Appendix A: Summary of evidence from surveillance

8-year surveillance (2016) – stroke and transient ischaemic attack in over 16s (2008) NICE guideline CG68

Summary of new evidence from surveillance

Rapid recognition of symptoms and diagnosis

Preamble to the recommendations in this section of the guideline

There is evidence that rapid treatment improves outcome after stroke or transient ischaemic attack (TIA). The recommendations in this section cover the rapid diagnosis of people who have had sudden onset of symptoms that are indicative of stroke and TIA. How to identify risk of subsequent stroke in people who have had a TIA is also covered.

68 – 01 What is the accuracy of a pre-hospital health professional assessment tool/checklist for identifying signs and symptoms of suspected stroke/TIA?

Recommendations derived from this question

1.1.1.1 In people with sudden onset of neurological symptoms a validated tool, such as FAST (Face Arm Speech Test), should be used outside hospital to screen for a diagnosis of stroke or TIA.

1.1.1.2 In people with sudden onset of neurological symptoms, hypoglycaemia should be excluded as the cause of these symptoms.

1.1.1.3 People who are admitted to accident and emergency (A&E) with a suspected stroke or TIA should have the diagnosis established rapidly using a validated tool, such as ROSIER (Recognition of Stroke in the Emergency Room).

Surveillance decision

This review question should not be updated.

Cincinatti Prehospital Stroke Scale

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary
A study[1] assessed the use of the Cincinatti Prehospital Stroke Scale (CPSS) compared with the National Guidelines for Telephone Triage (NGTT) tool on telephone triage of people with acute stroke. The study took place at one emergency medical dispatch centre, and

patients were randomly assigned to triage with CPSS or NGTT. The difference in accurate triage was not statistically significant.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The study showed no evidence of an effect of the CPSS over the existing tool; therefore, there is no effect on current recommendations.

New evidence is unlikely to change guideline recommendations.

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68 – 02 How accurately do scoring systems predict which patients with suspected TIA need to be referred urgently for specialist assessment?

Recommendations derived from this question

1.1.2.1 People who have had a suspected TIA (that is, they have no neurological symptoms at the time of assessment [within 24 hours]) should be assessed as soon as possible for their risk of subsequent stroke using a validated scoring system*, such as ABCD².

* These scoring systems exclude certain populations that may be at particularly high risk of stroke, such as those with recurrent TIAs and those on anticoagulation treatment, who also need urgent evaluation. They also may not be relevant to patients who present late.

Surveillance decision

This review question should be updated.

Scoring systems

3-year surveillance summary
A systematic review[2] of independent validations in 20 cohorts (n=9,808) showed that ABCD and ABCD² scores had good predictive value.

A systematic review[3] of 16 validation studies (n=6,282) showed that after TIA the ABCD² score correctly predicted occurrence of stroke at 7 days across three risk categories.

6-year surveillance summary
A systematic review[4] of 33 studies (n=16,070) suggested that the ABCD² score is associated with small revisions of baseline stroke risk.

8-year surveillance summary
A systematic review and meta-analysis[5] of 29 studies (n=13,766) assessed the ability of ABCD² to predict secondary stroke risk. About half of included trials calculated stroke risk retrospectively. ABCD² score greater than 4 was sensitive but not specific for predicting stroke within 7 days. ABCD² score greater than 4 was seen in up to 41% of stroke mimics and 66% of true TIAs.

A Health Technology Assessment[6] indicated that ABCD² score does not identify patients with key stroke causes or identify mimics: 66% of specialist-diagnosed true TIAs and 35-41% of mimics had an ABCD² score greater than 4; 20% of true TIAs with ABCD² score lower than 4 had key risk factors.

Topic expert feedback
Topic expert feedback indicated a need to assess the effectiveness of ABCD² in context with newer scoring systems such as SOAR or with MRI, but no evidence for newer scoring systems was identified.

Impact statement
Current recommendations suggest ABCD² as an option, but do not specify it as the only tool to use. The new evidence suggests that ABCD² may not be useful for determining whether people with TIA are at high risk of subsequent stroke.

Therefore, the current recommendation to triage people using a scoring system may need to be re-evaluated.

New evidence identified that may change current recommendations.

Early versus late assessment for TIA

3-year surveillance summary
A randomised controlled trial[7] (RCT; n=149) assessed an accelerated diagnostic protocol compared with traditional inpatient admission in people with TIA presenting to an emergency department. The accelerated diagnostic protocol was associated with lower median length of stay in hospital and lower 90-day costs.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
This evidence is generally consistent with current recommendations, which recommend assessment as soon as possible.

New evidence is unlikely to change guideline recommendations.

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68 – 03 In patients with a suspected minor stroke/TIA, does early versus late expert assessment reduce mortality or morbidity?

Recommendations derived from this question

1.1.2.2 People who have had a suspected TIA who are at high risk of stroke (that is, with an ABCD² score of 4 or above) should have:

- aspirin (300 mg daily) started immediately
- specialist assessment* and investigation within 24 hours of onset of symptoms
- measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

1.1.2.3 People with crescendo TIA (two or more TIAs in a week) should be treated as being at high risk of stroke, even though they may have an ABCD² score of 3 or below.

1.1.2.4 People who have had a suspected TIA who are at lower risk of stroke (that is, an ABCD² score of 3 or below) should have:

- aspirin (300 mg daily) started immediately
- specialist assessment* and investigation as soon as possible, but definitely within 1 week of onset of symptoms
- measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

1.1.2.5 People who have had a TIA but who present late (more than 1 week after their last symptom has resolved) should be treated as though they are at lower risk of stroke.

* Specialist assessment includes exclusion of stroke mimics, identification of vascular treatment, identification of likely causes, and appropriate investigation and treatment.

Surveillance decision

This review question should be updated.

Early versus late expert assessment

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary
A Health Technology Assessment[6] indicated that ABCD² score does not identify patients with key stroke causes or identify mimics: 66% of specialist-diagnosed true TIAs and 35-41% of mimics had an ABCD² score greater than 4; 20% of true TIAs with ABCD² score lower than 4 had key risk factors.

Topic expert feedback
Topic experts indicated a need to update the recommendations on specialist assessment after TIA.

Impact statement
The new evidence suggests that the ABCD² score does not accurately distinguish between people who are at higher risk of stroke after TIA and those who are at lower risk. Therefore, the current recommendations to stratify the urgency of specialist assessment by ABCD² score should be considered in an update.

New evidence identified that may change current recommendations.

Using aspirin after stroke or TIA

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary
An individual patient data meta-analysis[8] (n=15,778) assessed the effects of aspirin versus control for preventing recurrent stroke in people with TIA or stroke. Effects were estimated for the time periods: up to 6 weeks, 6–12 weeks and over 12 weeks.

Aspirin was associated with significantly lower stroke recurrence up to 6 weeks after TIA or stroke of all severities. Results in favour of aspirin remained significant at 6–12 weeks, but there was no significant effect of aspirin after 12 weeks. The greatest benefit of aspirin was seen in the first 2 weeks in people who had TIA or minor stroke. Additionally, aspirin was associated with reduced severity of recurrent stroke. The authors concluded: 'The considerable early benefit from aspirin warrants public education about self-administration after possible TIA.'

Topic expert feedback
Topic experts indicated that the new evidence would be unlikely to change current recommendations because aspirin is already recommended as an early treatment for TIA and minor stroke.

However, there was concern about the message about self-administration of aspirin, particularly because this conclusion was widely reported in the mainstream media. If people self-administer aspirin, there is a risk that they may delay contact with health services, or try to self-administer aspirin even if they have continuing rather than transient symptoms. A final risk of self-administration of aspirin without any medical advice is worsening if the person has symptoms due to haemorrhage.

Impact statement
Although there may be no effect on the recommendation for people with suspected TIA to start aspirin immediately, there may be a need for clarity around who should provide the initial suggestion to start aspirin for example, telephone triage services, paramedics, or doctors (emergency physicians or general practitioners). Additionally, recommendations may need to emphasise that starting aspirin is not sufficient; all people with suspected TIA or mild stroke will still need urgent medical assessment.

New evidence identified that may change current recommendations.

Areas not covered in current guidance

In addition to the studies directly related to existing review questions, additional studies relevant to the topic 'Rapid recognition of symptoms and diagnosis' were identified and evaluated as potential new questions.

A further 7 studies[9-15] relevant to this topic were identified but were not thought to have a substantial effect on the evidence base.

NQ – 01 What is the effectiveness of other diagnostic or prognostic investigations in stroke?

Surveillance decision

This review question should not be added.

Investigating cardiac causes of stroke

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary

Echocardiography

A Health Technology Assessment[16] investigated 65 studies of routine echocardiography in first stroke or TIA. Pathologies that are potential cardiac sources of stroke detected by echocardiography included patent foramen ovale, atrial septal aneurysm and mitral valve prolapse. Prevalence rates varied widely across studies. The pooled sensitivity to detect left atrial thrombus in 3 studies using transthoracic echocardiography in second harmonic imaging mode was 0.79, with a pooled specificity of 1.00 compared with transoesophageal echocardiography. Transthoracic echocardiography in second harmonic imaging mode was found to be a cost-effective use of NHS resources compared with transoesophageal echocardiography when clinicians deem it the most appropriate test. No adverse events data were reported.

Diagnosing atrial fibrillation

A systematic review and meta-analysis[17] assessed 50 studies (n=11,658) of diagnosis of atrial fibrillation after stroke. It evaluated diagnosis during sequential phases: in the emergency department; in hospital; first ambulatory period (ambulatory Holter) and second ambulatory period (mobile cardiac outpatient telemetry). Random effects meta-analysis was used to determine a summary proportion of people diagnosed with atrial fibrillation after stroke. In the emergency department, 7.7% of patients were diagnosed with atrial fibrillation and 5.1% were diagnosed in hospital; 10.7% were diagnosed in the first ambulatory period, and 16.9% in the second ambulatory period. Overall, 23.7% of people who underwent cardiac monitoring after stroke were diagnosed with atrial fibrillation.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Echocardiography may be effective in diagnosing cardiac disorders that are potential causes of stroke. The wide variety in prevalence reports by individual studies means that it is difficult to determine the clinical need for and variance in clinical practice in investigating cardiac causes of stroke.

Atrial fibrillation is common in people who have had stroke although diagnosis rates are lower in the acute phase. Ambulatory monitoring appears to have a better diagnostic yield than in-hospital monitoring.

The scope of NICE CG68 notes that: 'specific issues relating to the general management of underlying conditions will not be considered, but the immediate management to reduce the extent of brain damage will be included.' However, diagnosis of underlying conditions in the acute phase may be important if benefits of starting treatment in the acute phase become

apparent. This area will be evaluated again at the next surveillance review.

New evidence is unlikely to impact on the guideline.

Angiography versus CT perfusion

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary
In a diagnostic performance study[18] (n=108), people with suspected stroke underwent CT angiography and CT perfusion imaging. Data from CT perfusion imaging were used to derive timing invariant CT angiography results. Images were reviewed in a random manner by blinded researchers. Both CT angiography and perfusion-derived CT angiography had high sensitivity and specificity. Inter-rater agreement was described as good for both techniques.

A systematic review[19] assessed 21 studies of the diagnostic value of cerebral CT angiography and CT. CT angiography was judged by the authors to have high diagnostic value in detecting cerebral arterial stenosis and CT perfusion was noted to have high specificity for detecting ischaemia and infarct tissue. The mean sensitivity, specificity, positive predictive value, negative predictive value and accuracy were significantly higher for CT angiography than for CT perfusion.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Evidence suggests that CT angiography and CT perfusion imaging are. However, the guideline does not currently recommend the method of imaging to use, and these studies do not provide information on comparative effectiveness against other methods, such as MRI.

New evidence is unlikely to impact on the guideline.

Imaging in people who have had a suspected TIA or non-disabling stroke

Preamble to the recommendations in this section of the guideline

While all people with symptoms of acute stroke need urgent brain scanning, there is less evidence to recommend brain scanning in those people whose symptoms have completely resolved by the time of assessment. This section contains recommendations about which people with suspected TIA need brain imaging and the type of imaging that is most helpful.

Some people who have had a stroke or TIA have narrowing of the carotid artery that may require surgical intervention. Carotid imaging is required to define the extent of carotid artery narrowing. Sections 1.2.3 and 1.2.4 cover the optimum timing of carotid imaging, and the selection of appropriate patients for, and timing of, carotid endarterectomy. The use of carotid stenting was also reviewed by the GDG. However, no evidence for early carotid stenting was found on which the GDG felt they could base a recommendation. For more information, see chapter 6 of the full guideline.

68 – 04 Which patients with suspected TIA should be referred for urgent brain imaging?

Recommendations derived from this question

1.2.1.1 People who have had a suspected TIA (that is, whose symptoms and signs have completely resolved within 24 hours) should be assessed by a specialist (within 1 week of symptom onset) before a decision on brain imaging is made.

1.2.1.2 People who have had a suspected TIA who are at high risk of stroke (for example, an ABCD² score of 4 or above, or with crescendo TIA) in whom the vascular territory or pathology is uncertain* should undergo urgent brain imaging** (preferably diffusion-weighted MRI [magnetic resonance imaging]).

1.2.1.3 People who have had a suspected TIA who are at lower risk of stroke (for example, an ABCD² score of less than 4) in whom the vascular territory or pathology is uncertain* should undergo brain imaging† (preferably diffusion-weighted MRI).

* Examples where brain imaging is helpful in the management of TIA are: people being considered for carotid endarterectomy where it is uncertain whether the stroke is in the anterior or posterior circulation; people with TIA where haemorrhage needs to be excluded, for example long duration of symptoms or people on anticoagulants; where an alternative diagnosis (for example migraine, epilepsy or tumour) is being considered.

** The GDG felt that urgent brain imaging is defined as imaging that takes place 'within 24 hours of onset of symptoms'. This is in line with the National Stroke Strategy.

† The GDG felt that brain imaging in people with a lower risk of stroke should take place 'within 1 week of onset of symptoms'. This is in line with the National Stroke Strategy.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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68 – 05 After TIA, which modality (MRI or CT) should be used?

Recommendations derived from this question

1.2.2.1 People who have had a suspected TIA who need brain imaging (that is, those in whom vascular territory or pathology is uncertain) should undergo diffusion-weighted MRI except where contraindicated*, in which case CT (computed tomography) scanning should be used.

* Contraindications to MRI include people who have any of the following: a pacemaker, shrapnel, some brain aneurysm clips and heart valves, metal fragments in eyes, severe claustrophobia.

Surveillance decision

This review question should be updated.

MRI versus CT

3-year surveillance summary

A Cochrane review[20] assessed the diagnostic accuracy of diffusion-weighted MRI compared with CT for acute ischaemic stroke and estimated the diagnostic accuracy of MRI for acute haemorrhagic stroke. Diffusion-weighted MRI was more sensitive than CT for early detection of ischaemic stroke in highly selected

patients. However, the authors concluded that: 'variability in the quality of included studies and the presence of spectrum and incorporation biases render the reliability and generalisability of observed results questionable.'

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary
A Health Technology Assessment[6] investigated 53 studies (n=30,558) of MRI (including diffusion-weighted imaging) compared with CT in preventing stroke in people with TIA or minor stroke. Overall, stroke recurred in 5.2% of people who had TIA or mild stroke. Diffusion-weighted MRI showed an acute ischaemic lesion in 34.3% of people with TIA, but 69% of people with mild stroke had negative diffusion-weighted MRI. MRI was more expensive and no more cost-effective than CT, except to diagnose haemorrhage in people presenting more than a week after symptoms. MRI plus CT was not cost-effective.

Topic expert feedback
Topic expert feedback indicated that there was increasing evidence on MRI in TIA.

Impact statement
Diffusion-weighted MRI may be effective in detecting stroke, but may not be as effective in detecting TIA. This is contrary to current recommendations to do diffusion-weighted MRI in suspected TIA.

The full-text of the HTA suggested that the scenarios of MRI use modelled in the HTA do not correlate with the pathway of care recommended in NICE CG68. This suggests a need to review this area.

New evidence identified that may change current recommendations.

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68 – 06 Which patients with suspected stroke/TIA should be referred for urgent carotid imaging?

Recommendations derived from this question

1.2.3.1 All people with suspected non-disabling stroke or TIA who after specialist assessment are considered as candidates for carotid endarterectomy should have carotid imaging within 1 week of onset of symptoms. People who present more than 1 week after their last symptom of TIA has resolved should be managed using the lower-risk pathway.

Surveillance decision

This review question should not be updated.

Identifying people who need urgent carotid imaging

3-year surveillance summary
A cost-effectiveness analysis[21] of non-invasive diagnostic imaging strategies in patients with TIA or minor stroke and suspected carotid artery stenosis concluded:

- carotid artery stenosis should be initially diagnosed with duplex ultrasonography with subsequent CT if results are positive. Patients with 70–99% stenosis should undergo carotid endarterectomy.
- immediate CT angiography and surgery for 50–99% stenosis was suggested for patients with a high risk profile, a high probability of carotid artery stenosis, or who can undergo surgery without delay.

6-year surveillance summary
A systematic review[22] with individual patient data meta-analysis from 2 studies (n=359) suggested that symptomatic vertebrobasilar stenosis, particularly intracranial stenosis, is a strong independent predictor of stroke recurrence.

8-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence supports the need to investigate carotid arterial stenosis in people with suspected non-disabling stroke or TIA, as recommended in the guideline.

New evidence is unlikely to change guideline recommendations.

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68 – 07 Which patients with symptomatic carotid stenosis should be referred for urgent carotid procedures (carotid endarterectomy and stenting)?

Recommendations derived from this question

1.2.4.1 People with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of 50–99% according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria, or 70–99% according to the ECST (European Carotid Surgery Trialists' Collaborative Group) criteria, should:

- be assessed and referred for carotid endarterectomy within 1 week of onset of stroke or TIA symptoms
- undergo surgery within a maximum of 2 weeks of onset of stroke or TIA symptoms
- receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice).

1.2.4.2 People with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of less than 50% according to the NASCET criteria, or less than 70% according to the ECST criteria, should:

- not undergo surgery
- receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice).

1.2.4.3 Carotid imaging reports should clearly state which criteria (ECST or NASCET) were used when measuring the extent of carotid stenosis.

Surveillance decision

This review question should not be updated.

Carotid endarterectomy

3-year surveillance
A Cochrane review[23] with individual patient data meta-analysis of 3 trials (n=6,092) assessed carotid endarterectomy compared with medical management in patients with recent TIA or non-disabling stroke. Carotid endarterectomy was of marginal benefit in patients with 50–69% stenosis, and was highly beneficial in patients with 70–99% stenosis without near-occlusion. Benefit from surgery was greatest in men, people older than aged 75 years, and in people randomised within 2 weeks of their last ischaemic event, but fell rapidly with increasing delay. Benefit in patients with carotid near-occlusion was marginal in the short-term and uncertain in the long-term.

A systematic review[24] of operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery was identified. The pooled absolute risks of stroke and death after urgent carotid endarterectomy were high in patients with stroke-in-evolution and in patients with

crescendo TIA. However, in neurologically stable patients with recent TIA or non-disabling stroke there were no significant differences between early and later carotid endarterectomy.

A systematic review and meta-analysis[25] assessed 2 cohort studies and 8 RCTs of carotid endarterectomy compared with stenting. Stenting was associated with greater 30-day risk of stroke or death. Subgroup analysis showed the difference in risk to be significant for people with symptomatic stenosis but not for asymptomatic stenosis.

A meta-analysis[26] of 3 RCTs indicated that only age significantly modified the treatment effect between carotid stenting and carotid endarterectomy. Stenting was as safe as endarterectomy in patients under 70 years, but was associated with double the risk of stroke or death in people older than 70 years compared with endarterectomy.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
A systematic review[27] of 9 studies (n=118) assessed the safety of carotid interventions after thrombolysis. Early carotid endarterectomy had rates of 30-day stroke or death that were similar to rates seen for the intervention without thrombolysis. No patients had stroke or death after angioplasty, but only 4 angioplasties were included.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
New evidence is consistent with current recommendations about the level of occlusion for which people would benefit from surgery. There seems to be no contraindication to carotid surgery after thrombolysis.

A meta-analysis suggested that stenting is as safe as endarterectomy in people younger than 70 years. Carotid artery stent placement for symptomatic extracranial carotid stenosis (NICE IPG389) covers use of this technique. The preamble to the recommendation noted that no evidence was found for early stenting and new evidence has not clearly filled this gap.

People older than 70 years may have greater risks with stenting. Discussing the risks and benefits of treatment options with the patient should be standard practice, so a new recommendation is unlikely to be necessary at this time.

New evidence is unlikely to change guideline recommendations.

Specialist care for people with acute stroke

Preamble to the recommendations in this section of the guideline

This section provides recommendations about the optimum care for people with acute stroke: where they should be cared for and how soon they should undergo brain imaging.

68 – 08 Does rapid admission to an acute unit reduce mortality, morbidity and length of hospital stay?

Recommendations derived from this question

1.3.1.1 All people with suspected stroke should be admitted directly to a specialist acute stroke unit* following initial assessment, either from the community or from the A&E department

*An acute stroke unit is a discrete area in the hospital that is staffed by a specialist stroke multidisciplinary team. It has access to equipment for monitoring and rehabilitating patients. Regular multidisciplinary team meetings occur for goal setting.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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68 – 09 In patients with suspected stroke, what are the benefits of being admitted to specialist care versus a non-specialised unit in terms of recovery time, morbidity and mortality?

Recommendations derived from this review question

1.3.1.1 All people with suspected stroke should be admitted directly to a specialist acute stroke unit* following initial assessment, either from the community or from the A&E department

*An acute stroke unit is a discrete area in the hospital that is staffed by a specialist stroke multidisciplinary team. It has access to equipment for monitoring and rehabilitating patients. Regular multidisciplinary team meetings occur for goal setting.

Surveillance decision

This review question should not be updated.

Specialist care

3-year surveillance summary

A systematic review[28] of 31 controlled trials (n=6,936) concluded that organised inpatient care in a stroke unit reduced the risk of death after stroke and risk of stroke progressions or recurrence.

An Australian cluster RCT[29] (n=1,696) assessed patient outcomes 90 days after hospital admission for stroke comparing a multidisciplinary intervention (management of fever, hyperglycaemia, and swallowing dysfunction) with abridged guideline recommendations (control) in acute stroke units. The multidisciplinary intervention significantly decreased mortality or dependence at 90 days compared with control.

An RCT[30] (n=150) indicated that admission to a stroke rehabilitation unit in the acute phase of cerebral infarction resulted in improvements in neurological function, capabilities of managing daily life, and shortened hospitalisation compared with standard care.

A cluster RCT[31] evaluated the effectiveness of an emergency clinical pathway (integrated emergency medical services, emergency departments and stroke units) for stroke patient referrals. An emergency clinical pathway was feasible and increased the proportion of patients referred to a stroke unit and the number of patients receiving intravenous thrombolysis.

A systematic review[32] of service delivery configurations concluded that regional collaborations achieve higher rates of thrombolysis than local services working in isolation.

6-year surveillance summary

A Cochrane review[33] of 28 trials (n=5,855) of stroke unit care compared with alternative forms of care in people with stroke. Stroke unit care reduced the odds of death at final follow-up (median 1 year), death or institutionalised care, and death or dependency. Stroke unit care was not associated with longer stay in hospital. Outcomes were independent of age, sex, initial stroke severity or stroke type, and appeared to be better in stroke units based in a discrete ward.

A systematic review[34] of 13 trials (n=3,570) noted that care in stroke units is equally beneficial for ischaemic stroke and haemorrhagic stroke.

8-year surveillance summary

A cluster RCT[35] (n=6,592) assessed quality improvement collaboratives' (Stroke 90:10)

effect on compliance in 24 NHS hospitals compared with control. The intervention focused on 9 processes already used in the national stroke audit, which were grouped into two distinct care bundles: early hours care and rehabilitation. Hospitals in the quality improvement collaborative had modest but statistically significant improvements in compliance compared with control.

A systematic review and meta-analysis[36] of 21 cohort studies (n=1,421,914) suggested that presenting with stroke out of hours was associated with higher short-term mortality and greater disability at discharge. However, the association between out-of-hours care and poorer outcomes was not significant for people presenting at accredited stroke centres.

An RCT (n=41)[37] evaluated a model of combined acute and rehabilitation stroke care compared with conventional care at separate acute care and rehabilitation facilities. Functional independence did not differ at discharge or at 90 days after discharge. Combined care was associated with a reduction of length of hospital stay of 5 days, but this was not statistically significant.

Topic expert feedback

Topic experts indicated concerns about organisation of stroke services, including: geographical disparity; out-of-hours access to specialists and diagnostic investigations.

Impact on guideline

People presenting with stroke out of hours may have poorer outcomes than those presenting in regular hours. However, accredited stroke units may not have the association between out-of-hours care and poorer outcomes. There is some evidence that collaborating at a regional level may be beneficial. Overall, evidence is consistent with the recommendation to admit people with suspected stroke to specialist acute stroke units.

New evidence is unlikely to change guideline recommendations.

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68 – 10 How quickly should brain imaging be performed following an acute stroke?

Recommendations derived from this review question

1.3.2.1 Brain imaging should be performed immediately* for people with acute stroke if any of the following apply:

- indications for thrombolysis or early anticoagulation treatment
- on anticoagulant treatment
- a known bleeding tendency
- a depressed level of consciousness (Glasgow Coma Score below 13)
- unexplained progressive or fluctuating symptoms
- papilloedema, neck stiffness or fever
- severe headache at onset of stroke symptoms.

1.3.2.2 For all people with acute stroke without indications for immediate brain imaging, scanning should be performed as soon as possible.**

* The GDG felt that 'immediately' is defined as 'ideally the next slot and definitely within 1 hour, whichever is sooner', in line with the National Stroke Strategy.

** The GDG felt that 'as soon as possible' is defined as 'within a maximum of 24 hours after onset of symptoms'.

Surveillance decision

This review question should not be updated.

Time to brain imaging

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
A report from a cluster RCT[38] (INSTINCT; n=557) assessed the effect of a behavioural change intervention in the time to imaging for people with ischaemic stroke. Door-to-imaging time decreased over time but there was no significant difference between the intervention and control hospitals. After adjustment, arriving by ambulance and having severe stroke were associated with shorter time to imaging.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The study did not provide evidence of an effect on time to imaging. Current guidance recommends imaging within an hour for people with stroke and indications for immediate brain imaging, and within 24 hours for people with stroke who do not have indications for immediate brain imaging.

New evidence is unlikely to change guideline recommendations.

Pharmacological treatments for people with acute stroke

Preamble to the recommendations in this section of the guideline

Urgent treatment has been shown to improve outcome in stroke. This section contains recommendations about urgent pharmacological treatment in people with acute stroke.

68 – 11 Thrombolysis in people with acute ischaemic stroke

Recommendations derived from this question

1.4.1.1 Alteplase is recommended for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke. It should only be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation.*

1.4.1.2 Alteplase should be administered only within a well organised stroke service with:

- staff trained in delivering thrombolysis and in monitoring for any complications associated with thrombolysis
- level 1 and level 2 nursing care staff trained in acute stroke and thrombolysis**
- immediate access to imaging and re-imaging, and staff trained to interpret the images.

1.4.1.3 Staff in A&E departments, if appropriately trained and supported, can administer alteplase† for the treatment of acute ischaemic stroke provided that patients can be managed within an acute stroke service with appropriate neuroradiological and stroke physician support.

1.4.1.4 Protocols should be in place for the delivery and management of thrombolysis, including post-thrombolysis complications.

*This recommendation is from 'Alteplase for the treatment of acute ischaemic stroke' (NICE technology appraisal guidance 122).

**See NHS Data Dictionary, 'Critical care level' [online].

†In accordance with its marketing authorisation.

Surveillance decision

This review question should be updated.

An editorial or factual correction is needed to the footnote to recommendation 1.4.1.1. The cross-reference to TA122 is out of date and this guidance has been replaced by TA264.

Pharmacological thrombolysis

Alteplase

Studies relating to 'Alteplase for the treatment of acute ischaemic stroke' (NICE TA264) have not been summarised. The NICE technology appraisals team has been informed about all evidence identified by cumulative surveillance reviews.

3-year surveillance summary
'Alteplase for the treatment of acute ischaemic stroke' (NICE TA122) was noted to need updating because new relevant trial data had published. Since the 3-year surveillance, this technology appraisal has been updated (see NICE TA264).

Overall, 54 studies[39-88;89-92] were identified relating to thrombolysis (alteplase, tissue plasminogen activator [TPA], or unspecified thrombolysis).

6-year surveillance summary
A Cochrane review[92,93] and 5 systematic reviews[94-98] relating to alteplase were identified.

8-year surveillance summary
Eleven systematic reviews and meta-analyses[99-109] and 10 RCTs[110-119] relating to alteplase or unspecified thrombolysis were identified.

Two systematic reviews and meta-analyses[120,121] and an RCT[122] comparing alteplase with endovascular therapy were identified (summarised in mechanical thrombectomy sections below).

Topic expert feedback
Topic experts raised concerns about thrombolysis, but also noted that these had been addressed by a review by the MHRA. The MHRA found the benefits of alteplase outweighed the harms.

Impact statement
The NICE technology appraisals team has been informed about all new evidence.

New evidence is unlikely to change guideline recommendations.

Sonothrombolysis

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance
A Cochrane review[123] of 5 studies (n=233) found that people with acute ischaemic stroke treated with sonothrombolysis were less likely to be dead or disabled at 3 months compared with conventional treatment. However, the authors noted that the confidence intervals were wide. Additionally, some studies assessed use of ultrasound compared with no ultrasound in people who all had pharmacological thrombolysis. One study tested the application of ultrasound in the absence of pharmacological thrombolysis.

8-year surveillance
A subgroup analysis[124] of the CLOTBUST trial assessed TPA (thrombolysis) plus transcranial Doppler monitoring (sonothrombolysis) compared with thrombolysis alone in people with acute ischaemic stroke. Of 126 people enrolled in the trial, 85 had pretreatment National Institutes of Health (NIH) Stroke Scale scores greater than 10 points and proximal intracranial occlusions and were included in the subanalysis. Sonothrombolysis was associated with increased rates of complete recanalisation and functional independence at 90 days. Symptomatic intracranial haemorrhage rate was similar in both groups.

A systematic review and meta-analysis[125] of 7 RCTs and 3 case-control studies (number of participants not reported in the abstract) assessed sonolysis or sonothrombolysis. Sonolysis and sonothrombolysis were safe and effective, and associated with higher likelihood of favourable outcomes at 3 months. The

comparator group was not clearly reported in the abstract.

An RCT[126] (n=42) assessed sonothrombolysis within 24 hours of ischaemic stroke due to middle cerebral artery occlusion. All participants received aspirin. A 1-hour session of transcranial Doppler ultrasound was associated with significantly higher mean flow velocity. Thrombolytic drugs were not used.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence suggests potential for sonothrombolysis, but estimates of efficacy were imprecise because only small trials have been reported.

A larger study (NOR-SASS; n=183) was expected to complete in May 2015. The results of this trial, once published, may give robust data to support this intervention in the future.

New evidence is unlikely to change guideline recommendations.

Desmoteplase

3-year surveillance summary
An RCT[127] (DIAS-2; n=193) indicated that desmoteplase given 3–9 hours after ischaemic stroke did not improve clinical response or lesion volume compared with placebo.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
An RCT[128] (DIAS-3; n=492) assessed desmoteplase compared with placebo given 3–9 hours after ischaemic stroke. No significant differences were seen between groups in modified Rankin Scale score at day 90 or serious adverse events.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The studies show no evidence of an effect of desmoteplase. Development of desmoteplase for acute stroke has been discontinued.

New evidence is unlikely to change guideline recommendations.

Non-pharmacological interventions

Although the guideline addressed thrombolysis under the heading 'Pharmacological treatments for people with acute stroke' non-pharmacological methods of clot removal exist, particularly mechanical thrombectomy. Since the publication of NICE CG68, many studies have assessed the efficacy and safety of mechanical thrombectomy alone, in people treated with thrombolysis, and compared with thrombolysis. The overlap in the patient populations who could be eligible for thrombolysis or mechanical thrombectomy means that these interventions should be considered together.

Mechanical clot removal

3-year surveillance

*Thrombectomy in people **not** treated with thrombolysis*

A systematic review and meta-analysis[129] indicated that percutaneous mechanical embolectomy for acute ischaemic stroke was feasible and is an option for some patients seen after the interval for intravenous thrombolytic therapy has elapsed.

Two studies[130,131] of cost effectiveness assessed mechanical clot removal or disruption compared with standard therapy in patients who were ineligible for TPA. A cost–utility analysis[131] examined mechanical clot removal or disruption with angioplasty for acute ischaemic stroke. Available data (no RCTs) suggested that mechanical therapies in

patients with acute stroke beyond the window for intravenous alteplase appeared to be cost-effective; however, the results were sensitive to several assumptions. A Markov cost-effectiveness model[130] of the health benefits and costs indicated that mechanical thrombectomy was cost effective compared with standard medical therapy.

Thrombectomy in people treated with thrombolysis

An RCT[132] (IMS-3; n=656) assessed endovascular therapy after thrombolysis compared with thrombolysis alone in a 2:1 ratio. The study was stopped early because of futility. There was no significant difference in functional dependence at 90 days for people in the endovascular treatment plus thrombolysis group compared with those who had thrombolysis alone. Death and intracerebral haemorrhage also showed no significant differences between groups.

Thrombectomy in populations with mixed or unspecified use of thrombolysis

A systematic review and meta-analysis[133] of 31 studies of mechanical endovascular therapy (n=1,066) showed a pooled estimate of 40% for a favourable outcome, 28% for mortality, and 8% for symptomatic intracranial haemorrhage.

A Cochrane systematic review[134] of 4 studies (n=350) assessed the safety and efficacy of percutaneous vascular interventions in people with acute ischaemic stroke. Included studies tested intra-arterial urokinase or recombinant pro-urokinase. One trial also used guidewire-mediated clot disruption in some patients randomised to the intervention group. The authors concluded that intervention resulted in a significant increase in patients with a favourable outcome, despite a significant increase in intracranial haemorrhage.

Intra-arterial thrombolysis

A Cochrane systematic review[134] of 4 studies (n=350) assessed the safety and efficacy of percutaneous vascular interventions in people with acute ischaemic stroke. Included studies tested intra-arterial urokinase or recombinant pro-urokinase. One trial also used guidewire-mediated clot disruption in some patients randomised to the intervention group. The authors concluded that intervention resulted in a significant increase in patients with a favourable outcome, despite a significant increase in intracranial haemorrhage.

6-year surveillance summary

No relevant evidence was identified.

8-year surveillance

Thrombectomy compared with thrombolysis

A systematic review and meta-analysis[120] of 8 studies (n=2,423) assessed mechanical thrombectomy compared with standard medical care (including thrombolysis). Mechanical thrombectomy was associated with significantly improved scores on the modified Rankin scale and increased functional independence at 90 days compared with standard medical care. Rates of symptomatic intracranial haemorrhage and mortality at 90 days did not differ between groups.

Thrombectomy in people treated with thrombolysis

An RCT[135] (SWIFT PRIME; n=196) assessed thrombectomy within 6 hours plus thrombolysis compared with thrombolysis alone in people with confirmed proximal anterior stroke and an absence of large ischaemic-core lesions. Thrombectomy was associated with significantly greater reductions in disability at 90 days and increased functional independence. Symptomatic intracranial haemorrhage and deaths at 90 days were not significantly different between groups. The study was stopped early because of efficacy of thrombectomy.

An RCT[136] (EXTEND-IA; n=70) assessed thrombectomy with the SOLITAIRE device plus thrombolysis versus thrombolysis alone in people with stroke. Participants had occlusion of the internal carotid or middle cerebral artery and evidence of salvageable brain tissue and ischaemic core of less than 70 ml on CT perfusion imaging. The proportion of ischaemic tissue that had achieved reperfusion was significantly greater in the thrombectomy group. Functional independence was significantly more common in the thrombectomy group and there were no differences in symptomatic intracranial haemorrhage or deaths. The study was stopped early by the data monitoring committee because of efficacy of thrombectomy.

A pooled analysis[137] of the IMS-3 and MR CLEAN trials (n=342) assessed endovascular therapy versus usual care in people with acute stroke who were also treated with alteplase within 3 hours of stroke onset. Outcomes at

90 days were significantly better in the group receiving endovascular therapy.

Thrombectomy in populations with mixed or unspecified use of thrombolysis

An RCT[138] (REVASCAT; n=206) assessed thrombectomy with the Solitaire device plus medical therapy compared with medical therapy alone within 8 hours of stroke. Thrombectomy was associated with reduction in severity of disability and higher rates of functional independence. No differences in symptomatic intracranial haemorrhage or deaths were seen.

An RCT[139] (n=118) assessed mechanical embolectomy within 8 hours of stroke onset versus standard care in people with large-vessel anterior-circulation stroke. Randomisation was stratified according to favourable penumbral pattern (58% of participants) or non-penumbral pattern. Revascularisation was achieved in 67% of people in the embolectomy group. There was no difference between groups in 90-day mortality (21%) or symptomatic intracranial haemorrhage (4%). At 90 days, outcomes on the modified Rankin scale were not significantly different between groups. Penumbral pattern had no effect on outcomes.

An analysis[140] of data from the SWIFT trial assessed major complications defined as symptomatic intracranial haemorrhage within 36 hours, symptomatic subarachnoid haemorrhage, air emboli, vessel dissection, major groin complications, and emboli to new vascular territories. Complications occurred in 18 of 144 participants. The most common complications were symptomatic intracranial haemorrhage, vessel dissection and subarachnoid haemorrhage. No clinical characteristics were significantly associated with complications. Symptomatic cerebral haemorrhage was significantly more common with the Merci device than with the Solitaire device.

An RCT[141] (ESCAPE) assessed thrombectomy in addition to usual care (including thrombolysis, if appropriate) compared with usual care alone. Participants had acute ischaemic stroke with a small infarct core, proximal intracranial arterial occlusion, and moderate-to-good collateral circulation. Thrombolysis was used in 238 of 316 participants. Functional independence was significantly higher in people receiving thrombectomy compared with usual care. Modified Rankin Scale scores and mortality were significantly better with thrombolysis. Symptomatic intracranial haemorrhage did not differ significantly between groups. The study was stopped early by the data monitoring committee because of efficacy of thrombectomy.

An RCT[142] (MR CLEAN; n=500) assessed intra-arterial treatment (retrievable stents) plus usual care compared with usual care alone in people with proximal intracranial intra-arterial occlusion. Modified Rankin Score was significantly improved in the intra-arterial treatment group compared with usual care, with no significant differences in mortality or symptomatic intracranial haemorrhage.

A meta-analysis[143] assessed 15 RCTs (n=2,899) of endovascular therapy in acute ischaemic stroke, with sub-analyses of stent retriever trials and trials comparing endovascular therapy with thrombolysis. Endovascular therapy was associated with increases in good outcomes and reductions in poor outcomes compared with control, without increases in symptomatic intracranial haemorrhage or death. Comparisons of endovascular therapy with thrombolysis showed similar efficacy and safety. Comparisons of endovascular therapy plus thrombolysis compared with thrombolysis increased good outcomes and reduced disability and death (to a greater degree than endovascular therapy alone).

A meta-analysis[144] of 5 RCTs (n=1,287) of stent retrievers showed a significantly greater proportion of people with Rankin Scale score of 2 or lower at 90 days compared with standard therapy control. Intracranial bleeding and mortality did not differ between groups.

A systematic review and meta-analysis[145] assessed 9 studies of endovascular thrombectomy that included anterior circulation strokes. Thrombectomy was associated with increases in good outcome compare with control.

A systematic review and meta-analysis[146] assessed 17 studies (number of participants not reported in abstract) of mechanical thrombectomy. Stent retrievers had safety and mortality rates similar to the Merci device. However recanalisation rates were higher with the Solitaire and Trevo devices.

Endovascular treatment with multiple or mixed therapies

A systematic review and meta-analysis[147] assessed 8 studies (n=2,729) of endovascular therapy for acute stroke in people aged 80 years or older. Studies used intra-arterial thrombolysis, mechanical endovascular therapy or both. One study additionally used stenting, angioplasty and antiplatelet infusion. Compared with younger participants, people aged 80 years or older were less likely to have good functional outcome at 90 days, and were more likely to have symptomatic haemorrhage. Successful recanalisation was not significantly different.

An RCT[120] (n=362) investigated endovascular therapy compared with intravenous TPA in people with acute ischaemic stroke. Endovascular therapy included intra-arterial TPA or mechanical thrombectomy or both. The proportion of people alive without disability at 3 months, rates of symptomatic intracranial haemorrhage and mortality did not differ significantly between groups.

A report[148] from the IMS-3 trial (n=656) assessed 12-month outcomes for endovascular therapy after thrombolysis compared with thrombolysis alone. The endovascular therapy group could have mechanical thrombectomy or intra-arterial thrombolysis, selected as by the clinician as appropriate for each patient. In people with severe stroke, endovascular therapy plus thrombolysis was associated with more people having modified Rankin Scale scores of less than 2 at 12 months compared with thrombolysis alone. There were no significant differences between groups for moderately-severe stroke.

An analysis[149] of data from the endovascular therapy arm (n=434) of the IMS-3 trial suggested that people who underwent general anaesthesia for medical reasons had worse outcomes and increased mortality compared with local anaesthesia. Risks of subarachnoid and intracerebral haemorrhage did not differ between groups.

A meta-analysis[121] of 6 RCTs assessed endovascular therapy compared with medical management. The data were categorised as confirmed large-vessel occlusion (n=1,183) and all people randomised irrespective of vascular imaging (n=1,903). Endovascular therapy differed across included studies and included:

- intra-arterial prourokinase or urokinase plus heparin,
- mechanical thrombectomy with intra-arterial TPA (some trials used TPA only if appropriate) plus heparin in 2 studies.

In people with confirmed large-vessel occlusion, endovascular therapies significantly improved outcomes compared with control. The effect size was smaller but still significant when the full dataset (including unconfirmed large-vessel occlusion) was used.

A meta-analysis[150] assessed 7 RCTs (n=2,217) of endovascular therapy in ischaemic stroke stratified by use of CT angiography to select patients. Interventions tested in included studies were mechanical thrombectomy or intra-arterial TPA with or without intravenous TPA. In all included studies the control group had TPA or standard medical care including TPA if appropriate. Endovascular therapy significantly increased 90-day functional independence in patients with a CTA-confirmed large-vessel occlusion, and reduced 90-day mortality in patients with occlusion stroke with small ischaemic core. The functional benefit was significantly greater in patients with CT angiography-based selection than in those without. The mortality benefit was significantly greater in patients with large-vessel occlusion and a small ischaemic core than in those without CT angiography-based selection.

A systematic review and meta-analysis[151] assessed 9 studies (n=1956) reporting general anaesthesia compared with conscious sedation during intra-arterial therapy for acute ischaemic stroke. People who had general anaesthesia had higher odds of death and respiratory complications and lower odds of good functional outcome. Procedure time did not differ significantly between types of anaesthesia.

A systematic review and meta-analysis[152] assessed intra-arterial treatment versus intravenous thrombolysis. The number of studies and participants, and the drugs used were not specified in the abstract. However, the baseline characteristics of included studies showed that intra-arterial treatments were:

- endovascular treatment (defined as intra-arterial TPA, or mechanical thrombectomy, or both)
- TPA or alteplase

- urokinase
- pro-urokinase.

Intravenous thrombolytic strategies were:

- TPA or alteplase
- urokinase
- heparin.

A favourable outcome and survival at 90 days were both more likely with intra-arterial administration than with intravenous administration.

Topic expert feedback
Topic experts indicated a need to review guidance on endovascular thrombectomy.

Impact statement
Intra-arterial administration of antithrombotic drugs may have potential benefits. However, alteplase is not licensed in the UK for intra-arterial administration and urokinase is not licensed in the UK for use in stroke.

Evidence consistently shows that endovascular thrombectomy improves outcomes after stroke. This technique is covered by Mechanical clot retrieval for treating acute ischaemic stroke (NICE IPG548).

NICE IPG548 recommends use of mechanical thrombectomy using standard arrangements for audit and consent. However, this type of guidance does not consider the service arrangements needed to support the wider adoption of mechanical thrombectomy, including imaging to determine the suitability of the procedure for patients.

Additionally, there is a need to consider how to select the most appropriate treatment for people with stroke – thrombolysis, thrombectomy or both.

New evidence identified that may change current recommendations.

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68 – 12 What is the safety and efficacy of antiplatelet agents and anticoagulants after acute ischaemic stroke?

Subquestions

What is the safety and efficacy of aspirin versus other antiplatelet agents for the treatment of patients with acute ischaemic stroke?

What is the safety and efficacy of antiplatelet agents versus placebo for the treatment of patients with acute ischaemic stroke?

What is the safety and efficacy of anticoagulants versus placebo for the treatment of patients with acute ischaemic stroke?

What is the safety and efficacy of antiplatelet agents versus anticoagulants for the treatment of patients with acute ischaemic stroke?

Recommendations derived from this question

1.4.2.1 All people presenting with acute stroke who have had a diagnosis of primary intracerebral haemorrhage excluded by brain imaging should, as soon as possible but certainly within 24 hours, be given:

- aspirin 300 mg orally if they are not dysphagic or
- aspirin 300 mg rectally or by enteral tube if they are dysphagic.

Thereafter, aspirin 300 mg should be continued until 2 weeks after the onset of stroke symptoms, at which time definitive long-term antithrombotic treatment should be initiated. People being discharged before 2 weeks can be started on long-term treatment earlier.

1.4.2.2 Any person with acute ischaemic stroke for whom previous dyspepsia associated with aspirin is reported should be given a proton pump inhibitor in addition to aspirin.

1.4.2.3 Any person with acute ischaemic stroke who is allergic to or genuinely intolerant of aspirin* should be given an alternative antiplatelet agent.

1.4.2.4 Anticoagulation treatment should not be used routinely** for the treatment of acute stroke.

* Aspirin intolerance is defined in NICE technology appraisal guidance 90 ('Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events') as either of the following: proven hypersensitivity to aspirin-containing medicines; or history of severe dyspepsia induced by low-dose aspirin.

**There may be a subgroup of people for whom the risk of venous thromboembolism outweighs the risk of haemorrhagic transformation. People considered to be at particularly high risk of venous thromboembolism include anyone with complete paralysis of the leg, a previous history of venous thromboembolism, dehydration or comorbidities (such as malignant disease), or who is a current or recent smoker. Such people should be kept under regular review if they are given prophylactic anticoagulation.

Surveillance decision

This review question should not be updated.

An editorial or factual correction is needed on the footnote to recommendation 1.4.2.3. The cross reference to NICE TA90 is out of date. This guidance has been replaced by NICE TA210. Additionally, NICE TA210 does not contain a definition of aspirin intolerance, so this definition should be integrated into the recommendation without reference to an external source.

Clopidogrel and dipyramidole

Studies relating to 'Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events' (NICE TA210) have not been summarised. The NICE technology appraisals team has been informed about all evidence identified by cumulative surveillance reviews.

3-year surveillance
Seven studies[153-159] relating to clopidogrel or dipyridamole were identified.

6-year surveillance
Two systematic reviews[160,161] relating to clopidogrel or dipyridamole were identified.

8-year surveillance
A systematic review[162] and 9 RCTs[163-171] relating to clopidogrel or dipyridamole were identified.

Topic expert feedback
Topic experts initially suggested a need to assess dual antiplatelet therapy. However, further discussion with topic experts resulted in a decision not to update this review question.

Impact statement
The NICE technology appraisals team has been informed about all new evidence.

New evidence is unlikely to change guideline recommendations.

Aspirin and other antiplatelet agents

3-year surveillance
A Cochrane review[172] assessed 12 trials (n=43,041) of antiplatelet therapy in acute ischaemic stroke. Aspirin 160–300 mg daily and started within 48 hours of onset of presumed ischaemic stroke reduced the risk of early recurrent ischaemic stroke without a major risk of early haemorrhagic complications and improved long-term outcome.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
An update[173] of the Cochrane review identified at 3-year surveillance[172] assessed 8 randomised trials (n=41,483) of oral antiplatelet treatment staring within 14 days of stroke. No new trials were identified, but 4 trials from the previous review appear to have been excluded. With treatment, there was a significant decrease in death or dependency at the end of follow-up. For every 1000 people treated with aspirin, 13 people would avoid death or dependency (number needed to treat=79).

A pooled analysis[174] of 17 RCTs (n=42,234) assessed antiplatelet therapy compared with placebo in lacunar stroke. Antiplatelet therapy was associated with reductions in recurrence of stroke and ischaemic stroke but did not significantly affect the outcome of 'stroke, myocardial infarction, or death'. Compared with aspirin, other antiplatelet drugs did not significantly improve outcomes, and dual antiplatelet therapy had no additional benefit.

An individual patient data meta-analysis[175] of 3 studies (n=39,166) assessed aspirin compared with placebo in acute ischaemic stroke to develop prediction models for recurrent events. Prediction models had weak ability to discriminate between people who would and those who would not have recurrent thrombotic or haemorrhagic events. However, the ability to discriminate between poor outcome or not was better.

An individual patient data meta-analysis[8] (n=15,778) assessed the effects of aspirin versus control for preventing recurrent stroke in people with TIA or stroke. Effects were estimated for the time periods: up to 6 weeks, 6–12 weeks and over 12 weeks. Aspirin was associated with significantly lower stroke recurrence up to 6 weeks after TIA or stroke of all severities. Results in favour of aspirin remained significant at 6–12 weeks, but there was no significant effect of aspirin after 12 weeks. The greatest benefit of aspirin was seen in the first 2 weeks in people who had TIA or minor stroke. Additionally, aspirin was associated with reduced severity of recurrent stroke.

Topic expert feedback
Topic experts noted that the individual patient data meta-analysis was unlikely to affect current recommendations for use of aspirin in the first 2 weeks after stroke, because the study confirmed that this period is when the greatest benefit of aspirin occurs.

Impact statement
Studies consistently show benefit of aspirin after stroke, which supports the recommendation to use aspirin in people who have had a stroke unless they are allergic to or genuinely intolerant of aspirin.

New evidence is unlikely to change guideline recommendations.

Anticoagulants

3-year surveillance
A Cochrane review[176] assessed 24 trials (n=23,748) of anticoagulant therapy versus control in the early treatment (within 14 days) of acute ischaemic stroke. Anticoagulants included unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors. The authors concluded that immediate anticoagulant therapy was not associated with short or long-term benefit and the data do not support the routine use of any currently available anticoagulants in acute ischaemic stroke.

A second Cochrane review[177] compared low-molecular-weight heparins or heparinoids with unfractionated heparin in people with acute, confirmed or presumed, ischaemic stroke. It concluded that treatment with low-molecular-weight heparin or heparinoid after acute ischaemic stroke appears to decrease the occurrence of deep vein thrombosis compared with standard unfractionated heparin, but data are too few to provide reliable information on effects on other important outcomes, including death and intracranial haemorrhage.

A Cochrane review[178] assessed 11 trials (n=2,487) of anticoagulants compared with control in presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. Anticoagulants did not have a significant effect on recurrent stroke, death or dependency or non-fatal stroke, myocardial infarction or vascular death. However, major extracranial haemorrhage and fatal intracranial haemorrhage were significantly increased with anticoagulants.

An RCT[179] (n=75) investigated low-dose low molecular weight heparin compared with long compression stockings for prevention of deep venous thrombosis (DVT) after the first 48 hours in patients with intracerebral haemorrhage. Haematoma enlargement was not observed in either group. However, asymptomatic DVT was more common, but not significantly increased, with low molecular weight heparin.

6-year surveillance
A Cochrane review[180] of 8 RCTs (n=5,762) assessed anticoagulants in TIA or non-disabling ischaemic stroke of presumed arterial origin. Anticoagulants did not effectively prevent vascular events at any intensity (low, medium, or high). Low-intensity anticoagulants were not associated with increased bleeding risk, but medium and high intensities were associated with significantly higher risk of major bleeding complications.

8-year surveillance
An update[181] to a Cochrane review identified in 3-year surveillance[176] found no new studies. The authors' conclusions remained the same as in their previous review: data do not support routine use of anticoagulants in acute ischaemic stroke.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Studies of anticoagulants, particularly heparins, consistently show that they do not improve outcomes after stroke.

Evidence suggests that anticoagulants are associated with no benefit but substantial risks in presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. These findings support the recommendation to not use anticoagulation treatment routinely in acute stroke.

Heparins, and the heparinoid danaparoid, are not licensed in the UK for treatment of stroke.

New evidence is unlikely to change guideline recommendations.

Glycoprotein IIb-IIIa inhibitors

3-year surveillance
The AbESTT-II trial[182,183] assessed intravenous abciximab in acute ischaemic stroke. This trial did not demonstrate either safety or efficacy of intravenous abciximab in acute ischaemic stroke regardless of end point or population studied. The study was stopped early because of 'unfavourable risk-benefit profile'.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
A Cochrane review[184] assessed 4 RCTs (n=1,365) of glycoprotein IIb-IIIa inhibitors in acute ischaemic stroke. Abciximab was assessed in 3 trials, and tirofiban was assessed in 1 trial. Abciximab did not significantly reduce long-term death or dependency compared with placebo and tirofiban did not improve this outcome compared with aspirin. Abciximab was associated with increased rates of symptomatic intracranial haemorrhage but tirofiban showed no evidence of increased bleeding complications.

A post-hoc analysis[185] of an RCT (CLEAR-ER) assessed eptifibatide plus thrombolysis compared with thrombolysis alone in ischaemic stroke. The present analysis of severe stroke included 53 people who received eptifibatide plus thrombolysis and 209 people who received thrombolysis only. No significant differences were seen in 'excellent' or 'good' outcomes at 90 days or in 'a favourable shift'.

Another post-hoc analysis[186] from CLEAR-ER assessed outcomes of people who received eptifibatide plus thrombolysis compared with propensity-matched participants who received thrombolysis in 2 other RCTs (AAS part 2 and IMS-III). At 90 days, differences between groups on modified Rankin Score were not significant, but more people who received eptifibatide had 'excellent' outcomes.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Studies of several glycoprotein IIb-IIIa inhibitors consistently show no evidence of benefit in acute stroke. These antiplatelet agents are not covered in current guidance.

Abciximab, tirofiban and eptifibatide are not licensed in the UK for treatment of stroke.

New evidence is unlikely to change guideline recommendations.

Cilostazol

3-year surveillance
An RCT[187] (CAIST; n=458) comparing aspirin with cilostazol within 48 hours of acute ischaemic stroke found that cilostazol was non-inferior to aspirin 200 or 300 mg/day. However, adverse events were more common in cilostazol-treated patients.

A Cochrane review[188] assessed 2 RCTs of cilostazol (n=3,477) compared with aspirin for secondary prevention of vascular events after stroke. Cilostazol was associated with lower rates of vascular events and haemorrhagic stroke.

6-year surveillance
A systematic review and meta-analysis[189] of 4 RCTs (n=3,917) comparing off-label use of cilostazol with aspirin was identified. Cilostazol was associated with reduction in: haemorrhagic stroke; the composite end point of stroke, myocardial infarction, or vascular death; and in total haemorrhagic events. It was not clear from the abstract whether this study was in acute stroke care.

8-year surveillance
A subgroup analysis[190] from the ECLIPse trial assessed the effect of cilostazol compared with placebo in acute lacunar infarction based on the pulsatility index of transcranial Doppler. The ECLIPse trial included 203 people, 130 of whom had measurable cerebral white matter hyperintensity volume, and were included in the subanalysis. Cilostazol was associated with lower transcranial Doppler pulsatility index at 90 days, particularly in patients with white matter hyperintensity volumes less than 4.9 cm^3.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Studies suggest that cilostazol may be beneficial in secondary prevention of stroke, but the benefit in acute care has not been established. Cilostazol is not covered in current guidance.

Cilostazol is not licensed in the UK for treatment of stroke

New evidence is unlikely to change guideline recommendations.

Fibrinogen depleting agents

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance
A Cochrane review[191] assessed 8 RCTs (n=5,701) of fibrinogen-depleting agents started within 14 days of acute ischaemic stroke. Fibrinogen-depleting agents had a small but statistically significant reduction in death or disability at the end of follow-up. Symptomatic intracranial haemorrhage was about twice as common in the treatment group compared with the control group.

8-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Studies suggest that fibrinogen-depleting agents may have some benefit in acute stroke but this comes with increased risk of intracranial haemorrhage. Fibrinogen-depleting agents are not covered by current guidance and may not be safe in acute stroke.

New evidence is unlikely to change guideline recommendations.

68 – 13 What is the safety and efficacy of anticoagulants versus placebo or treatment as usual for the treatment of patients with acute venous stroke?

Recommendations derived from this question

1.4.2.5 People diagnosed with cerebral venous sinus thrombosis (including those with secondary cerebral haemorrhage) should be given full-dose anticoagulation treatment (initially full-dose heparin and then warfarin [INR 2–3]) unless there are comorbidities that preclude its use.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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68 – 14 What is the safety and efficacy of anticoagulants versus antiplatelet agents for the treatment of patients with acute arterial dissection?

Recommendations derived from this question

1.4.2.6 People with stroke secondary to acute arterial dissection should be treated with either anticoagulants or antiplatelet agents, preferably as part of a randomised controlled trial to compare the effects of the two treatments.

Surveillance decision

This review question should not be updated.

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
An RCT[192] (CADISS; n=250) assessed antiplatelet agents compared with anticoagulants in cervical artery dissection within 7 days of symptom onset in stroke or TIA. Treating clinicians chose the specific drug used within each class. Overall, stroke recurred in 2% of participants; the follow-up time was not clear in the abstract. There was no significant difference in stroke recurrence between groups.

Topic expert feedback
Topic experts highlighted the CADISS trial.

Impact statement
The study shows no evidence to guide the choice of anticoagulants or antiplatelets in people with arterial dissection.

New evidence is unlikely to change guideline recommendations.

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68 – 15 **What is the safety and efficacy of anticoagulants versus antiplatelet agents for the treatment of antiphospholipid syndrome in patients with acute ischaemic stroke?**

Recommendations derived from this question

1.1.2.7 People with antiphospholipid syndrome who have an acute ischaemic stroke should be managed in same way as people with acute ischaemic stroke without antiphospholipid syndrome*.

* There was insufficient evidence to support any recommendation on the safety and efficacy of anticoagulants versus antiplatelets for the treatment of people with acute ischaemic stroke associated with antiphospholipid syndrome.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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68 – 16 **For patients with acute warfarin associated haemorrhagic stroke, what is the safety and efficacy of i) vitamin K, ii) fresh frozen plasma, iii) prothrombin complex conjugate?**

Recommendations derived from this question

1.4.2.8 Clotting levels in people with a primary intracerebral haemorrhage who were receiving anticoagulation treatment before their stroke (and have elevated INR) should be returned to normal as soon as possible, by reversing the effects of the anticoagulation treatment using a combination of prothrombin complex concentrate and intravenous vitamin K.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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68 – 17 **What is the safety and efficacy of anticoagulants versus antiplatelet agents or placebo for patients with acute stroke who may require anticoagulation for comorbidities (e.g. atrial fibrillation, prosthetic heart valve (mitral/aortic), deep vein thrombosis or pulmonary embolism)?**

Subquestion

What is the safety and efficacy of caval filters for deep vein thrombosis or pulmonary embolism?

Recommendations derived from this question

1.4.3.1 People with disabling ischaemic stroke who are in atrial fibrillation should be treated with aspirin 300 mg for the first 2 weeks before considering anticoagulation treatment.

1.4.3.2 In people with prosthetic valves who have disabling cerebral infarction and who are at significant risk of haemorrhagic transformation, anticoagulation treatment should be stopped for 1 week and aspirin 300 mg substituted.

1.4.3.3 People with ischaemic stroke and symptomatic proximal deep vein thrombosis or pulmonary embolism should receive anticoagulation treatment in preference to treatment with aspirin unless there are other contraindications to anticoagulation.

1.4.3.4 People with haemorrhagic stroke and symptomatic deep vein thrombosis or pulmonary embolism should have treatment to prevent the development of further pulmonary emboli using either anticoagulation or a caval filter.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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68 – 18 For patients with acute stroke (including haemorrhagic stroke), what is the safety and efficacy of i) initiating statin therapy, ii) continuing statin therapy?

Subquestion

Do patients on statins, and who subsequently have a stroke, have reduced mortality and morbidity?

Recommendations derived from this question

1.4.4.1 Immediate initiation of statin treatment is not recommended in people with acute stroke*.

1.4.4.2 People with acute stroke who are already receiving statins should continue their statin treatment.

* The consensus of the GDG is that it would be safe to start statins after 48 hours.

Surveillance decision

This review question should not be updated.

3-year surveillance

A Cochrane review[193] of 8 RCTs concluded that data are insufficient to establish whether statins are safe and effective in acute ischaemic stroke and TIA.

A pilot RCT[194] (n=60) compared simvastatin with placebo in acute stroke. Simvastatin was associated with significant improvement neurological outcome by day 3, but was also associated with increased infection rates.

An RCT[195] (n=62) assessed atorvastatin compared with placebo in acute ischaemic stroke. NIH Stroke Scale was significantly worse in the atorvastatin group at 7 days.

6-year surveillance summary

No relevant evidence was identified.

8-year surveillance

A systematic review[196] of 70 articles (number of participants not reported in the abstract) assessed the effect of statins in acute ischaemic stroke. Statin use before stroke was associated with lower severity of stroke, increased likelihood of good functional outcome and lower mortality. In-hospital statin use was associated with good functional outcome and lower mortality. Stopping statin treatment after stroke was associated with poor function outcome. Using statins in people treated with thrombolysis was associated with good

functional outcome but an increased risk of symptomatic haemorrhage. The comparator group for analyses was not reported in the abstract.

A meta-analysis[197] of 5 studies (n=8,791) assessed the effect of statins on infections after stroke or TIA. No significant effects on infections were seen either overall or in sensitivity analyses.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Evidence on early use of statins shows both benefits and risks. Immediate initiation of statin treatment is not recommended in people with acute stroke. The new evidence does not show a clear need for a change in clinical practice.

New evidence is unlikely to change guideline recommendations.

Areas not covered in current guidance

In addition to the studies directly related to existing review questions, studies relevant to the topic 'Pharmacological treatments for people with acute stroke' were identified and evaluated as potential new questions.

These included: 2 studies of uric acid;[198,199] 2 studies of magnesium;[200,201] 3 studies of cerebrolysin;[202-204] 3 studies of antibacterial agents;[205-207] 8 studies of blood components and colony stimulating factors;[208-215] plus 20 studies on various other agents.[216-235] All these studies were thought not to have a substantial effect on the evidence base because of lack of evidence of efficacy.

A further 3 studies[236-238] on alternative therapies, and 15 studies on Chinese medicines,[239-253] were identified but were not thought to have a substantial effect on the evidence base because of lack of evidence of efficacy.

Maintenance or restoration of homeostasis

Preamble to the recommendations in this section of the guideline

A key element of care for people with acute stroke is the maintenance of cerebral blood flow and oxygenation to prevent further brain damage after stroke. This section contains recommendations on oxygen supplementation, maintenance of normoglycaemia, and acute blood pressure manipulation.

68 – 19 What is the safety and efficacy of supplemental oxygen therapy versus treatment as usual in patients with acute stroke?

Recommendations derived from this recommendation

1.5.1.1 People who have had a stroke should receive supplemental oxygen only if their oxygen saturation drops below 95%. The routine use of supplemental oxygen is not recommended in people with acute stroke who are not hypoxic.

Surveillance decision

This review question should not be updated.

3-year surveillance
A Cochrane review[254] of 6 RCTs (n=283) assessed whether hyperbaric oxygen therapy in acute ischaemic stroke improves clinical outcomes. The authors concluded that the evidence was insufficient to provide clear guidelines for practice; however, the possibility of clinical benefit could not be excluded.

A pilot RCT[255] (n=40) found that normobaric high-flow oxygen therapy for 12 hours in patients presenting with acute ischaemic stroke did not improve stroke outcome compared with control at 7 days or 3 months.

A pilot RCT[256] (n=289) reported that routine oxygen supplementation for 72 hours within 24hr of admission for acute stroke improved oxygen saturation during the intervention and neurological outcomes at 1 week. However, there was an imbalance in baseline stroke severity between the two groups.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
An additional report[257] from the pilot RCT identified in 3-year surveillance[256] (n=289) of routine oxygen supplementation assessed outcomes at 6 months. There was no significant difference in rates of death, disability (measured by modified Rankin Score), quality of life or activities of daily living with oxygen supplementation compared with room air control.

An update[258] to the Cochrane review (identified in 3-year surveillance[254] assessed 11 RCTs (n=705) of hyperbaric oxygen therapy compared with sham or no treatment in acute ischaemic stroke. Data could be pooled only for the outcome of case fatalities, which showed no differences between groups. Overall, the conclusions did not differ from the previous review: that evidence is insufficient to guide clinical practice, but benefits cannot be ruled out.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Studies show no clear evidence that routine oxygen supplementation has beneficial effects in acute stroke. This finding supports the recommendation not to use supplemental oxygen routinely in the absence of hypoxia.

New evidence is unlikely to change guideline recommendations.

68 – 20 What is the safety and efficacy of the interventions to control hyperglycaemia versus treatment as usual in patients with acute stroke?

Recommendations derived from this question

1.5.2.1 People with acute stroke should be treated to maintain a blood glucose concentration between 4 and 11 mmol/litre.

1.5.2.2 Provide optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, to all adults with type 1 diabetes with threatened or actual stroke. Critical care and emergency departments should have a protocol for such management.*

* This recommendation is from the NICE guideline on type 1 diabetes in adults.

Surveillance decision

This review question should not be updated.

3-year surveillance summary
A small RCT[259] (n=50) in non-diabetic patients with acute stroke assessed 24-hour intravenous insulin infusion adjusted to maintain plasma glucose levels of 4.5–7.0 mmol/L compared with subcutaneous insulin if plasma glucose level were greater than 10.0 mmol/L. Two patients from the intravenous insulin infusion group needed intravenous glucose infusion for symptomatic

hypoglycaemia. The findings indicated that in nondiabetic patients with mild hyperglycaemia, intravenous insulin therapy aimed at maintaining strict glycaemic control was relatively safe and may improve 30-day neurological outcome.

A small RCT[260] (n=49) investigated two basal bolus insulin regimens (intravenous or subcutaneous) compared with conventional glucose lowering therapy in people with ischaemic stroke. Strict glycaemic control between day 2 and day 5 with basal bolus insulin did lower postprandial glucose.

A small RCT[261] (n=46) compared aggressive intravenous insulin with usual care (subcutaneous insulin) in patients with cerebral infarction and hyperglycaemia. Intravenous insulin corrected hyperglycaemia during acute cerebral infarction significantly better than usual care but showed no significant difference in any other clinical outcome.

A small RCT[262] in patients with moderate hyperglycaemia assessed glucose potassium insulin infusion compared with placebo within 24 hours of ischaemic stroke. Although glucose potassium insulin infusion lowered blood glucose and attenuated an increase in brain lactate, it did not affect cerebral infarct growth.

An RCT[263] (n=40) assessed insulin infusion aiming for blood glucose of 4.44–6.11 mmol/l compared with subcutaneous insulin given if blood glucose was above 11 mmol/l. Intensive insulin treatment was associated with a greater risk of hypoglycaemia, but severe hyperglycaemia was less common than in the subcutaneous 'as-needed' group.

6-year surveillance summary
A Cochrane review[264] of 7 RCTs (n=1,296) assessed intensively monitored insulin treatment compared with control in the first 24 hours of acute ischaemic stroke. There was no difference in the outcome 'death or disability and dependence' or in final neurological deficit. Symptomatic hypoglycaemia was higher in the treatment group.

8-year surveillance summary
A systematic review and meta-analysis[265] of 9 RCTs (n=1,491) assessed intravenous insulin compared with control for treating hyperglycaemia in people with acute stroke. No significant differences were seen for mortality or functional outcome. People in the insulin group had higher hypoglycaemia and symptomatic hypoglycaemia.

An update[266] of the Cochrane review identified in 6-year surveillance[264] assessed 11 RCTs (n=1,583) of intensively monitored insulin treatment. The findings remained the same as in the previous review. There was no difference in the outcome 'death or disability and dependence' or in final neurological deficit. Symptomatic hypoglycaemia was higher in the treatment group.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Current recommendations to maintain blood sugar levels of 4–11 mmol/litre mean that hypoglycaemia (blood sugar less than 4 mmol/litre) would be treated; however the range allows for a level of hyperglycaemia (7–11 mmol/litre) to exist before treatment is necessary. Studies show no clear evidence that intensive control of glycaemia to maintain normal blood sugar (generally 4–7 mmol/litre) has beneficial effects in acute stroke.

New evidence is unlikely to change guideline recommendations.

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68 – 21 What is the safety and efficacy of measures to manipulate blood pressure versus treatment as usual in patients with acute stroke?

Recommendations derived from this question

1.5.3.1 Anti-hypertensive treatment in people with acute stroke is recommended only if there is a hypertensive emergency with one or more of the following serious concomitant medical issues:

- hypertensive encephalopathy
- hypertensive nephropathy
- hypertensive cardiac failure/myocardial infarction
- aortic dissection
- pre-eclampsia/eclampsia
- intracerebral haemorrhage with systolic blood pressure over 200 mmHg.

1.5.3.2 Blood pressure reduction to 185/110 mmHg or lower should be considered in people who are candidates for thrombolysis.

Surveillance decision

This review question should be updated.

3-year surveillance summary

Mixed ischaemic and haemorrhagic stroke populations

An RCT[267] (CHHIPS; n=180) in people with hypertension and stroke onset of less than 36 hours indicated that oral and sublingual lisinopril and oral and intravenous labetalol lowered blood pressure but did not affect neurological outcomes (death or dependency). This study was noted to be underpowered to detect an effect at 2 weeks. An accompanying economic evaluation[268] from the acute hospital perspective indicated that antihypertensive therapy, when indicated immediately post stroke, may be cost effective compared with placebo based on 3 month outcomes of continuing therapy.

An RCT[269] (COSSACS; n=763) assessed the efficacy and safety of continuing or stopping antihypertensive drugs in patients who had recently had a stroke. No substantial differences were observed between groups in rates of serious adverse events, 6-month mortality, or major cardiovascular events.

Two Cochrane reviews were identified[270,271] including 12 studies (n=1,153) and 43 studies (n=7,649) respectively. The reviews concluded that evidence is insufficient to evaluate the effect of altering blood pressure on outcomes during the acute phase of stroke. The following agents lowered blood pressure:

- angiotensin converting enzyme inhibitors,
- angiotensin receptor antagonists,
- calcium channel blockers,
- clonidine,
- glyceryl trinitrate,
- thiazide diuretics,
- mixed antihypertensive therapy,
- beta receptor antagonists,
- nitric oxide
- prostacyclin.

Phenylephrine and diaspirin cross-linked haemoglobin increased blood pressure.

Ischaemic stroke

A further systematic review[272] included 11 controlled trials that administered antihypertensive agents within 7 days of ischaemic stroke and measured cerebral blood flow or cerebral blood flow velocity. It showed that little evidence exists to suggest that these agents reduce cerebral blood flow despite their blood pressure lowering effects. The number of participants in analyses was not reported in the abstract.

An RCT[273] (n=40) indicated that low doses of candesartan or perindopril reduced blood pressure but had no effect on neurological outcomes in hypertensive patients with acute ischaemic stroke.

An RCT[274] (n=40) found that lisinopril lowered blood pressure compared with placebo in hypertensive patients with acute ischaemic stroke; however, neurological and functional measures were similar between groups at follow-up.

Haemorrhagic stroke

An RCT[275,276] (INTERACT; n=404) in hypertensive patients with acute spontaneous intracranial haemorrhage indicated that early intensive blood pressure lowering treatment did not alter the risks of adverse events or

secondary clinical outcomes at 90 days but reduced haematoma growth over 72 hours.

An RCT[277] (n=42) investigated reducing blood pressure to lower than presently recommended levels in patients with acute intracerebral haemorrhage. No significant differences were seen between standard and aggressive blood pressure treatment for the outcomes of early neurological deterioration, haematoma and oedema growth, and clinical outcome at 90 days.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance

Mixed ischaemic and haemorrhagic stroke populations

A post-hoc analysis[278] of 2 RCTs, (PRACTISE and PASS) included all patients (n=224) with blood pressure above 185/110 mm Hg at presentation but otherwise eligible for IV thrombolysis. Active or conservative blood pressure treatment was based on local hospital guidelines. Active blood pressure lowering was used in 66 of patients (29%) and 158 people (71%) had conservative treatment. Active blood pressure lowering was associated with an increase in use of thrombolysis of 28% (95% CI 16 to 40%). Symptomatic intracranial haemorrhage occurred in 7% of people who had thrombolysis, with no difference between blood pressure treatment groups.

An RCT[279] (SCAST, n=2,029) assessed candesartan versus placebo in people with acute ischaemic or haemorrhagic stroke and systolic blood pressure of 140 mm Hg or higher. Participants were recruited within 30 hours of stroke onset and received candesartan for 7 days. Blood pressures were significantly lower in the candesartan group after 7 days compared with placebo. At 6 months there was no difference between groups in the composite vascular endpoint (vascular death, myocardial infarction, or stroke). In both groups, about 1% of participants developed hypotension during follow-up, and renal failure occurred in 2% of people taking candesartan and 1% of people on placebo. Further analyses from SCAST reported the following results:

- vascular events did not differ with later, gradual blood-pressure lowering with candesartan in 274 people with haemorrhagic stroke compared with placebo, but candesartan was associated with worse functional outcome.[280]
- effects were significantly better in larger infarcts than in smaller infarcts.[281]
- no significant effects were seen on the composite primary outcome of stroke, myocardial infarction, or vascular death or in any secondary outcome in long-term follow-up for 3 years.[282]
- no significant effects on activities of daily living were seen in (Barthel Index or level of care).[283]
- no significant difference was seen in this sub-population for the composite endpoint of stroke, myocardial infarction or vascular death or for functional outcome in 87 people in the candesartan group and 100 people in the control group who had moderate or severe carotid artery stenosis.[284]

An RCT[285] (ENOS; n=4,011) assessed nitric oxide (transdermal glyceryl trinitrate) compared with no nitric oxide in people with acute ischaemic or haemorrhagic stroke. A second randomisation assessed the effects of participants continuing or stopping pre-existing antihypertensive treatment. Blood pressure was significantly lower after 1 day in the nitric oxide group, and on day 7 for 1,053 people who continued pre-existing antihypertensive treatment compared with 1,044 people who stopped. Functional outcome did not differ significantly between people who did or did not have nitric oxide or between those who did or did not stop pre-existing antihypertensive treatment.

An RCT[286] (n=393) assessed 7 days of valsartan treatment compared with no treatment in acute ischaemic stroke. There was no significant difference in death or dependency or major vascular events between groups. People receiving valsartan had significantly greater risk of early neurological deterioration.

A Cochrane review[287] of 26 trials (n=17,011) assessed blood pressure manipulation with various drug classes compared with control in acute stroke. Most antihypertensive drugs reduced blood pressure by small, statistically non-significant amounts in the first 24 hours. There were no differences in death or dependency by drug class, type of stroke, or time to treatment. However treatment within 6 hours of stroke was associated with

reductions in death and dependency but not death alone. Analysis of stopping or continuing existing antihypertensive treatment after stroke suggested an increase in disability with continued treatment.

A meta-analysis[288] of 17 trials (n=13,236) assessed early blood-pressure lowering compared with placebo on early and long-term outcomes after acute stroke. Early blood-pressure lowering was associated with increased rates of death within 30 days. No significant differences were seen for early neurological deterioration, death within 7 days or early or long-term dependency.

Ischaemic stroke

A subgroup analysis[289] of the IST-3 trial (n=3,035) assessed the effects of blood pressure lowering during the first 24 hours in people with acute ischaemic stroke. The IST-3 trial investigated recombinant tissue-type plasminogen activator within 6 hours of stroke onset compared with open control. High baseline blood pressure and high blood pressure variability in the first 24 hours were associated with more early adverse events and early deaths (several analyses were statistically significant). Larger reductions in blood pressure and the use of blood pressure-lowering treatment in the first 24 hours were associated with reduced risk of poor outcome at 6 months irrespective of whether recombinant tissue-type plasminogen activator was used.

An RCT[290] (CATIS; n=2,038) assessed antihypertensive treatment compared with no antihypertensive treatment in acute ischaemic stroke. Blood pressure reduced in both groups in the first 24 hours, but the group on antihypertensive treatment had significantly greater reductions than the control group. The primary outcome of death and major disability at 14 days (or hospital discharge) did not differ between groups.

A meta-analysis[291] of 13 RCTs (n=12,703) assessed early blood pressure lowering in ischaemic stroke compared with control. No significant differences were observed in the risk of death or dependency at 3 months or trial end. No effects on recurrent vascular events or serious adverse events were seen.

A meta-analysis[292] of 22 studies (n=11,088) assessed early blood-pressure lowering in acute ischaemic stroke compared with placebo. Blood-pressure was significantly lower in people who received antihypertensive treatment compared with placebo but no differences were seen for short term or long term dependency or mortality.

Haemorrhagic stroke

An RCT[293] (INTERACT2; n=2,839) assessed rapid blood pressure lowering compared with standard blood-pressure lowering in people with intracerebral haemorrhage in the previous 6 hours. Death or disability at 90 days did not differ significantly between groups; however, Rankin scores were lower in the rapid treatment group.

An RCT[294] (ATACH-2; n=1000) assessed intensive blood pressure lowering compared with standard blood pressure lowering in people with haemorrhagic stroke. Intravenous nicardipine was used in both groups, and administered within 4.5 hours of stroke. Death or disability at 3 months did not differ significantly between groups. The study was stopped early because of futility after interim analysis. However, significantly more people in the intensive treatment group had renal adverse events.

Topic expert feedback

Topic experts highlighted several trials of antihypertensive treatment (CHIPPS, COSSACS, SCAST, ENOS, INTERACT2, and ATACH-2). Topic experts also indicated a need to assess blood pressure lowering in acute haemorrhagic stroke.

Topic experts indicated that although studies showed an absence of efficacy of blood pressure lowering, these studies may show an absence of harm associated with early blood pressure lowering.

Impact statement

Studies consistently suggest that early blood-pressure lowering is not beneficial in acute haemorrhagic or ischaemic stroke. Current guidance recommends early antihypertensive treatment only if the person has a hypertensive emergency. No new evidence was found relating to hypertensive emergencies.

A review of this area is necessary to establish whether early blood pressure treatment in haemorrhagic stroke is associated with an absence of harm.

New evidence identified that may change current recommendations.

Nutrition and hydration

Preamble to the recommendations in this section of the guideline

Many people with acute stroke are unable to swallow safely, and may require supplemental hydration and nutrition. This section provides recommendations on assessment of swallowing, hydration and nutrition.

68 – 22 In patients with acute stroke a) what is the accuracy of i) bedside swallowing assessment, ii) videofluoroscopy, iii) fibreoptic endoscopic evaluation of swallowing, and b) how do the results of these assessments affect clinical outcomes?

Recommendations derived from this question

1.6.1.1 On admission, people with acute stroke should have their swallowing screened by an appropriately trained healthcare professional before being given any oral food, fluid or medication.

1.6.1.2 If the admission screen indicates problems with swallowing, the person should have a specialist assessment of swallowing, preferably within 24 hours of admission and not more than 72 hours afterwards.

1.6.1.3 People with suspected aspiration on specialist assessment, or who require tube feeding or dietary modification for 3 days, should be:

- re-assessed and considered for instrumental examination
- referred for dietary advice.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

68 – 23 In patients with acute stroke who are unable to take adequate fluids orally, does a) early versus late initiation of tube feeding, or b) nasogastric (NG) studies (including nasal bridles) versus percutaneous endoscopically guided gastrostomy (PEG) (including radiologically inserted gastronomy tubes (RIGs)) reduce mortality and morbidity?

Recommendations derived from this question

1.6.1.4 People with acute stroke who are unable to take adequate nutrition and fluids orally should:

- receive tube feeding with a nasogastric tube within 24 hours of admission
- be considered for a nasal bridle tube or gastrostomy if they are unable to tolerate a nasogastric tube
- be referred to an appropriately trained healthcare professional for detailed nutritional assessment, individualised advice and monitoring.

Surveillance decision

This review question should not be updated.

3-year surveillance
An RCT[295] (n=104) evaluated looped compared with conventional nasogastric tubes for feeding in acute stroke patients with dysphagia. It concluded that looped nasogastric tube feeding improved delivery of feed and fluids and reduced nasogastric tube reinsertion with little additional cost.

A systematic review[296] of 8 studies indicated that the odds of being malnourished were increased in people with dysphagia after stroke. The number of participants included in analyses was not reported in the abstract.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
A Cochrane review[297] of 33 studies (n=6,779) evaluated interventions for dysphagia and nutritional and fluid supplementation in acute and subacute stroke. The abstract did not report results separately for acute and subacute stroke.

For dysphagia:

- Case fatality or combined death and dependency in people with dysphagia were not reduced by
  - acupuncture,
  - drug therapy,
  - neuromuscular
  - electrical stimulation,
  - pharyngeal electrical stimulation,
  - physical stimulation (thermal, tactile),
  - transcranial direct current stimulation,
  - transcranial magnetic stimulation.
- Dysphagia was significantly reduced after behavioural interventions and acupuncture.

For route of feeding:

- Case fatality and death and dependency did not differ significantly between percutaneous endoscopic gastrostomy (PEG) and nasogastric tube, although PEG feeding was associated with fewer treatment failures, lower gastrointestinal bleeding, higher feed delivery and higher albumin concentration.
- Looped nasogastric tube feeding was associated with higher feed delivery compared with conventional nasogastric tube feeding, but there were no differences in case fatality or death and dependency.

For timing of feeding:

- Early versus late feeding did not affect case fatality or death or dependency.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Evidence is generally consistent with current recommendations, which recommend interventions including nasogastric feeding and gastrostomy.

New evidence suggests that looped nasogastric feeding is less likely to fail than conventional feeding. NICE CG68 recommends nasal bridle as a method for securing the nasogastric tube.

No new evidence comparing nasogastric bridles with looped nasogastric tubes was identified. Evidence does not suggest that new recommendations in this area are urgently needed.

New evidence is unlikely to change guideline recommendations.

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68 – 24 In patients with acute stroke who can take adequate fluids orally, does oral nutritional supplementation reduce mortality and morbidity?

Recommendations derived from this recommendation

1.6.2.1 All hospital inpatients on admission should be screened for malnutrition and the risk of malnutrition. Screening should be repeated weekly for inpatients*.

1.6.2.2 Screening should assess body mass index (BMI) and percentage unintentional weight loss and should also consider the time over which nutrient intake has been unintentionally reduced and/or the likelihood of future impaired nutrient intake. The Malnutrition Universal Screening Tool (MUST), for example, may be used to do this*.

1.6.2.3 When screening for malnutrition and the risk of malnutrition, healthcare professionals should be aware that dysphagia, poor oral health and reduced ability to self-feed will affect nutrition in people with stroke.

1.6.2.4 Screening for malnutrition and the risk of malnutrition should be carried out by healthcare professionals with appropriate skills and training*.

1.6.2.5 Routine nutritional supplementation is not recommended for people with acute stroke who are adequately nourished on admission.

1.6.2.6 Nutrition support should be initiated for people with stroke who are at risk of malnutrition. This may include oral nutritional supplements, specialist dietary advice and/or tube feeding.

*This recommendation is adapted from 'Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition' (NICE clinical guideline 32).

Surveillance decision

This review question should not be updated.

Nutritional support

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
A Cochrane review[297] of 33 studies (n=6,779) assessed interventions for dysphagia and nutritional and fluid supplementation in acute and subacute stroke. The abstract did not report results separately for acute and subacute stroke. Nutritional supplementation did not affect case fatality or death and dependency, but was associated with reductions in pressure sores, increased energy intake, and increased protein intake. The comparator was not specified in the abstract.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Evidence suggests that nutritional support may not affect stroke outcomes, but successfully affects nutritional status, which is consistent with current recommendations.

New evidence is unlikely to change guideline recommendations.

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68 – 25 In patients with acute stroke, does fluid therapy reduce mortality and morbidity?

Recommendations derived from this question

1.6.2.7 All people with acute stroke should have their hydration assessed on admission, reviewed regularly and managed so that normal hydration is maintained.

Surveillance decision

This review question should not be updated.

Fluid therapy

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
A Cochrane review[297] of 33 studies (n=6,779) assessed interventions for dysphagia and nutritional and fluid supplementation in acute and subacute stroke. The abstract did not report results separately for acute and subacute stroke. Fluid therapy did not affect case fatality or death and dependency. The comparator was not specified in the abstract.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Evidence suggests that fluid therapy has no beneficial effects on stroke outcomes. The new evidence has no bearing on the need to maintain normal hydration in people with acute stroke.

New evidence is unlikely to change guideline recommendations.

Early mobilisation and optimum positioning of people with acute stroke

Preamble to the recommendations in this section of the guideline

Early mobilisation is considered a key element of acute stroke care. Sitting up will help to maintain oxygen saturation and reduce the likelihood of hypostatic pneumonia.

68 – 26 Does early mobilisation versus treatment as usual reduce mortality and morbidity in patients with acute stroke?

Subquestion

Does placing patients with acute stroke in specific positions reduce mortality and morbidity?

Recommendations derived from this question

1.7.1.1 People with acute stroke should be mobilised as soon as possible (when their clinical condition permits) as part of an active management programme in a specialist stroke unit.

1.7.1.2 People with acute stroke should be helped to sit up as soon as possible (when their clinical condition permits).

Surveillance decision

This review question should not be updated.

Early mobilisation

3-year surveillance

An RCT[298] (n=223) evaluated a "turn-mob" program: turning and passive mobilisation carried out by a previously trained relative compared with standard treatment. The turn-mob program applied on patients during the acute phase of an ischaemic stroke decreased the incidence of nosocomial pneumonia.

A Cochrane review[299] assessed very early mobilisation (commenced within 48 hours of stroke) compared with conventional care. The review found insufficient evidence (1 RCT: the AVERT trial) to support or refute the efficacy of routine very early mobilisation after stroke, compared with conventional care.

Six reports from the phase II AVERT trial[300-305] (n=71) indicated that very early mobilisation (within 24 hours of stroke):

- was safe and feasible[300]
- promoted recovery and reduced complications[303]
- improved quality of life at 12 months[304]
- was cost effective[305]
- reduced depressive symptoms in stroke patients at 7 days post-stroke[301]
- and improved functional recovery.[302]

In addition, a pooled analysis[306] of data from the AVERT trial and the Very Early Rehabilitation or Intensive Telemetry after Stroke trial indicated that very early mobilisation improved independence at 3 months compared with standard care.

6-year surveillance summary

No relevant evidence was identified.

8-year surveillance

A report[307] from the phase III AVERT trial (n=2104) assessed very early mobilisation (within 24 hours) after ischaemic or haemorrhagic stroke. In the very early mobilisation group, 965 (92%) patients were mobilised within 24 hours compared with 623 (59%) patients in the usual care group. Fewer patients in the very early mobilisation group had a favourable outcome than those in the usual care group. Deaths did not differ significantly. A dose-response analysis[308] from this study suggested that when time to first mobilisation and duration of mobilisation were constant, increased frequency of out-of-bed sessions was associated with improved odds of favourable outcome. Increasing duration of mobilisation was associated with reduced odds of favourable outcome.

A systematic review[309] of 5 RCTs (n=159) and 38 cohort studies assessed timing of physical rehabilitation after stroke. Physical rehabilitation starting within 24 hours of stroke was associated with a possible increase in risk of mortality. The analysis was not significant and the confidence intervals were very wide but the direction of effect was in the direction of harm. The cohort studies suggested that earlier rather than later transfer to rehabilitation was associated with better functional outcomes, but there was no consensus about timeframes.

Additional studies

A further 3 studies[310-312] relevant to this question were identified but were not thought to have a substantial effect on the evidence base.

Topic expert feedback

Topic experts highlighted the AVERT trials.

Impact statement

Studies suggest that early mobilisation is effective, which is consistent with current recommendations. However, the differentiation between early mobilisation and early rehabilitation was not clear in all abstracts reviewed.

Evidence for very early mobilisation from the phase II and phase III AVERT trials is inconsistent, with effects seen in the phase II trial not replicated in the phase III trial.

In the AVERT phase III trial, a large proportion of people (59%) in the usual care group were mobilised in the first 24 hours, suggesting that early mobilisation guided by the person's clinical condition may be more successful than very early mobilisation according to a protocol.

Current guidance recommends mobilising people with acute stroke as soon as possible (when their clinical condition permits) as part of

an active management programme in a specialist stroke unit.	New evidence is unlikely to change guideline recommendations.

Avoidance of aspiration pneumonia

Preamble to the recommendations in this section of the guideline

Aspiration pneumonia is a complication of stroke that is associated with increased mortality and poor outcomes.

68 – 27 Does withdrawal or modification of oral intake prevent aspiration pneumonia after stroke?

Recommendations derived from this question

1.8.1.1 In people with dysphagia, food and fluids should be given in a form that can be swallowed without aspiration, following specialist assessment of swallowing.

Surveillance decision

This review question should not be updated.

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary
An RCT[313] (n=60) assessed metoclopramide within 7 days of stroke and within 48 hours of inserting a nasogastric tube in people with no signs of pneumonia. Participants received metoclopramide or placebo via the nasogastric tube for 21 days or until nasogastric feeding was stopped. Pneumonia was significantly less frequent in the metoclopramide group. The authors noted 'these findings need to be confirmed in larger randomised and blinded trials.'

A pilot RCT[314] (n=82) assessed the effects of 4 weeks of respiratory muscle training or sham, started within 2 weeks of stroke, on aspiration pneumonia. Respiratory muscle training was associated with improvements in physiological measures of maximum inspiratory and expiratory mouth pressure, and peak expiratory cough flow. However, capsaicin-induced cough flow and rates of pneumonia did not differ between groups.

A meta-analysis[315] of observational studies suggested that the top 5 risk factors for lung infection in people with stroke are: multiple vertebrobasillar stroke; NIH Stroke Scale score of greater than 15; mechanical ventilation; nasogastric tube; and dysphagia.

An open-label cluster RCT[316] (STROKE-INF; n=1,224) in the UK assessed prophylactic antibiotics for reducing pneumonia compared with standard care in people with acute stroke and dysphagia. Prophylactic antibiotics did not affect the incidence of algorithm-defined, or physician-defined, post-stroke pneumonia. Other infections (mainly urinary tract infections) were significantly less common in the group that had prophylactic antibiotics. Hospital-acquired infections were infrequent and did not differ notably between the groups.

Topic expert feedback
Topic experts highlighted the STROKE-INF trial.

Impact statement
New evidence noting dysphagia as a risk factor for lung infection after stroke is consistent with current recommendations. New evidence for interventions (respiratory muscle training and

prophylactic antibiotics) does not show clear clinical benefit.

A small study suggested that metoclopramide may reduce incidence of pneumonia in people who have a nasogastric tube. Current guidance has no recommendations about drug treatments for prophylaxis of aspiration pneumonia. The study's authors noted that confirmatory trials are needed. Metoclopramide is not licensed in the UK for use in stroke.

New evidence is unlikely to change guideline recommendations.

Surgery for people with acute stroke

Preamble to the recommendations in this section of the guideline

There is evidence that neurosurgical treatment may be indicated for a very small number of carefully selected people with stroke. This section contains recommendations for surgical intervention in people with intracerebral haemorrhage or severe middle cerebral artery infarction.

68 – 28 Which patients with primary intracerebral haemorrhage should be referred for surgery?

Recommendations derived from this question

1.9.1.1 Stroke services should agree protocols for the monitoring, referral and transfer of people to regional neurosurgical centres for the management of symptomatic hydrocephalus.

1.9.1.2 People with intracranial haemorrhage should be monitored by specialists in neurosurgical or stroke care for deterioration in function and referred immediately for brain imaging when necessary.

1.9.1.3 Previously fit people should be considered for surgical intervention following primary intracranial haemorrhage if they have hydrocephalus.

1.9.1.4 People with any of the following rarely require surgical intervention and should receive medical treatment initially:

- small deep haemorrhages
- lobar haemorrhage without either hydrocephalus or rapid neurological deterioration
- a large haemorrhage and significant comorbidities before the stroke
- a score on the Glasgow Coma Scale of below 8 unless this is because of hydrocephalus
- posterior fossa haemorrhage.

Surveillance decision

This review question should not be updated.

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
A Cochrane review[317] of 10 trials (n=2,059) assessed RCTs or surgery compared with medical treatment for supratentorial intracerebral haematoma. Surgery was associated with a significant reduction in death or dependency. However the authors concluded that 'the result is not very robust' because trial quality was acceptable but not high, and the largest trial was sensitive to losses in follow-up.

An individual patient data meta-analysis[318] of data from 8 studies (n=2,186) of surgery in spontaneous supratentorial intracerebral

haemorrhage. Surgery was associated with improved outcome if randomisation took place within 8 hours of stroke, the volume of haematoma was low (20–50 ml), Glasgow Coma Scale was 9–12 and if the patient was aged 50–69 years.

An RCT[319] (STICH II; n=601) assessed early surgery versus initial conservative treatment in people with superficial lobar intracerebral haemorrhage admitted within 48 hours of stroke. No significant difference was seen between groups for unfavourable outcome on Extended Glasgow Outcome Scale at 6 months.

8-year surveillance summary
No relevant evidence was identified.

Additional studies
A further study[320] relevant to this question was identified but was not thought to have a substantial effect on the evidence base.

Topic expert feedback
Topic experts highlighted the STICH II trial.

Impact statement
Evidence from the STICH II trial is consistent with current recommendations for initial medical management for superficial lobar intracerebral haemorrhage. There are no clear and validated criteria for early selection of patients who would benefit from surgery after intracerebral haemorrhage.

New evidence is unlikely to change guideline recommendations.

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68 – 29 Which patients should be referred for decompressive hemicraniectomy?

Recommendations derived from this question

1.9.2.1 People with middle cerebral artery infarction who meet all of the criteria below should be considered for decompressive hemicraniectomy. They should be referred within 24 hours of onset of symptoms and treated within a maximum of 48 hours.

- Aged 60 years or under.
- Clinical deficits suggestive of infarction in the territory of the middle cerebral artery, with a score on the National Institutes of Health Stroke Scale (NIHSS) of above 15.
- Decrease in the level of consciousness to give a score of 1 or more on item 1a of the NIHSS.
- Signs on CT of an infarct of at least 50% of the middle cerebral artery territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume greater than 145 cm^3 as shown on diffusion-weighted MRI.

1.9.2.2 People who are referred for decompressive hemicraniectomy should be monitored by appropriately trained professionals skilled in neurological assessment.

Surveillance decision

This review question should be updated.

3-year surveillance
Two RCTs[321,322] showed that decompressive surgery reduced mortality for patients with either space-occupying hemispheric infarction treated within 48hr of stroke onset[321] (n=64) or massive cerebral infarction (n=32).[322] This operation did not improve functional outcome if delayed for up to 96 hours after stroke onset in patients with space-occupying hemispheric infarction.

6-year surveillance
A Cochrane review[323] of 3 RCTs (n=134) assessed decompressive surgery plus medical treatment compared with medical treatment alone for acute ischaemic stroke. Surgery was performed within 30 hours in 2 studies and within 96 hours in 1 study. Surgical decompression reduced the risk of death and risk of death and disability at 12 months.

8-year surveillance
A systematic review and meta-analysis[324] of 14 studies including 8 RCTs (n=747) assessed decompressive craniectomy for malignant middle cerebral artery infarction. Decompressive craniectomy within 48 hours of stroke was associated with lower mortality and fewer people had poor functional outcome at 12 months. Decompressive craniectomy later than 48 hours after stroke may not be effective. The comparator group for analyses was not reported in the abstract.

An RCT[325] (n=112) assessed hemicraniotomy compared with conservative treatment in people aged 61 years and older with malignant middle cerebral artery infarction. A greater proportion of people who had hemicraniotomy survived without severe disability.

A meta-analysis[326] (number of studies and participants not reported in the abstract) assessed decompressive hemicraniectomy compared with medical management in people with malignant oedema after middle cerebral artery infarct. Death was significantly less common in the surgical group compared with medical management; however, survivors may be more likely to have poor functional outcome.

Topic expert feedback
Topic experts indicated the need to assess the role of hemicraniectomy in people older than 60 years. New evidence was identified for use of this intervention in people aged 61 years and over. However, outcomes for survivors remain very poor.

Impact statement
Evidence is generally consistent with current recommendations, particularly in the timescale for effective treatment in malignant middle cerebral artery infarction.

New evidence suggests that hemicraniectomy in people older than 60 years may reduce mortality but outcomes for survivors remain very poor. Review of this area is necessary to establish the role of hemicraniectomy in people older than 60 years.

New evidence identified that may change current recommendations.

Areas not currently covered in the guideline

NQ – 02 What is the effectiveness of non-pharmacological treatments for stroke?

Surveillance decision

This review question should not be added.

Thrombectomy

Several studies on thrombectomy were identified and are covered in the section Pharmacological treatments for people with acute stroke above. Because of the close relationship, and often overlap, between thrombolysis and thrombectomy these treatments were discussed together although the guideline currently does not cover non-pharmacological treatments.

Head position

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance summary
A systematic review and meta-analysis[327] of 4 studies (n=57) assessed the effect of sitting-up compared with lying flat head position on mean cerebral blood flow velocity in people with acute ischaemic stroke. Mean flow velocity was significantly greater in lying flat positions of 0° or 15°, compared with 30°.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Although this study provides evidence of effects of head position on physiological measures, it is a small study and clinical outcomes are not established. The clinical significance of these findings is being assessed in the HeadPoST trial.

Current recommendations do not cover head positioning in acute stroke. This topic will be evaluated again at the next surveillance review.

New evidence is unlikely to impact on the guideline.

Induced hypothermia

3-year surveillance
A Cochrane review[328] assessed the effects of strategies to reduce body or brain temperature in patients with acute stroke. It found no evidence from RCTs to support routine use of physical or pharmacological strategies to reduce temperature in patients with acute stroke.

An RCT[329] of high-dose paracetamol for reducing body temperature and preventing fever within 12 hours of symptom onset in patients with acute stroke found no significant improvement in outcome.

An RCT[330] (n=44) assessed hypothermia compared with normal temperature in acute ischaemia stroke. All participants had thrombolysis. No significant differences were seen between groups for function, death. However, pneumonia was significantly more common in the hypothermia group.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance
A pilot RCT[331] (n=20) compared cold infusions with nasopharyngeal cooling in people with stroke who were intubated and had an indication for an intracranial pressure or temperature brain probe. Cold infusion was associated with quicker cooling than nasopharyngeal cooling, but once the infusion ceased, brain temperature rose quickly. Cold infusion was associated with 3 severe adverse events (2 affecting systolic arterial pressure and 1 case of shivering). Nasopharyngeal cooling was associated with 4 severe adverse events (2 affecting systolic arterial pressure and 1 affecting intracranial pressure) and 2 cases of ventilation failure.

A systematic review and meta-analysis[332] assessed 6 RCTs (n=212) of therapeutic hypothermia in acute ischaemic stroke. Therapeutic hypothermia was not associated with differences in neurological outcomes or mortality compared with control. Pneumonia was significantly higher in the hypothermia group.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The studies consistently suggest no evidence of benefit of inducing hypothermia in people with stroke. Current recommendations do not cover inducing hypothermia in acute stroke.

New evidence is unlikely to impact on the guideline.

Electronic decision support

3-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

8-year surveillance

A cluster RCT[333] (29 clinics; n=291) assessed an electronic decision support tool to guide management of TIA or stroke compared with usual care. The decision support tool was associated with higher rates of guideline-adherent care, lower 90-day TIA or stroke recurrence and lower rates of vascular events or deaths.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

This study shows that an electronic decision support tool may increase adherence to guidance and improve outcomes after stroke. NICE has developed tools to help put the guidance into practice.

New evidence is unlikely to impact on the guideline.

Additional studies

A further 13 studies[334-346] on various non-drug interventions for people with acute stroke were identified but were thought not to have a substantial effect on the evidence base.

NQ – 03 What is the effectiveness of interventions to reduce risk of venous thromboembolism (VTE)?

Surveillance decision

This review question should not be added.

Compression stockings

3-year surveillance

Compression stockings

A large RCT[347] (CLOTS) was identified that assessed the effectiveness of thigh-length graduated compression stockings compared with normal care to reduce deep-vein thrombosis (DVT) after stroke in patients who were immobile. The risk of DVT was not reduced but the occurrence of skin breaks, ulcers, blisters, and skin necrosis were increased in the intervention group. The data did not support the use of thigh-length graduated compression stockings in patients admitted to hospital with acute stroke.

6-year surveillance summary

No relevant evidence was identified.

8-year surveillance

Compression stockings

An RCT[348] (CLOTS-2; n=3,114) assessed the effectiveness of thigh-length compression stockings compared with below-knee compression stockings to prevent DVT after stroke. Thigh-length stockings were associated with significantly fewer DVTs of the popliteal or femoral veins.

Pneumatic compression

A UK-based RCT[349] (CLOTS-3; n=2,876) assessed intermittent pneumatic compression versus no intermittent pneumatic compression in people with acute stroke who were immobile. Intermittent pneumatic compression significantly reduced DVT in the proximal veins detected on a screening compression duplex ultrasound or any symptomatic DVT in the proximal veins, confirmed on imaging, within 30 days. Significantly more people in the intervention group had skin breaks, but there was no difference in falls or deaths.

Topic expert feedback

Topic experts indicated a need to assess intermittent pneumatic compression after stroke.

Impact statement
Compression stockings do not show consistent benefit in preventing DVT after stroke. Intermittent pneumatic compression may reduce DVT after stroke.

Venous thromboembolism: reducing the risk for patients in hospital (NICE CG92) recommends against use of compression stockings after stroke.

An addendum to NICE CG92 recommends considering intermittent pneumatic compression for VTE prophylaxis in immobile patients who are admitted within 3 days of acute stroke.

NICE CG92 is currently being updated. Evidence from the CLOTS trials was evaluated in surveillance of NICE CG92 and contributed to the decision to update that guideline.

New evidence is unlikely to impact on the guideline.

Editorial and factual corrections identified during surveillance

During surveillance editorial or factual corrections were identified.

- The guideline contains the following recommendation from 'Alteplase for the treatment of acute ischaemic stroke' (2007) NICE technology appraisal guidance 122.

  '1.4.1.1 Alteplase is recommended for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke. It should only be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation.'

  NICE TA122 has been replaced by: Alteplase for treating acute ischaemic stroke (2012) NICE technology appraisal guidance 264'. The updated technology appraisal guidance does not contain this recommendation.

  Decision: Recommendation 1.4.1.1 should be amended to reflect current technology appraisal guidance.

- The guideline contains the following recommendation:

  '1.4.2.3 Any person with acute ischaemic stroke who is allergic to or genuinely intolerant of aspirin[21] should be given an alternative antiplatelet agent.'

  Footnote 21 in the guideline contains a cross-reference to 'Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events' (2005) NICE technology appraisal guidance TA90. It cites the following definition of aspirin intolerance:

  'proven hypersensitivity to aspirin-containing medicines; or history of severe dyspepsia induced by low-dose aspirin.'

  This guideline has been replaced by: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (2010) NICE technology appraisal guidance TA210. The updated technology appraisal guidance does not include a definition of aspirin intolerance.

  Decision: The definition of aspirin intolerance should be integrated into the recommendation without reference to an external source.

Research recommendations

RR – 01 Does the withdrawal of oral liquids or the use of modified (thickened) oral fluids prevent the development of aspiration pneumonia after an acute stroke?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 02 Does modified-release dipyridamole or clopidogrel with aspirin improve outcome compared with aspirin alone when administered early after acute ischaemic stroke?

New evidence relating to clopidogrel or dipyridamole was identified. However, these drugs are covered by 'Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events' (NICE TA210). New evidence was not summarised. The NICE technology appraisals team has been informed about all evidence identified by cumulative surveillance reviews.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 03 Should a person who has a stroke or a TIA and is already taking aspirin be offered the same or an increased dose of aspirin after the stroke?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 04 How safe and effective is very early mobilisation delivered by appropriately trained professionals after stroke?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence supports current recommendations.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 05 How safe and effective is the early manipulation of blood pressure after stroke?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence supports the current guideline recommendations.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 06 What is the safety and efficacy of carotid stenting compared with carotid endarterectomy within 2 weeks of TIA or recovered stroke when these procedures are carried out?

New evidence relating to these procedures was identified, but it was not specific to acute care.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 07 **A randomised trial comparing direct admission to an acute stroke unit versus admission to a medical ward at least while the latter remains standard clinical practice.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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