from 276 patients in 1 studies. <sup>4</sup> (Randomized controlled) Follow up 1 week	<b>135</b> per 1000	<b>312</b> per 1000	<b>Low</b> Due to serious imprecision, Due to serious risk of bias <sup>5</sup>	Early routine oxygen supplementation may improve neurological outcome at 1 week
<b>Disability (mRS &gt;= 3)</b> 6 months  8 Critical	Odds Ratio 1.01 (CI 95% 0.62 - 1.65) Based on data from 256 patients in 1 studies. <sup>6</sup> (Randomized controlled) Follow up 6 months	<b>554</b> per 1000	<b>556</b> per 1000	<b>Low</b> Due to serious imprecision, Due to serious risk of bias <sup>7</sup>	early routine oxygen supplementation may have little or no difference on disability (mrs >= 3)
<b>QOL <sup>8</sup></b> 6 months  7 Critical	Based on data from 222 patients in 1 studies. <sup>9</sup>	Adjusted mean scores favoured the oxygen group but the difference was not statistically significant		<b>Very Low</b> Due to very serious risk of bias, Due to serious imprecision <sup>10</sup>	We are uncertain whether early routine oxygen supplementation improves or worsen QOL

- Risk of bias: Serious** . Single blinded trial ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: Serious** . Only data from one study ; **Publication bias: No serious** .
- Risk of bias: Serious** . Single blinded trial ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: Serious** . Only data from one study, Wide confidence intervals ; **Publication bias: No serious** .
- Significant improvement was defined as reduction of 4 or more points in the NIHSS from baseline to week 1.
- Primary study [135]. **Baseline/comparator::** Control arm of reference used for intervention .
- Risk of bias: Serious** . single blinded trial ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: Serious** . Only data from one study ; **Publication bias: No serious** .
- Primary study [134]. **Baseline/comparator::** Control arm of reference used for intervention .

7. **Risk of bias: Serious** . single blinded trial ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: Serious** . Only data from one study, Wide confidence intervals ; **Publication bias: No serious** .
8. Measured by EQ-5D and EQ-VAS
9. Primary study **Supporting references:** [134], Adjusted mean scores favoured the oxygen group (high rate of missing data)..
10. **Risk of bias: Very Serious** . Incomplete data and/or large loss to follow up, 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; heterogeneity did not allow pooled data ; **Publication bias: No serious** .

### References

- [134] Ali K, Warusevitane A, Lally F, Sim J, Sills S, Pountain S, Nevatte T, Allen M, Roffe C : The stroke oxygen pilot study: a randomized controlled trial of the effects of routine oxygen supplementation early after acute stroke--effect on key outcomes at six months.. PloS one 2014;8(6):e59274 [Pubmed Journal](#)
- [135] Roffe C, Ali K, Warusevitane A, Sills S, Pountain S, Allen M, Hodsoll J, Lally F, Jones P, Crome P : The SOS pilot study: a RCT of routine oxygen supplementation early after acute stroke--effect on recovery of neurological function at one week.. PloS one 2011;6(5):e191113 [Pubmed Journal](#)
- [136] Rønning OM, Guldvog B : Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial.. Stroke; a journal of cerebral circulation 1999;30(10):2033-7 [Pubmed](#)

Weak Recommendation

AGAINST

For acute ischaemic stroke patients, hyperbaric oxygen therapy is not recommended. (Bennett et al. 2014 [133])

### Key Info

#### 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 [133]).

#### Quality of 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 [133]).

#### 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

Factors not considered

## Rationale

Low-quality evidence shows ambivalent results for hyperbaric oxygen therapy for acute stroke patients (Bennett et al. 2014 [133]). Considering the extra cost incurred and uncertainty in the benefit, routine use of supplemental oxygen cannot be recommended.

## Clinical Question/ PICO

**Population:** Adults with acute ischaemic stroke  
**Intervention:** Hyperbaric oxygen therapy  
**Comparator:** Standard practice

### Summary

Bennet et al (2014) [133] 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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Standard practice	Hyperbaric oxygen therapy		
<b>Death</b> 3-6 months  9 Critical	Relative risk 0.97 (CI 95% 0.34 - 2.75) Based on data from 144 patients in 4 studies. <sup>1</sup> (Randomized controlled) Follow up 3- to 6-months	<b>85</b> per 1000  Difference: <b>3 fewer</b> per 1000 ( CI 95% 56 fewer - 149 more )	<b>82</b> per 1000	<b>Low</b> Due to serious imprecision, Due to serious risk of bias <sup>2</sup>	hyperbaric oxygen therapy may have little or no difference on death
<b>Functional outcome</b> 1 to 365 days  7 Critical	Based on data from 705 patients in 11 studies.	Four of 14 scale measures of disability and functional performance indicated improvement following HBOT.		<b>Very Low</b> Due to very serious risk of bias and serious inconsistency <sup>3</sup>	We are uncertain whether hyperbaric oxygen therapy increases or decreases functional outcome

1. Systematic review [133] . **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** .

## References

[133] Bennett MH, Weibel S, Wasiaak J, Schnabel A, French C, Kranke P : Hyperbaric oxygen therapy for acute ischaemic stroke.. The Cochrane database of systematic reviews 2014;11 CD004954 [Pubmed Journal](#)

## Practice Statement

### Consensus-based recommendation

Stroke patients who are hypoxic (i.e. < 95% oxygen saturation) should be given supplemental oxygen.

## Rationale

There is inadequate evidence of benefits of supplemental oxygen therapy in normoxic ischaemic stroke patients. Many other non-stroke studies have found benefits in supplemental oxygen therapy for those who are hypoxic, and it was the strong opinion of the working party that such benefits are likely in those with stroke.

## 15 - 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 [143]; Muir et al. 2004 [144]; Krams et al. 2003 [145]; Muir et al. 2003 [146]; Diener et al. 2008 [147]; Lyden et al. 2007 [148]; Davalos et al. 2012 [138]; Chamorro et al. 2014 [139]; Ginsberg et al. 2013 [140]; Saver et al. 2015 [142]; Heiss et al. 2012 [141]).

### 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 [149]). 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.

## 16 - 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 [152]). Previously undetected diabetes is found in 16–24% of patients admitted with stroke (Gray et al. 2004 [153]; Kernan et al. 2005 [154]). 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 [155]). Observational data also reveal poorer outcomes for non-diabetic patients with hyperglycaemia (Capes et al. 2001 [152]). Glucose intolerance after stroke is also common (approximately 25%) (Kernan et al. 2005 [154]; Allport et al. 2006 [155]) and linked to higher stroke recurrence (Vermeer et al. 2006 [156]).

There is now good evidence that hyperglycaemia needs management regardless of the patient's diabetic status (Bellolio et al. 2014 [151]; Ntaios et al. 2014 [150]; Middleton et al. 2011 [157] and Drury et al. 2014 [158]). 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 94% of Australian stroke hospitals have locally agreed protocols for glucose control in place (Stroke Foundation 2015 [26]).

### 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 [157])

### Practical Info

The trials in the Cochrane review (Bellolio et al. 2014 [151]) used tight control of blood glucose (4–7.5mmol/L), however the QASC trial (Middleton et al. 2011 [157]) 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.

### Key Info

#### 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  $\geq 11$  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 [157]).

#### Quality of 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

##### 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 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  $\geq 11$  mmol/L in the first 72 hours improves outcomes at 90 days (Middleton et al. 2011 [157]).

## 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) [157] 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  $\geq 11$  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) [158] 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) [157] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		No FeSS protocol	Fever, Sugar, Swallow (FeSS) protocol		
Death or dependency <sup>1</sup> 90 days  9 Critical	n/a  Based on data from 1,007 patients in 1 studies. (Randomized controlled) Follow up 90 days	<b>577</b> per 1000	<b>420</b> per 1000	<b>Moderate</b> Due to serious imprecision, Due to serious indirectness <sup>2</sup>	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
		Difference: <b>157 fewer</b> per 1000 ( CI 95% 58 fewer - 254 fewer )			

<p><b>Functional dependency (Barthel Index &gt;= 60)</b><sup>3</sup> 90 days 7 Critical</p>	<p>n/a Based on data from 955 patients in 1 studies. (Randomized controlled) Follow up 90 days</p>	<p><b>898</b> per 1000 <b>923</b> per 1000 Difference: <b>25 more</b> per 1000 ( CI 95% 36 fewer - 86 more )</p>	<p><b>Moderate</b> Due to serious imprecision, Due to serious indirectness<sup>4</sup></p>	<p>protocols.  There is little or no difference in functional dependency as measured by Barthel Index &gt;= 60 for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.</p>
<p><b>Functional dependency (Barthel Index &gt;= 95)</b><sup>5</sup> 90 days 7 Critical</p>	<p>n/a Based on data from 955 patients in 1 studies. (Randomized controlled) Follow up 90 days</p>	<p><b>600</b> per 1000 <b>695</b> per 1000 Difference: <b>95 more</b> per 1000 ( CI 95% 50 fewer - 195 fewer )</p>	<p><b>Moderate</b> Due to serious imprecision, Due to serious indirectness<sup>6</sup></p>	<p>There is little or no difference in functional dependency as measured by Barthel Index &gt;= 95 for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.</p>
<p><b>Length of stay</b><sup>7</sup> 7 Critical</p>	<p>Measured by: Length of Stay Lower better Based on data from: 1,086 patients in 1 studies. (Randomized controlled) Follow up 90 days</p>	<p><b>13.7</b> days (Mean) <b>11.3</b> days (Mean) Difference: <b>MD 1.5 fewer</b> ( CI 95% 0.5 more - 3.5 fewer )</p>	<p><b>Moderate</b> Due to serious imprecision, Due to serious indirectness<sup>8</sup></p>	<p>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.</p>

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 .**

## References

[157] Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, Evans M, Cadilhac D, Levi C : Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial.. *Lancet (London, England)* 2011;378(9804):1699-706 [Pubmed Journal](#)

[158] Drury P, Levi C, McInnes E, Hardy J, Ward J, Grimshaw JM, D' Este C, Dale S, McElduff P, Cheung NW, Quinn C, Griffiths R, Evans M, Cadilhac D, Middleton S : Management of fever, hyperglycemia, and swallowing dysfunction following hospital admission for acute stroke in New South Wales, Australia.. *International journal of stroke : official journal of the International Stroke Society* 2014;9(1):23-31 [Pubmed Journal](#)

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 [151]; Ntaios et al. 2014 [150])

## Practical Info

The trials in the Cochrane review used tight control of blood glucose (4–7.5 mmol/L) the QASC trial (Middleton et al. 2011 [157]) used 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.

## Key Info

### 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 [151]; Ntaios et al. 2014 [150]).

### Quality of evidence

Moderate

The quality of evidence would be considered moderate due to a serious 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

Factors not considered

## Rationale

Two systematic reviews (Bellolio et al. 2014 [151]; Ntaios et al. 2014 [150]) were included. The Cochrane systematic review (Bellolio et al. 2014 [151]) included 11 trials (N = 1583 participants) and the other review (Ntaios et al. 2014 [150]) 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). Early and intense therapy via intravenous insulin is not recommended.

## Clinical Question/ PICO

**Population:** Adults with stroke  
**Intervention:** Insulin for glycaemic control  
**Comparator:** Usual care

### Summary

Two systematic reviews (Bellolio et al 2014 [151]; Ntaios et al 2014 [150]) were included. The Cochrane systematic review (Bellolio et al 2014) included 11 trials (N=1583 participants) and the other review (Ntaios et al 2014 [150]) 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). Early and intense therapy via IV insulin is not recommended.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Usual care	Insulin for glycaemic control in acute ischaemic stroke		
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. <sup>1</sup> (Randomized controlled) Follow up <30 days to 90 days	<b>658</b> per 1000	<b>656</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>2</sup>	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. <sup>3</sup> (Randomized controlled) Follow up discharge-120 days	<b>224</b> per 1000	<b>239</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>4</sup>	Insulin for glycaemic control in acute ischaemic stroke probably has little or no difference on death
Dependency or death - patients with diabetes mellitus  9 Critical	Odds Ratio 0.66 (CI 95% 0.35 - 1.24) Based on data from 194 patients in 3 studies. <sup>5</sup> (Randomized controlled) Follow up 30-90 days	<b>524</b> per 1000	<b>421</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>6</sup>	Insulin for glycaemic control in acute ischaemic stroke probably has little or no difference on dependency or death among patients with diabetes mellitus.

<p><b>Dependency or death - patients without diabetes mellitus</b></p> <p>9 Critical</p>	<p>Odds Ratio 1.02 (CI 95% 0.81 - 1.3) Based on data from 1,288 patients in 6 studies.<sup>7</sup> (Randomized controlled)</p>	<p><b>676</b> per 1000</p> <p><b>680</b> per 1000</p> <p>Difference: <b>4 more</b> per 1000 ( CI 95% 48 fewer - 55 more )</p>	<p><b>Moderate</b> Due to serious risk of bias<sup>8</sup></p> <p>Insulin for glycaemic control in acute ischaemic stroke probably has little or no difference on dependency or death among patients without diabetes mellitus</p>
<p><b>Independent in daily activities</b></p> <p>8 Critical</p>	<p>Odds Ratio 1.03 (CI 95% 0.81 - 1.32) Based on data from 1,224 patients in 9 studies.<sup>9</sup> (Randomized controlled) Follow up Discharge to 120 Days</p>	<p><b>317</b> per 1000</p> <p><b>323</b> per 1000</p> <p>Difference: <b>6 more</b> per 1000 ( CI 95% 44 fewer - 63 more )</p>	<p><b>Moderate</b> Due to serious risk of bias<sup>10</sup></p> <p>Insulin for glycaemic control probably has little or no difference on independence in daily activities when compared to usual care</p>
<p><b>Symptomatic hypoglycaemia</b></p> <p>6 Important</p>	<p>Odds Ratio 14.6 (CI 95% 6.62 - 32.21) Based on data from 1,455 patients in 10 studies.<sup>11</sup> (Randomized controlled) Follow up 5 to 120 days</p>	<p><b>4</b> per 1000</p> <p><b>55</b> per 1000</p> <p>Difference: <b>51 more</b> per 1000 ( CI 95% 22 more - 111 more )</p>	<p><b>Moderate</b> Due to serious risk of bias<sup>12</sup></p> <p>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</p>
<p><b>Hypoglycaemia (with or without symptoms)</b></p> <p>6 Important</p>	<p>Odds Ratio 18.41 (CI 95% 9.09 - 37.27) Based on data from 1,455 patients in 10 studies.<sup>13</sup> (Randomized controlled) Follow up 5 to 120 days</p>	<p><b>10</b> per 1000</p> <p><b>157</b> per 1000</p> <p>Difference: <b>147 more</b> per 1000 ( CI 95% 74 more - 264 more )</p>	<p><b>Moderate</b> Due to serious risk of bias<sup>14</sup></p> <p>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).</p>
<p><b>Functional neurological outcome at the end of the follow-up - NIHSS or ESS<sup>15</sup></b></p> <p>7 Critical</p>	<p>Measured by: NIHSS and ESS Lower better Based on data from: 1,432 patients in 8 studies.<sup>16</sup> (Randomized controlled) Follow up Discharge to 120 days</p>	<p>Difference: <b>SMD 0.09 fewer</b> ( CI 95% 0.19 fewer - 0.01 more )</p>	<p><b>Moderate</b> Due to serious risk of bias<sup>17</sup></p> <p>Insulin for glycaemic control probably has little or no difference on functional neurological outcome at the end of the follow-up</p>
<p><b>Functional neurological outcome -</b></p>	<p>Measured by: NIHSS and ESS Lower better Based on data from: 146</p>	<p>Difference: <b>SMD 0.06 fewer</b> ( CI 95% 0.43 fewer - 0.31 more )</p>	<p><b>Moderate</b> Due to serious risk of bias<sup>20</sup></p> <p>Insulin for glycaemic control probably has little or no difference on functional neurological</p>

<p><b>patients with diabetes mellitus</b><sup>18</sup></p> <p>7 Critical</p>	<p>patients in 3 studies.<sup>19</sup> (Randomized controlled) Follow up 30 to 60 days</p>	<p>Difference: <b>SMD 0.08 fewer</b> ( CI 95% 0.19 fewer - 0.03 more )</p>	<p>outcome among patients with diabetes mellitus</p>
<p><b>Functional neurological outcome - patients without diabetes mellitus</b><sup>21</sup></p> <p>7 Critical</p>	<p>Measured by: NIHSS and ESS Lower better Based on data from: 1,286 patients in 6 studies.<sup>22</sup> (Randomized controlled) Follow up 5 to 120 days</p>		<p><b>Moderate</b> Due to serious risk of bias<sup>23</sup></p> <p>Insulin for glycaemic control probably has little or no difference on functional neurological outcome among patients without diabetes mellitus</p>

1. Systematic review [151] with included studies: Vynychuk 2005, INSULINFARCT 2012, Kreisel 2009, McCormick 2010, Staszewski 2011, Azevedo 2009, GIST-UK 2007, GRASP 2009, THIS 2008. **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 [151] with included studies: Walters 2006, GIST-UK 2007, GRASP 2009, Kreisel 2009, McCormick 2010, INSULINFARCT 2012, Azevedo 2009, Staszewski 2011, THIS 2008. **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 [151] with included studies: Vynychuk 2005, GRASP 2009, THIS 2008. **Baseline/comparator::** Control arm of reference used for intervention .
6. **Risk of bias: Serious** . Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias for all three studies. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias in the Vynychuk 2005 study. ; **Inconsistency: No serious** . **Indirectness: No serious** . **Imprecision: No serious** . Low number of patients in each study but better numbers when pooled. ; **Publication bias: No serious** .
7. Systematic review [151] with included studies: Staszewski 2011, Vynychuk 2005, GIST-UK 2007, INSULINFARCT 2012, Kreisel 2009, McCormick 2010. **Baseline/comparator::** Control arm of reference used for intervention .
8. **Risk of bias: Serious** . Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias for all three studies. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias in the Vynychuk 2005 study., 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** . Low number of patients in each study but better numbers when pooled. ;
9. Systematic review [151] . **Baseline/comparator::** Control arm of reference used for intervention .
10. **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 .**

11. Systematic review [151] . **Baseline/comparator::** Control arm of reference used for intervention .

12. **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 in the 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 .**

13. Systematic review [151] . **Baseline/comparator::** Control arm of reference used for intervention .

14. **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 except 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 .**

15. Studies measured neurological deficit using National Institutes of Health Stroke Scale (NIHSS) and the European Stroke Scale (ESS)

16. Systematic review [151] . **Baseline/comparator::** Control arm of reference used for intervention .

17. **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 .**

18. Functional neurological outcome measured by NIHSS and ESS in different studies.

19. Systematic review [151] . **Baseline/comparator::** Control arm of reference used for intervention .

20. **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 .**

21. Functional neurological outcome measured by NIHSS and ESS in different studies.

22. Systematic review [151] . **Baseline/comparator::** Control arm of reference used for intervention .

23. **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 .**

## References

[150] Ntaios G, Papavasileiou V, Bargiota A, Makaritsis K, Michel P : Intravenous insulin treatment in acute stroke: a systematic review and meta-analysis of randomized controlled trials.. International journal of stroke : official journal of the International Stroke Society 2014;9(4):489-93 [PubMed Journal](#)

[151] Bellolio MF, Gilmore RM, Ganti L : Insulin for glycaemic control in acute ischaemic stroke. Cochrane Database Syst Rev 2014; [PubMed](#)

## 17 - 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 [162]). Pyrexia is associated with poorer outcomes after stroke (Greer et al. 2008 [163]) and the most common causes of pyrexia are chest or urinary infections (Langhorne et al. 2000 [164]). 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 (Middleton et al. 2011 [157]).

### Strong Recommendation

All stroke patients should have their temperature monitored at least four times a day for 72 hours. (Middleton et al. 2011 [157])

### 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.

### Key Info

#### 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 [157]).

#### Quality of 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 [157]).

Drury et al. (2014) [158] 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

##### 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 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  $\geq 37.5^\circ\text{C}$  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**

<b>Population:</b>	Adults with stroke
<b>Intervention:</b>	FeSS protocol (Fever, Sugar, Swallow)
<b>Comparator:</b>	No FeSS protocol

**Summary**

The Quality in Acute Stroke Care (QASC) trial reported by Middleton et al (2011) [157] 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  $\geq 37.5^{\circ}\text{C}$  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) [158] 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) [157] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		No FeSS protocol	FeSS protocol (Fever, Sugar, Swallow)		
<b>Functional dependency (Barthel Index <math>\geq 95</math>)<sup>1</sup></b> 90 days  7 Critical	n/a  Based on data from 955 patients in 1 studies. (Randomized controlled) Follow up 90 days	<b>600</b> per 1000	<b>695</b> per 1000	<b>High</b> 2	There is little or no difference in functional dependency as measured by Barthel Index $\geq 95$ for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.
<b>Death or dependency<sup>3</sup></b> 90 days	n/a  Based on data from 1,007	<b>577</b> per 1000	<b>420</b> per 1000	<b>High</b> 4	Patients treated in stroke care units with FeSS protocols have improved

9 Critical	patients in 1 studies. (Randomized controlled) Follow up 90 days	Difference: <b>157 fewer</b> per 1000 ( CI 95% 58 fewer - 254 fewer )		death or dependency outcomes when compared to patients treated in stroke care units without FeSS protocols.
<b>Functional dependency (Barthel Index &gt;= 60)<sup>5</sup></b> 90 days 7 Critical	n/a Based on data from 955 patients in 1 studies. (Randomized controlled) Follow up 90 days	<b>898</b> per 1000	<b>923</b> per 1000	There is little or no difference in functional dependency as measured 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.
<b>Length of stay<sup>7</sup></b> 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	<b>13.7</b> days (Mean)	<b>11.3</b> days (Mean)	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.
		Difference: <b>MD 1.5 fewer</b> ( CI 95% 0.5 more - 3.5 fewer )		
				<b>High<sub>6</sub></b>
				<b>High<sub>8</sub></b>

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 .**

## References

[157] Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, Evans M, Cadilhac D, Levi C : Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial.. Lancet (London, England) 2011;378(9804):1699-706  
[Pubmed Journal](#)

[158] Drury P, Levi C, McInnes E, Hardy J, Ward J, Grimshaw JM, D' Este C, Dale S, McElduff P, Cheung NW, Quinn C, Griffiths R, Evans M, Cadilhac D, Middleton S : Management of fever, hyperglycemia, and swallowing dysfunction following hospital admission

for acute stroke in New South Wales, Australia.. International journal of stroke : official journal of the International Stroke Society 2014;9(1):23-31 [Pubmed Journal](#)

#### Weak Recommendation

Stroke patients with fever  $\geq 37.5$  °C may be treated with paracetamol as an antipyretic therapy. (den Hertog et al. 2009 [160]; Middleton et al. 2011 [157])

### Practical Info

The PAIS trial evaluated use of high-dose paracetamol (6 g per day x 3 days) for those with temperature between 36–39 degrees celsius. Exclusions included any trial participants with liver dysfunction or alcohol abuse, and pre-morbid mRS > 2.

For those with dysphagia, antipyretics can be given orally or via a nasogastric tube or suppository.

### Key Info

#### 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 [157]).

Therapeutic hypothermia probably has little or no difference on death or disability and may increase length of stay, but further research is needed.

Results from the PAIS trial do not support the routine use of high-dose paracetamol for all acute stroke patients, but some benefit was observed for those patients with temperature 37–39 degrees celsius (den Hertog et al. 2009 [160]). No statistical significance, although improvement was noted in disability (mRS) for those treated with paracetamol; no adverse events or harms were observed in the treatment group or comparator (den Hertog et al. 2009 [160]).

#### Quality of 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. 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 PAIS study (Paracetamol vs placebo) was of high quality, however the benefit of paracetamol was only present in a subgroup analysis. There was no difference between the groups using either tool.

#### Preference and values

No substantial variability 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  $\geq 37.5$  °C improve outcomes at 90 days, when used as part of a bundle of care.

Results from the PAIS trial do not support routine use of high-dose paracetamol for all acute stroke patients, but some benefit was observed for those patients with temperature 37–39 degrees celsius, although this subgroup was not defined in advance.

The PAIS trial showed no difference between treatment groups. They also updated the meta-analyses (Cochrane 2009) using these data, which showed no significant difference when comparing active treatment and control; therefore routine paracetamol is not recommended.

**Clinical Question/ PICO**

- Population:** Adults with stroke
- Intervention:** Paracetamol
- Comparator:** Placebo

**Summary**

A Cochrane review (Den Hertog et al 2009 [161]) 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 [160]) 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 as well as the trials in the earlier review showed no significant increase in favourable outcomes.

**Note:** Den Hertog et al (2009) [160] reported both unadjusted and covariate-adjusted odds ratios for the disability outcome. The covariate-adjusted value is reported here.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo	Paracetamol		
<p><b>Disability: favourable outcome (mRS <math>\leq 2</math>)<sup>1</sup></b></p> <p>9 Critical</p>	<p>Odds Ratio 1.02 (CI 95% 0.78 - 1.32) Based on data from 1,400 patients in 1 studies. (Randomized controlled) Follow up 3 months</p>	<p><b>500</b> per 1000</p>	<p><b>505</b> per 1000</p>	<p><b>Moderate</b> Due to serious imprecision<sup>2</sup></p>	<p>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</p>
		<p>Difference: <b>5 more</b> per 1000 ( CI 95% 69 more - 62 fewer )</p>			

<b>Serious adverse events</b>	n/a	<b>100</b> per 1000	<b>80</b> per 1000	<b>High</b>	Paracetamol has little or no difference on serious adverse events
8 Critical	Based on data from 1,400 patients in 1 studies. (Randomized controlled) Follow up Discharge	Difference: <b>20 fewer</b> per 1000 CI 95%			

1. Reported estimates are odds of a favourable outcome - so odds ratios > 1 mean the intervention improves outcomes
2. **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: Serious .** Wide confidence intervals ; **Publication bias: No serious .**

### References

[160] den Hertog HM, van der Worp HB, van Gemert HMA, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ, Dippel DWJ : The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial.. The Lancet. Neurology 2009;8(5):434-40 [Pubmed Journal](#)

[161] Den Hertog HM, van der Worp HB, Tseng M-C, Dippel DW : Cooling therapy for acute stroke.. The Cochrane database of systematic reviews 2009;(1):CD001247 [Pubmed Journal](#)

### 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) [157] 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  $\geq 37.5^{\circ}\text{C}$  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) [158] 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) [157] 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	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		No FeSS protocol	FeSS protocol (Fever, Sugar, Swallow)		
<b>Functional dependency (Barthel Index <math>\geq 95</math>)</b> <sup>1</sup> 90 days 7 Critical	n/a Based on data from 955 patients in 1 studies. (Randomized controlled) Follow up 90 days	<b>600</b> per 1000	<b>695</b> per 1000	<b>High</b> 2	There is little or no difference in functional dependency as measured by Barthel Index $\geq 95$ for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.
<b>Death or dependency</b> <sup>3</sup> 90 days 9 Critical	n/a Based on data from 1,007 patients in 1 studies. (Randomized controlled) Follow up 90 days	<b>577</b> per 1000	<b>420</b> per 1000	<b>High</b> 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.
<b>Functional dependency (Barthel Index <math>\geq 60</math>)</b> <sup>5</sup> 90 days 7 Critical	n/a Based on data from 955 patients in 1 studies. (Randomized controlled) Follow up 90 days	<b>898</b> per 1000	<b>923</b> per 1000	<b>High</b> 6	There is little or no difference in functional dependency as measured by Barthel Index $\geq 60$ for those treated in stroke care units with FeSS protocols when compared to those treated in stroke care units without FeSS protocols.
<b>Length of stay</b> <sup>7</sup> 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	<b>13.7</b> days (Mean)	<b>11.3</b> days (Mean)	<b>High</b> 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
		Difference: <b>95 more</b> per 1000 ( CI 95% 50 fewer - 195 fewer )			
		Difference: <b>157 fewer</b> per 1000 ( CI 95% 58 fewer - 254 fewer )			
		Difference: <b>25 more</b> per 1000 ( CI 95% 36 fewer - 86 more )			
		Difference: <b>MD 1.5 fewer</b> ( CI 95% 0.5 more - 3.5 fewer )			

units without FeSS protocols.

1. Barthel Index  $\geq 95\%$
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  $\geq 2$
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  $\geq 60$
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 .**

## References

[157] Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, Evans M, Cadilhac D, Levi C : Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial.. *Lancet (London, England)* 2011;378(9804):1699-706 [PubMed Journal](#)

[158] Drury P, Levi C, McInnes E, Hardy J, Ward J, Grimshaw JM, D' Este C, Dale S, McElduff P, Cheung NW, Quinn C, Griffiths R, Evans M, Cadilhac D, Middleton S : Management of fever, hyperglycemia, and swallowing dysfunction following hospital admission for acute stroke in New South Wales, Australia.. *International journal of stroke : official journal of the International Stroke Society* 2014;9(1):23-31 [PubMed Journal](#)

## 18 - 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.
- Penumbra-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 plasminogen 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

## References

- [1] Thrift AG, Hayman N : Aboriginal and Torres Strait Islander peoples and the burden of stroke.. International journal of stroke : official journal of the International Stroke Society 2007;2(1):57-9 [Pubmed Journal](#)
- [2] National Stroke Foundation : National Stroke Unit Program. Aboriginal Stroke Project.. 2003;
- [3] Kilkenny MF, Harris DM, Ritchie EA, Price C, Cadilhac DA, : Hospital management and outcomes of stroke in Indigenous Australians: evidence from the 2009 Acute Care National Stroke Audit.. International journal of stroke : official journal of the International Stroke Society 2013;8(3):164-71 [Pubmed Journal](#)
- [4] Australian Institute of Health and Welfare : Stroke and its management in Australia: an update. 2013;
- [5] National Vascular Disease Prevention Alliance : Guidelines for the management of absolute cardiovascular disease risk. 2012;
- [6] Heart Foundation : Guideline for the diagnosis and management of hypertension in adults . 2016;
- [7] Stroke Unit Trialists' Collaboration : Organised inpatient (stroke unit) care for stroke. Cochrane Database of Systematic Reviews 2013;(9): [Journal](#)
- [8] Sun Y, Paulus D, Eyssen M, Maervoet J, Saka O : A systematic review and meta-analysis of acute stroke unit care: what's beyond the statistical significance?. BMC medical research methodology 2013;13 132 [Pubmed Journal](#)
- [9] Chan DK, Cordato D., O'Rourke F., Chan DL, Pollack M., Middleton S., Levi C. : Comprehensive stroke units: a review of comparative evidence and experience. International Journal of Stroke 2013;8(4):260-4 [Journal](#)
- [10] Ciccone A, Celani MG, Chiaramonte R, Rossi C, Righetti E : Continuous versus intermittent physiological monitoring for acute stroke. Cochrane Database of Systematic Reviews 2013;(2): [Journal](#)
- [11] Moodie M, Cadilhac D, Pearce D, Mihalopoulos C, Carter R, Davis S, Donnan G : Economic evaluation of Australian stroke services: a prospective, multicenter study comparing dedicated stroke units with other care modalities.. Stroke; a journal of cerebral circulation 2006;37(11):2790-5 [Pubmed](#)
- [12] Hunter RM, Davie C, Rudd A, Thompson A, Walker H, Thomson N, Mountford J, Schwamm L, Deanfield J, Thompson K, Dewan B, Mistry M, Quoraishi S, Morris S : Impact on clinical and cost outcomes of a centralized approach to acute stroke care in London: a comparative effectiveness before and after model.. PloS one 2013;8(8):e70420 [Pubmed Journal](#)
- [13] Te Ao BJ, Brown PM, Feigin VL, Anderson CS : Are stroke units cost effective? Evidence from a New Zealand stroke incidence and population-based study.. International journal of stroke : official journal of the International Stroke Society 2012;7(8):623-30 [Pubmed Journal](#)
- [14] National Stroke Foundation : National Acute Stroke Services Framework. 2015;
- [15] National Stroke Foundation : National Stroke Audit - Rehabilitation Services Report 2016. 2016;
- [16] Silvestrelli G, Parnetti L, Paciaroni M, Caso V, Corea F, Vitali R, Capocchi G, Agnelli G : Early admission to stroke unit influences clinical outcome.. European journal of neurology 2006;13(3):250-5 [Pubmed](#)

- [17] León-Jiménez C, Ruiz-Sandoval JL, Chiquete E, Vega-Arroyo M, Arauz A, Murillo-Bonilla LM, Ochoa-Guzmán A, Carrillo-Loza K, Ramos-Moreno A, Barinagarrementeria F, Cantú-Brito C : Hospital arrival time and functional outcome after acute ischaemic stroke: results from the PREMIER study.. *Neurología (Barcelona, Spain)* 2014;29(4):200-9 [PubMed](#) [Journal](#)
- [18] Naganuma M, Toyoda K, Nonogi H, Yokota C, Koga M, Yokoyama H, Okayama A, Naritomi H, Minematsu K : Early hospital arrival improves outcome at discharge in ischemic but not hemorrhagic stroke: a prospective multicenter study.. *Cerebrovascular diseases (Basel, Switzerland)* 2009;28(1):33-8 [PubMed](#) [Journal](#)
- [19] Brady BK, McGahan L, Skidmore B : Systematic review of economic evidence on stroke rehabilitation services.. *International journal of technology assessment in health care* 2005;21(1):15-21 [PubMed](#)
- [20] Patel A, Knapp M, Perez I, Evans A, Kalra L : Alternative strategies for stroke care: cost-effectiveness and cost-utility analyses from a prospective randomized controlled trial.. *Stroke; a journal of cerebral circulation* 2004;35(1):196-203 [PubMed](#)
- [21] Edwards DF, Hahn MG, Baum CM, Perlmutter MS, Sheedy C, Dromerick AW : Screening patients with stroke for rehabilitation needs: validation of the post-stroke rehabilitation guidelines.. *Neurorehabilitation and neural repair* 2006;20(1):42-8 [PubMed](#)
- [22] Australian Stroke Coalition Rehabilitation Working Group : Assessment for Rehabilitation: Pathway and Decision-Making Tool. 2012; [Website](#)
- [23] Lynch EA, Luker JA, Cadilhac DA, Hillier SL : Rehabilitation assessments for patients with stroke in Australian hospitals do not always reflect the patients' rehabilitation requirements.. *Archives of physical medicine and rehabilitation* 2015;96(5):782-9 [PubMed](#) [Journal](#)
- [24] Lynch EA, Luker JA, Cadilhac DA, Fryer CE, Hillier SL : A qualitative study using the Theoretical Domains Framework to investigate why patients were or were not assessed for rehabilitation after stroke.. *Clinical rehabilitation* 2016; [PubMed](#)
- [25] Lynch EA, Luker JA, Cadilhac DA, Hillier SL : Inequities in access to rehabilitation: exploring how acute stroke unit clinicians decide who to refer to rehabilitation.. *Disability and rehabilitation* 2016;38(14):1415-24 [PubMed](#) [Journal](#)
- [26] National Stroke Foundation : National Stroke Audit – Acute Services Clinical Audit Report. 2015;
- [27] National Stroke Foundation : National Stroke Services Rehabilitation Framework. 2013;
- [28] Gade G, Venohr I, Conner D, McGrady K, Beane J, Richardson RH, Williams MP, Liberson M, Blum M, Della Penna R : Impact of an inpatient palliative care team: a randomized control trial.. *Journal of palliative medicine* 2008;11(2):180-90 [PubMed](#) [Journal](#)
- [29] Creutzfeldt CJ, Holloway RG, Walker M. : Symptomatic and palliative care for stroke survivors. *Journal of General Internal Medicine* 2012;27(7):853-860 [Journal](#)
- [30] Burton CR, Payne S. : Integrating palliative care within acute stroke services: Developing a programme theory of patient and family needs, preferences and staff perspectives. *BMC Palliative Care* 2012;11(22): [Journal](#)
- [31] Payne S., Burton C., Addington-Hall J., Jones A. : End-of-life issues in acute stroke care: a qualitative study of the experiences and preferences of patients and families. *Palliative Medicine* 2010;24(2):146-53 [Journal](#)
- [32] de Boer ME, Depla M, Wojtkowiak J, Visser MC, Widdershoven GAM, Francke AL, Hertogh CPM : Life-and-death decision-making in the acute phase after a severe stroke: Interviews with relatives.. *Palliative medicine* 2015;29(5):451-7 [PubMed](#) [Journal](#)

- [33] Blacquiere D, Bhimji K, Meggison H, Sinclair J, Sharma M : Satisfaction with palliative care after stroke: a prospective cohort study.. *Stroke; a journal of cerebral circulation* 2013;44(9):2617-9 [Pubmed Journal](#)
- [34] Stevens T, Payne SA, Burton C, Addington-Hall J, Jones A : Palliative care in stroke: a critical review of the literature.. *Palliative medicine* 2007;21(4):323-31 [Pubmed](#)
- [35] Jack C, Jones L, Jack BA, Gambles M, Murphy D, Ellershaw JE : Towards a good death: the impact of the care of the dying pathway in an acute stroke unit.. *Age and ageing* 2004;33(6):625-6 [Pubmed](#)
- [36] Thrift AG, Dewey HM, Macdonell RA, McNeil JJ, Donnan GA : Stroke incidence on the east coast of Australia: the North East Melbourne Stroke Incidence Study (NEMESIS).. *Stroke; a journal of cerebral circulation* 2000;31(9):2087-92 [Pubmed](#)
- [37] Wardlaw JM : Thrombolysis for acute ischaemic stroke. *Cochrane Database of Systematic Review* 2014; [Pubmed](#)
- [38] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W : Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials.. *Lancet (London, England)* 2014;384(9958):1929-35 [Pubmed Journal](#)
- [39] The IST-3 collaborative group : Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial.. *The Lancet. Neurology* 2013;12(8):768-76 [Pubmed Journal](#)
- [40] Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee T-H, Broderick JP, Chen X, Chen G, Sharma VK, Kim JS, Thang NH, Cao Y, Parsons MW, Levi C, Huang Y, Olavarria VV, Demchuk AM, Bath PM, Donnan GA, Martins S, Pontes-Neto OM, Silva F, Ricci S, Roffe C, Pandian J, Billot L, Woodward M, Li Q, Wang X, Wang J, Chalmers J : Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. *N Engl J Med* 2016; [Journal Website](#)
- [41] Wardlaw JM, Koumellis P, Liu M : Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke.. *The Cochrane database of systematic reviews* 2013;(5):CD000514 [Pubmed Journal](#)
- [42] Saqqur M, Tsvigoulis G, Nicolli F, Skoloudik D, Sharma VK, Larrue V, Eggers J, Perren F, Charalampidis P, Storie D, Shuaib A, Alexandrov AV : The role of sonolysis and sonothrombolysis in acute ischemic stroke: a systematic review and meta-analysis of randomized controlled trials and case-control studies.. *Journal of neuroimaging : official journal of the American Society of Neuroimaging* 2014;24(3):209-20 [Pubmed Journal](#)
- [43] Ricci S, Dinia L, Del Sette M, Anzola P, Mazzoli T, Cenciarelli S, Gandolfo C : Sonothrombolysis for acute ischaemic stroke.. *The Cochrane database of systematic reviews* 2012;(6):CD008348 [Pubmed Journal](#)
- [44] Demaerschalk BM, Hwang H-M, Leung G : Cost analysis review of stroke centers, telestroke, and rt-PA.. *The American journal of managed care* 2010;16(7):537-44 [Pubmed](#)
- [45] Tan Tanny SP, Busija L, Liew D, Teo S, Davis SM, Yan B : Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke: experience from Australian stroke center.. *Stroke; a journal of cerebral circulation* 2013;44(8):2269-74 [Pubmed Journal](#)
- [46] Pan Y, Chen Q, Zhao X, Liao X, Wang C, Du W, Liu G, Liu L, Wang C, Wang Y, Wang Y : Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke in China.. *PloS one* 2014;9(10):e110525 [Pubmed Journal](#)

- [47] Boudreau DM, Guzauskas GF, Chen ER, Lalla D, Tayama D, Fagan SC, Veenstra DL : Cost-effectiveness of recombinant tissue-type plasminogen activator within 3 hours of acute ischemic stroke: current evidence.. Stroke; a journal of cerebral circulation 2014;45(10):3032-9 [Pubmed Journal](#)
- [48] Tung CE, Win SS, Lansberg MG : Cost-effectiveness of tissue-type plasminogen activator in the 3- to 4.5-hour time window for acute ischemic stroke.. Stroke; a journal of cerebral circulation 2011;42(8):2257-62 [Pubmed Journal](#)
- [49] Boudreau DM, Guzauskas G, Villa KF, Fagan SC, Veenstra DL : A model of cost-effectiveness of tissue plasminogen activator in patient subgroups 3 to 4.5 hours after onset of acute ischemic stroke.. Annals of emergency medicine 2013;61(1):46-55 [Pubmed Journal](#)
- [50] Coutts SB, Modi J, Patel SK, Demchuk AM, Goyal M, Hill MD : CT/CT angiography and MRI findings predict recurrent stroke after transient ischemic attack and minor stroke: results of the prospective CATCH study.. Stroke; a journal of cerebral circulation 2012;43(4):1013-7 [Pubmed Journal](#)
- [51] Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY, Prabhakaran S, Saposnik G, Saver JL, Smith EE : Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association.. Stroke; a journal of cerebral circulation 2016;47(2):581-641 [Pubmed Journal](#)
- [52] Chiong W, Kim AS, Huang IA, Farahany NA, Josephson SA : Inability to consent does not diminish the desirability of stroke thrombolysis.. Annals of neurology 2014;76(2):296-304 [Pubmed Journal](#)
- [53] Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J, Kulkarni AV, Singh S, Alqahtani A, Rochweg B, Alshahrani M, Murty NK, Alhazzani A, Yarascavitch B, Reddy K, Zaidat OO, Almenawer SA : Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis.. JAMA 2015;314(17):1832-43 [Pubmed Journal](#)
- [54] Campbell BC, Hill MD, Rubiera M, Menon BK, Demchuk A, Donnan GA, Roy D, Thornton J, Dorado L, Bonafe A, Levy EI, Diener H-C, Hernández-Pérez M, Pereira VM, Blasco J, Quesada H, Rempel J, Jahan R, Davis SM, Stouch BC, Mitchell PJ, Jovin TG, Saver JL, Goyal M : Safety and Efficacy of Solitaire Stent Thrombectomy: Individual Patient Data Meta-Analysis of Randomized Trials . Stroke 2016/02/17 ; [Website](#)
- [55] Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos YBWEM, Bonafe A, Jahan R, Diener H-C, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG : Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.. Lancet (London, England) 2016;387(10029):1723-31 [Pubmed Journal](#)
- [56] Palesch YY, Yeatts SD, Tomsick TA, Foster LD, Demchuk AM, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, von Kummer R, Molina CA, Goyal M, Schonewille WJ, Mazighi M, Engelter ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Simpson A, Simpson KN, Broderick JP : Twelve-Month Clinical and Quality-of-Life Outcomes in the Interventional Management of Stroke III Trial.. Stroke; a journal of cerebral circulation 2015;46(5):1321-7 [Pubmed Journal](#)
- [57] Puñal-Riobóo J, Atienza G, Blanco M : Safety and Efficacy of Mechanical Thrombectomy Using Stent Retrievers in the Endovascular Treatment of Acute Ischaemic Stroke: A Systematic Review. Interventional Neurology 2015/06/03;3(3-4):149-164 [Journal Website](#)
- [58] Aronsson M, Persson J, Blomstrand C, Wester P, Levin L-Å : Cost-effectiveness of endovascular thrombectomy in patients with acute ischemic stroke.. Neurology 2016;86(11):1053-9 [Pubmed Journal](#)
- [59] Ganesalingam J, Pizzo E, Morris S, Sunderland T, Ames D, Lobotesis K : Cost-Utility Analysis of Mechanical Thrombectomy Using Stent Retrievers in Acute Ischemic Stroke.. Stroke; a journal of cerebral circulation 2015;46(9):2591-8 [Pubmed Journal](#)

- [60] Lobotesis K, Veltkamp R, Carpenter IH, Claxton LM, Saver JL, Hodgson R : Cost-effectiveness of stent-retriever thrombectomy in combination with IV t-PA compared with IV t-PA alone for acute ischemic stroke in the UK.. *Journal of medical economics* 2016;19(8):785-94 [Pubmed Journal](#)
- [61] Dippel DW, Majoie CB, Roos YB, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Lingsma HF, Koudstaal PJ, Treurniet KM, van den Berg LA, Beumer D, Franssen PS, Berkhemer OA : Influence of Device Choice on the Effect of Intra-Arterial Treatment for Acute Ischemic Stroke in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands).. *Stroke; a journal of cerebral circulation* 2016;47(10):2574-81 [Pubmed Journal](#)
- [62] Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CBLM, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, Cardona P, Devlin TG, Frei DF, du Mesnil de Rochemont R, Berkhemer OA, Jovin TG, Siddiqui AH, van Zwam WH, Davis SM, Castaño C, Sapkota BL, Franssen PS, Molina C, van Oostenbrugge RJ, Chamorro Á, Lingsma H, Silver FL, Donnan GA, Shuaib A, Brown S, Stouch B, Mitchell PJ, Davalos A, Roos YBWEM, Hill MD : Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis.. *JAMA* 2016;316(12):1279-1288 [Pubmed Journal](#)
- [63] Schonewille WJ, Wijman CAC, Michel P, Rueckert CM, Weimar C, Mattle HP, Engelter ST, Tanne D, Muir KW, Molina CA, Thijs V, Audebert H, Pfefferkorn T, Szabo K, Lindsberg PJ, de Freitas G, Kappelle LJ, Algra A : Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study.. *The Lancet. Neurology* 2009;8(8):724-30 [Pubmed Journal](#)
- [64] Macleod MR, Davis SM, Mitchell PJ, Gerraty RP, Fitt G, Hankey GJ, Stewart-Wynne EG, Rosen D, McNeil JJ, Bladin CF, Chambers BR, Herkes GK, Young D, Donnan GA : Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke.. *Cerebrovascular diseases (Basel, Switzerland)* 2005;20(1):12-7 [Pubmed](#)
- [65] Kumar G, Shahripour RB, Alexandrov AV : Recanalization of acute basilar artery occlusion improves outcomes: a meta-analysis.. *Journal of neurointerventional surgery* 2015;7(12):868-74 [Pubmed Journal](#)
- [66] Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, Frei D, Shownkeen H, Budzik R, Ajani ZA, Grossman A, Altschul D, McDougall C, Blake L, Fitzsimmons B-F, Yavagal D, Terry J, Farkas J, Lee SK, Baxter B, Wiesmann M, Knauth M, Heck D, Hussain S, Chiu D, Alexander MJ, Malisch T, Kirmani J, Miskolczi L, Khatri P : Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone.. *Stroke; a journal of cerebral circulation* 2016;47(9):2331-8 [Pubmed Journal](#)
- [67] Muir KW, Ford GA, Messow C-M, Ford I, Murray A, Clifton A, Brown MM, Madigan J, Lenthall R, Robertson F, Dixit A, Cloud GC, Wardlaw J, Freeman J, White P : Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial.. *Journal of neurology, neurosurgery, and psychiatry* 2016; [Pubmed Journal](#)
- [68] Schönenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S, Purrucker JC, Nagel S, Klose C, Pfaff J, Bendszus M, Ringleb PA, Kieser M, Möhlenbruch MA, Bösel J : Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy: A Randomized Clinical Trial.. *JAMA* 2016;316(19):1986-1996 [Pubmed Journal](#)
- [69] Löwhagen Hendén P, Rentzos A, Karlsson J-E, Rosengren L, Leiram B, Sundeman H, Dunker D, Schnabel K, Wikholm G, Hellström M, Ricksten S-E : General Anesthesia Versus Conscious Sedation for Endovascular Treatment of Acute Ischemic Stroke: The AnStroke Trial (Anesthesia During Stroke).. *Stroke* 2017;48(6):1601-1607 [Pubmed Journal](#)
- [70] Simonsen CZ, Sørensen LH, Juul N, Johnsen SP, Yoo AJ, Andersen G, Rasmussen M : Anesthetic strategy during endovascular therapy: General anesthesia or conscious sedation? (GOLIATH - General or Local Anesthesia in Intra Arterial Therapy) A single-center randomized trial.. *International journal of stroke : official journal of the International Stroke Society* 2016;11(9):1045-1052 [Pubmed](#)
- [71] Chen Y-W, Chang K-H, Chen H-C, Liang W-M, Wang Y-H, Lin Y-N : The effects of surface neuromuscular electrical stimulation on post-stroke dysphagia: a systemic review and meta-analysis.. *Clinical rehabilitation* 2016;30(1):24-35 [Pubmed Journal](#)

- [72] Huang K-L, Liu T-Y, Huang Y-C, Leong C-P, Lin W-C, Pong Y-P : Functional outcome in acute stroke patients with oropharyngeal Dysphagia after swallowing therapy.. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2014;23(10):2547-53 [Pubmed](#) [Journal](#)
- [73] Bath PM, Scutt P, Love JO, Clavé P, Cohen D, Dziewas R, Iversen HK, Ledl C, Ragab S, Soda H, Warusevitane A, Woisard V, Hamdy S : Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke: A Randomized Controlled Trial.. *Stroke; a journal of cerebral circulation* 2016;47(6):1562-70 [Pubmed](#) [Journal](#)
- [74] Scutt P, Lee HS, Hamdy S, Bath PM : Pharyngeal Electrical Stimulation for Treatment of Poststroke Dysphagia: Individual Patient Data Meta-Analysis of Randomised Controlled Trials.. *Stroke research and treatment* 2015;2015 429053 [Pubmed](#) [Journal](#)
- [75] Suntrup S, Marian T, Schröder JB, Suttrup I, Muhle P, Oelenberg S, Hamacher C, Minnerup J, Warnecke T, Dziewas R : Electrical pharyngeal stimulation for dysphagia treatment in tracheotomized stroke patients: a randomized controlled trial.. *Intensive care medicine* 2015;41(9):1629-37 [Pubmed](#) [Journal](#)
- [76] Long Y-B, Wu X-P : A meta-analysis of the efficacy of acupuncture in treating dysphagia in patients with a stroke.. *Acupuncture in medicine : journal of the British Medical Acupuncture Society* 2012;30(4):291-7 [Pubmed](#) [Journal](#)
- [77] Geeganage C, Beavan J, Ellender S, Bath PMW : Interventions for dysphagia and nutritional support in acute and subacute stroke.. *The Cochrane database of systematic reviews* 2012;10 CD000323 [Pubmed](#) [Journal](#)
- [78] Bakhtiyari J, Sarraf P, Nakhostin-Ansari N, Tafakhori A, Logemann J, Faghihzadeh S, Harirchian MH : Effects of early intervention of swallowing therapy on recovery from dysphagia following stroke.. *Iranian journal of neurology* 2015;14(3):119-24 [Pubmed](#)
- [79] Pisegna JM, Kaneoka A, Pearson WG, Kumar S, Langmore SE : Effects of non-invasive brain stimulation on post-stroke dysphagia: A systematic review and meta-analysis of randomized controlled trials.. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 2016;127(1):956-68 [Pubmed](#) [Journal](#)
- [80] Du J, Yang F, Liu L, Hu J, Cai B, Liu W, Xu G, Liu X : Repetitive transcranial magnetic stimulation for rehabilitation of poststroke dysphagia: A randomized, double-blind clinical trial.. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 2016;127(3):1907-13 [Pubmed](#) [Journal](#)
- [81] Crary MA, Carnaby GD, Sia I, Khanna A, Waters MF : Spontaneous swallowing frequency has potential to identify dysphagia in acute stroke.. *Stroke; a journal of cerebral circulation* 2013;44(12):3452-7 [Pubmed](#) [Journal](#)
- [82] Poorjavad M, Jalaie S : Systemic review on highly qualified screening tests for swallowing disorders following stroke: Validity and reliability issues.. *Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences* 2014;19(8):776-85 [Pubmed](#)
- [83] Schepp SK, Tirschwell DL, Miller RM, Longstreth WT : Swallowing screens after acute stroke: a systematic review.. *Stroke; a journal of cerebral circulation* 2012;43(3):869-71 [Pubmed](#) [Journal](#)
- [84] Daniels SK, Anderson JA, Willson PC : Valid items for screening dysphagia risk in patients with stroke: a systematic review.. *Stroke; a journal of cerebral circulation* 2012;43(3):892-7 [Pubmed](#) [Journal](#)
- [85] Kertscher B, Speyer R, Palmieri M, Plant C : Bedside screening to detect oropharyngeal dysphagia in patients with neurological disorders: an updated systematic review.. *Dysphagia* 2014;29(2):204-12 [Pubmed](#) [Journal](#)
- [86] Mortensen J, Jensen D, Kjaersgaard A : A validation study of the Facial-Oral Tract Therapy Swallowing Assessment of Saliva.. *Clinical*

rehabilitation 2016;30(4):410-5 [Pubmed Journal](#)

[87] O'Horo JC, Rogus-Pulia N, Garcia-Arguello L, Robbins J, Safdar N : Bedside diagnosis of dysphagia: a systematic review.. Journal of hospital medicine 2015;10(4):256-65 [Pubmed Journal](#)

[88] Kjaersgaard A, Nielsen LH, Sjölund BH : Randomized trial of two swallowing assessment approaches in patients with acquired brain injury: Facial-Oral Tract Therapy versus Fiberoptic Endoscopic Evaluation of Swallowing.. Clinical rehabilitation 2014;28(3):243-53 [Pubmed Journal](#)

[89] Kjaersgaard A, Nielsen LH, Sjölund BH : Factors affecting return to oral intake in inpatient rehabilitation after acquired brain injury.. Brain injury 2015;29(9):1094-104 [Pubmed Journal](#)

[90] Wilson RD, Howe EC : A cost-effectiveness analysis of screening methods for dysphagia after stroke.. PM & R : the journal of injury, function, and rehabilitation 2012;4(4):273-82 [Pubmed Journal](#)

[91] Leder SB, Suiter DM, Warner HL, Acton LM, Swainson BA : Success of recommending oral diets in acute stroke patients based on passing a 90-cc water swallow challenge protocol.. Topics in stroke rehabilitation 19(1):40-4 [Pubmed Journal](#)

[92] Crary MA, Carnaby GD, Shabbir Y, Miller L, Silliman S : Clinical Variables Associated with Hydration Status in Acute Ischemic Stroke Patients with Dysphagia.. Dysphagia 2016;31(1):60-5 [Pubmed Journal](#)

[93] Bray BD, Smith CJ, Cloud GC, Enderby P, James M, Paley L, Tyrrell PJ, Wolfe CDA, Rudd AG : The association between delays in screening for and assessing dysphagia after acute stroke, and the risk of stroke-associated pneumonia.. Journal of neurology, neurosurgery, and psychiatry 2017;88(1):25-30 [Pubmed Journal](#)

[94] Martino R, Maki E, Diamant N : Identification of dysphagia using the Toronto Bedside Swallowing Screening Test (TOR-BSST®): are 10 teaspoons of water necessary?. International journal of speech-language pathology 2014;16(3):193-8 [Pubmed Journal](#)

[95] Cichero JAY, Lam P, Steele CM, Hanson B, Chen J, Dantas RO, Duivesteyn J, Kayashita J, Lecko C, Murray J, Pillay M, Riquelme L, Stanschus S : Development of International Terminology and Definitions for Texture-Modified Foods and Thickened Fluids Used in Dysphagia Management: The IDDSI Framework.. Dysphagia 2017;32(2):293-314 [Pubmed Journal](#)

[96] Rothwell PM, Algra A, Chen Z, Diener H-C, Norrving BO, Mehta Z : Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. The Lancet 2016; [Journal Website](#)

[97] Sandercock PAG, Counsell C, Kane EJ : Anticoagulants for acute ischaemic stroke.. The Cochrane database of systematic reviews 2015;3 CD000024 [Pubmed Journal](#)

[98] He F, Xia C, Zhang J-H, Li X-Q, Zhou Z-H, Li F-P, Li W, Lv Y, Chen H-S : Clopidogrel plus aspirin versus aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke.. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2015;22(1):83-6 [Pubmed Journal](#)

[99] Yi X, Lin J, Wang C, Zhang B, Chi W : A comparative study of dual versus monoantiplatelet therapy in patients with acute large-artery atherosclerosis stroke.. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2014;23(7):1975-81 [Pubmed Journal](#)

[100] Sandercock PAG, Counsell C, Tseng M-C, Cecconi E : Oral antiplatelet therapy for acute ischaemic stroke.. The Cochrane database of systematic reviews 2014;3 CD000029 [Pubmed Journal](#)

[101] Pan Y, Wang A, Liu G, Zhao X, Meng X, Zhao K, Liu L, Wang C, Johnston SC, Wang Y, Wang Y : Cost-effectiveness of clopidogrel-aspirin versus aspirin alone for acute transient ischemic attack and minor stroke.. *Journal of the American Heart Association* 2014;3(3):e000912 [Pubmed Journal](#)

[102] Wong KSL, Wang Y, Leng X, Mao C, Tang J, Bath PMW, Markus HS, Gorelick PB, Liu L, Lin W, Wang Y : Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis.. *Circulation* 2013;128(15):1656-66 [Pubmed Journal](#)

[103] Whiteley WN, Adams HP, Bath PMW, Berge E, Sandset PM, Dennis M, Murray GD, Wong K-SL, Sandercock PAG : Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials.. *The Lancet. Neurology* 2013;12(6):539-45 [Pubmed Journal](#)

[104] Zinkstok SM, Roos YB : Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial.. *Lancet (London, England)* 2012;380(9843):731-7 [Pubmed Journal](#)

[105] Mihalopoulos C, Cadilhac DA, Moodie ML, Dewey HM, Thrift AG, Donnan GA, Carter RC : Development and application of Model of Resource Utilization, Costs, and Outcomes for Stroke (MORUCOS): an Australian economic model for stroke.. *International journal of technology assessment in health care* 2005;21(4):499-505 [Pubmed](#)

[106] Liu L, Wong KSL, Leng X, Pu Y, Wang Y, Jing J, Zou X, Pan Y, Wang A, Meng X, Wang C, Zhao X, Soo Y, Johnston SC, Wang Y : Dual antiplatelet therapy in stroke and ICAS: Subgroup analysis of CHANCE.. *Neurology* 2015;85(13):1154-62 [Pubmed](#)

[107] Lee M, Ovbiagele B, Hong K-S, Wu Y-L, Lee J-E, Rao NM, Feng W, Saver JL : Effect of Blood Pressure Lowering in Early Ischemic Stroke: Meta-Analysis . *Stroke* 2015/05/28 ; [Website](#)

[108] Bath PM, Krishnan K : Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database of Systematic Reviews* 2014; [Journal](#)

[109] Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, Toyoda K, Wang Y, Yamamoto H, Yoon B-W : Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage.. *The New England journal of medicine* 2016; [Pubmed](#)

[110] Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J : Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage.. *The New England journal of medicine* 2013;368(25):2355-65 [Pubmed Journal](#)

[111] Tsivgoulis G, Katsanos AH : Intensive blood pressure reduction in acute intracerebral hemorrhage: A meta-analysis.. *Neurology* 2015;84(24):2464 [Pubmed Journal](#)

[112] Back L, Nagaraja V, Kapur A, Eslick GD : Role of decompressive hemicraniectomy in extensive middle cerebral artery strokes: a meta-analysis of randomised trials.. *Internal medicine journal* 2015;45(7):711-7 [Pubmed Journal](#)

[113] Jüttler E, Unterberg A, Woitzik J, Bösel J, Amiri H, Sakowitz OW, Gondan M, Schiller P, Limprecht R, Luntz S, Schneider H, Pinzer T, Hohohm C, Meixensberger J, Hacke W : Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke.. *The New England journal of medicine* 2014;370(12):1091-100 [Pubmed Journal](#)

[114] Cruz-Flores S, Berge E, Whittle IR : Surgical decompression for cerebral oedema in acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2012; [Pubmed Journal](#)

- [115] Sandercock PA, Soane T : Corticosteroids for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2011; [Pubmed Journal](#)
- [116] Hofmeijer J, van der Worp HB, Kappelle LJ, Eshuis S, Algra A, Greving JP : Cost-effectiveness of surgical decompression for space-occupying hemispheric infarction.. Stroke; a journal of cerebral circulation 2013;44(10):2923-5 [Pubmed Journal](#)
- [117] Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V : Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review.. The Lancet. Neurology 2009;8(4):355-69 [Pubmed Journal](#)
- [118] Yang J, Liu M, Zhou J, Zhang S, Lin S, Zhao H : Edaravone for acute intracerebral haemorrhage. Cochrane Database of Systematic Reviews 2011; [Pubmed Journal](#)
- [119] Bajenaru O, Tiu C, Moessler H, Antochi F, Muresanu D, Popescu BO, Novak P : Efficacy and safety of Cerebrolysin in patients with hemorrhagic stroke.. Journal of medicine and life 3(2):137-43 [Pubmed](#)
- [120] Sprigg N, Renton CJ, Dineen RA, Kwong Y, Bath PMW : Tranexamic acid for spontaneous intracerebral hemorrhage: a randomized controlled pilot trial (ISRCTN50867461).. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2014;23(6):1312-8 [Pubmed Journal](#)
- [121] Steiner T, Poli S, Griebel M, Hüsing J, Hajda J, Freiberger A, Bendszus M, Bösel J, Christensen H, Dohmen C, Hennerici M, Kollmer J, Stetefeld H, Wartenberg KE, Weimar C, Hacke W, Veltkamp R : Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. The Lancet Neurology 15(6):566-573 [Journal Website](#)
- [122] Baharoglu MI, Cordonnier C, Salman RA-S, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, Nederkoorn PJ, de Haan RJ, Roos YB : Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial.. Lancet (London, England) 2016; [Pubmed Journal](#)
- [123] Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S : Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation.. Circulation 2007;115(21):2689-96 [Pubmed](#)
- [124] Pollack CV : Evidence Supporting Idarucizumab for the Reversal of Dabigatran.. The American journal of medicine 2016; [Pubmed Journal](#)
- [125] Connolly SJ, Milling TJ, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Goodman S, Leeds J, Wiens BL, Siegal DM, Zotova E, Meeks B, Nakamya J, Lim WT, Crowther M : Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors.. The New England journal of medicine 2016;375(12):1131-41 [Pubmed Journal](#)
- [126] Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM : Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial.. Lancet (London, England) 2013;382(9890):397-408 [Pubmed Journal](#)
- [127] Xiao BO, Wu F-F, Zhang H, Ma Y-B : A randomized study of urgent computed tomography-based hematoma puncture and aspiration in the emergency department and subsequent evacuation using craniectomy versus craniectomy only.. Journal of neurosurgery 2012;117(3):566-73 [Pubmed Journal](#)
- [128] King NKK, Lai JL, Tan LB, Lee KK, Pang BC, Ng I, Wang E : A randomized, placebo-controlled pilot study of patients with spontaneous intraventricular haemorrhage treated with intraventricular thrombolysis.. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2012;19(7):961-4 [Pubmed Journal](#)

- [129] Gregson BA, Broderick JP, Auer LM, Batjer H, Chen X-C, Juvela S, Morgenstern LB, Pantazis GC, Teernstra OPM, Wang W-Z, Zuccarello M, Mendelow AD : Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage.. *Stroke; a journal of cerebral circulation* 2012;43(6):1496-504 [Pubmed Journal](#)
- [130] Naff N, Williams MA, Keyl PM, Tuhim S, Bullock MR, Mayer SA, Coplin W, Narayan R, Haines S, Cruz-Flores S, Zuccarello M, Brock D, Awad I, Ziai WC, Marmarou A, Rhoney D, McBee N, Lane K, Hanley DF : Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial.. *Stroke; a journal of cerebral circulation* 2011;42(11):3009-16 [Pubmed Journal](#)
- [131] Chen C-C, Liu C-L, Tung Y-N, Lee H-C, Chuang H-C, Lin S-Z, Cho D-Y : Endoscopic surgery for intraventricular hemorrhage (IVH) caused by thalamic hemorrhage: comparisons of endoscopic surgery and external ventricular drainage (EVD) surgery.. *World neurosurgery* 2011;75(2):264-8 [Pubmed Journal](#)
- [132] Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, Karimi A, Shaw MDM, Barer DH : Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial.. *Lancet (London, England)* 365(9457):387-97 [Pubmed](#)
- [133] Bennett MH, Weibel S, Wasiak J, Schnabel A, French C, Kranke P : Hyperbaric oxygen therapy for acute ischaemic stroke.. *The Cochrane database of systematic reviews* 2014;11 CD004954 [Pubmed Journal](#)
- [134] Ali K, Warusevitane A, Lally F, Sim J, Sills S, Pountain S, Nevatte T, Allen M, Roffe C : The stroke oxygen pilot study: a randomized controlled trial of the effects of routine oxygen supplementation early after acute stroke--effect on key outcomes at six months.. *PloS one* 2014;8(6):e59274 [Pubmed Journal](#)
- [135] Roffe C, Ali K, Warusevitane A, Sills S, Pountain S, Allen M, Hodsoll J, Lally F, Jones P, Crome P : The SOS pilot study: a RCT of routine oxygen supplementation early after acute stroke--effect on recovery of neurological function at one week.. *PloS one* 2011;6(5):e19113 [Pubmed Journal](#)
- [136] Rønning OM, Guldvog B : Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial.. *Stroke; a journal of cerebral circulation* 1999;30(10):2033-7 [Pubmed](#)
- [137] Pountain SJ, Roffe C : Does routine oxygen supplementation in patients with acute stroke improve outcome?. *BMJ (Clinical research ed.)* 2012;345 e6976 [Pubmed Journal](#)
- [138] Dávalos A, Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Ferro J, Martínez-Vila E, Serena J, Segura T, Cruz VT, Masjuan J, Cobo E, Secades JJ : Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial).. *Lancet (London, England)* 2012;380(9839):349-57 [Pubmed Journal](#)
- [139] Chamorro A, Amaro S, Castellanos M, Segura T, Arenillas J, Martí-Fàbregas J, Gállego J, Krupinski J, Gomis M, Cánovas D, Carné X, Deulofeu R, Román LS, Oleaga L, Torres F, Planas AM : Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomised, double-blind phase 2b/3 trial.. *The Lancet. Neurology* 2014;13(5):453-60 [Pubmed Journal](#)
- [140] Ginsberg MD, Palesch YY, Hill MD, Martin RH, Moy CS, Barsan WG, Waldman BD, Tamariz D, Ryckborst KJ : High-dose albumin treatment for acute ischaemic stroke (ALIAS) Part 2: a randomised, double-blind, phase 3, placebo-controlled trial.. *The Lancet. Neurology* 2013;12(11):1049-58 [Pubmed Journal](#)
- [141] Heiss W-D, Brainin M, Bornstein NM, Tuomilehto J, Hong Z : Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial.. *Stroke; a journal of cerebral circulation* 2012;43(3):630-6 [Pubmed Journal](#)
- [142] Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, Conwit R, Liebeskind DS, Sung G, Kramer I, Moreau G, Goldweber R,

Sanossian N : Prehospital use of magnesium sulfate as neuroprotection in acute stroke.. The New England journal of medicine 2015;372(6):528-36 [PubMed Journal](#)

[143] Ladurner G, Kalvach P, Moessler H : Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial.. Journal of neural transmission (Vienna, Austria : 1996) 2005;112(3):415-28 [PubMed](#)

[144] Muir KW, Lees KR, Ford I, Davis S : Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial.. Lancet (London, England) 2004;363(9407):439-45 [PubMed](#)

[145] Krams M, Lees KR, Hacke W, Grieve AP, Orgogozo J-M, Ford GA : Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke.. Stroke; a journal of cerebral circulation 2003;34(11):2543-8 [PubMed](#)

[146] Muir KW, Lees KR : Excitatory amino acid antagonists for acute stroke.. The Cochrane database of systematic reviews 2003;(3):CD001244 [PubMed](#)

[147] Diener H-C, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, Shuaib A, Ashwood T, Wasiewski W, Alderfer V, Hårdemark H-G, Rodichok L : NXY-059 for the treatment of acute stroke: pooled analysis of the SAINT I and II Trials.. Stroke; a journal of cerebral circulation 2008;39(6):1751-8 [PubMed Journal](#)

[148] Lyden PD, Shuaib A, Lees KR, Davalos A, Davis SM, Diener H-C, Grotta JC, Ashwood TJ, Hardemark H-G, Svensson HH, Rodichok L, Wasiewski WW, Ahlberg G : Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT Trial.. Stroke; a journal of cerebral circulation 2007;38(8):2262-9 [PubMed](#)

[149] Blanco M, Nombela F, Castellanos M, Rodriguez-Yáñez M, García-Gil M, Leira R, Lizasoain I, Serena J, Vivancos J, Moro MA, Dávalos A, Castillo J : Statin treatment withdrawal in ischemic stroke: a controlled randomized study.. Neurology 2007;69(9):904-10 [PubMed](#)

[150] Ntaios G, Papavasileiou V, Bargiota A, Makaritsis K, Michel P : Intravenous insulin treatment in acute stroke: a systematic review and meta-analysis of randomized controlled trials.. International journal of stroke : official journal of the International Stroke Society 2014;9(4):489-93 [PubMed Journal](#)

[151] Bellolio MF, Gilmore RM, Ganti L : Insulin for glycaemic control in acute ischaemic stroke. Cochrane Database Syst Rev 2014; [PubMed](#)

[152] Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC : Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview.. Stroke; a journal of cerebral circulation 2001;32(10):2426-32 [PubMed](#)

[153] Gray CS, Scott JF, French JM, Alberti KGMM, O'Connell JE : Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke.. Age and ageing 2004;33(1):71-7 [PubMed](#)

[154] Kernan WN, Viscoli CM, Inzucchi SE, Brass LM, Bravata DM, Shulman GI, McVeety JC : Prevalence of abnormal glucose tolerance following a transient ischemic attack or ischemic stroke.. Archives of internal medicine 2005;165(2):227-33 [PubMed](#)

[155] Allport L, Baird T, Butcher K, Macgregor L, Prosser J, Colman P, Davis S : Frequency and temporal profile of poststroke hyperglycemia using continuous glucose monitoring.. Diabetes care 2006;29(8):1839-44 [PubMed](#)

[156] Vermeer SE, Sandee W, Algra A, Koudstaal PJ, Kappelle LJ, Dippel DWJ : Impaired glucose tolerance increases stroke risk in nondiabetic patients with transient ischemic attack or minor ischemic stroke.. Stroke; a journal of cerebral circulation 2006;37(6):1413-7 [PubMed](#)

[157] Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, Evans M, Cadilhac D, Levi C :

Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial.. *Lancet* (London, England) 2011;378(9804):1699-706 [Pubmed Journal](#)

[158] Drury P, Levi C, McInnes E, Hardy J, Ward J, Grimshaw JM, D' Este C, Dale S, McElduff P, Cheung NW, Quinn C, Griffiths R, Evans M, Cadilhac D, Middleton S : Management of fever, hyperglycemia, and swallowing dysfunction following hospital admission for acute stroke in New South Wales, Australia.. *International journal of stroke : official journal of the International Stroke Society* 2014;9(1):23-31 [Pubmed Journal](#)

[159] Ovesen C, Brizzi M, Pott FC, Thorsen-Meyer HC, Karlsson T, Ersson A, Christensen H, Norrlin A, Meden P, Krieger DW, Petersson J : Feasibility of endovascular and surface cooling strategies in acute stroke.. *Acta neurologica Scandinavica* 2013;127(6):399-405 [Pubmed Journal](#)

[160] den Hertog HM, van der Worp HB, van Gemert HMA, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ, Dippel DWJ : The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial.. *The Lancet. Neurology* 2009;8(5):434-40 [Pubmed Journal](#)

[161] Den Hertog HM, van der Worp HB, Tseng M-C, Dippel DW : Cooling therapy for acute stroke.. *The Cochrane database of systematic reviews* 2009;(1):CD001247 [Pubmed Journal](#)

[162] Castillo J, Dávalos A, Marrugat J, Noya M : Timing for fever-related brain damage in acute ischemic stroke.. *Stroke; a journal of cerebral circulation* 1998;29(12):2455-60 [Pubmed](#)

[163] Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC : Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis.. *Stroke; a journal of cerebral circulation* 2008;39(11):3029-35 [Pubmed Journal](#)

[164] Langhorne P, Stott DJ, Robertson L, MacDonald J, Jones L, McAlpine C, Dick F, Taylor GS, Murray G : Medical complications after stroke: a multicenter study.. *Stroke; a journal of cerebral circulation* 2000;31(6):1223-9 [Pubmed](#)