Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention

A national clinical guideline

December 2008
KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
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<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case control or cohort studies</td>
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<td></td>
<td>High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
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<tr>
<td>2+</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
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<tr>
<td>2-</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
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<tr>
<td>3</td>
<td>Non-analytic studies, eg case reports, case series</td>
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<tr>
<td>4</td>
<td>Expert opinion</td>
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GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

<table>
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<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
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<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
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GOOD PRACTICE POINTS

☑ Recommended best practice based on the clinical experience of the guideline development group.

NHS Quality Improvement Scotland (NHS QIS) is committed to equality and diversity. This guideline has been assessed for its likely impact on the six equality groups defined by age, disability, gender, race, religion/belief, and sexual orientation.

For the full equality and diversity impact assessment report please see the “published guidelines” section of the SIGN website at [www.sign.ac.uk/guidelines/published/numlist.html](http://www.sign.ac.uk/guidelines/published/numlist.html). The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our web site [www.sign.ac.uk](http://www.sign.ac.uk).

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Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention
A national clinical guideline

Scottish Intercollegiate Guidelines Network

December 2008
Introduction

1.1 THE NEED FOR A GUIDELINE

Stroke is the third biggest cause of mortality and the main cause of disability in Scotland. The Scottish Borders Stroke study measured the community based crude incidence of first-ever-in-a-lifetime stroke (FES) in Scotland at 2.8/1,000 of the population. Around 8,500 FESs occur per annum in Scotland, with around 130,000 in the UK.

Stroke is an age-dependent illness and approximately 80% of people with FES present at 65 years of age and over. The predicted increase in this proportion of the Scottish population and the greater increase in the older old (over 80 years), will be paralleled by a continuing increase in the number of strokes in Scotland.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline replaces SIGN 13 Management of patients with stroke I: Assessment, investigation, immediate management and secondary prevention and SIGN 14 Management of patients with stroke II: Management of carotid stenosis and carotid endarterectomy, which were published in 1997.

This guideline takes account of advances in both stroke treatment and imaging. The guideline uses an updated evidence base to support recommendations for all aspects of acute stroke care including the management of carotid stenosis.

The guideline complements SIGN 78 Management of patients with stroke: Identification and management of dysphagia and SIGN 64 Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. As stroke shares risk factors with cardiovascular disease, primary prevention of stroke has been covered in SIGN 97 Risk estimation and the prevention of cardiovascular disease and is not discussed in this guideline.

The guideline follows the patient pathway from the onset of a suspected stroke and covers management of suspected stroke by non-stroke specialist practitioners, and clinical and radiological assessment. Treatment, monitoring and prevention of recurrent stroke in patients with ischaemic stroke, transient ischaemic attack (TIA), primary intracerebral haemorrhage (PICH) and asymptomatic carotid disease are also covered. There is also a section addressing the information and support needs of patients and carers. Management of patients with subarachnoid haemorrhage has not been addressed.

The guideline development group has based the recommendations in this guideline on answers to a series of key questions (see Annex 1).

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of particular interest to stroke physicians, stroke nurses, specialists in geriatric medicine and care of the elderly, neurologists, neuroradiologists, radiologists, vascular surgeons, cardiologists, general physicians, speech and language therapists, physiotherapists, occupational therapists, pharmacists, specialists in emergency medicine, specialists in intensive care, paramedics, specialists in public health, nurse practitioners and general practitioners.
1.3 DEFINITIONS

The definitions of some terms vary from one study to another and these outlines are not rigid.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Stroke</td>
<td>The World Health Organization (WHO) definition of stroke is a focal neurological deficit (loss of function affecting a specific region of the nervous system) due to disruption of its blood supply. Most strokes result from a blood vessel being blocked by a clot, and around one in ten from a ruptured blood vessel causing a haemorrhage. This affects the supply of oxygen and nutrients, causing damage to the brain tissue.</td>
</tr>
<tr>
<td>Transient ischaemic attack (TIA)</td>
<td>Historically defined as a neurological deficit caused by interruption in blood supply to the brain (or retina), in which all symptoms resolve within 24 hours. Stroke and TIA have identical symptoms and represent a continuum, with only an arbitrary time limit distinguishing them. Proposals to change the definition recognise that most TIAs resolve fully within 30-60 minutes. Permanent damage to brain tissue occurs in at least half of TIAs. Retinal TIAs are usually brief episodes of monocular visual loss and may be referred to as amaurosis fugax or transient monocular blindness.</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>Arbitrarily, this is considered to be a stroke (ie symptoms persisting for 24 hours or longer) with minor neurological deficit, for example, scoring &lt;5 on the National Institutes of Health stroke scale (NIHSS, see Annex 2). Minor strokes may be associated with significant disability.</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>Defined as a stroke with persisting disability that impairs independence (for example a modified Rankin Score, mRS ≥ 3, see Annex 3).</td>
</tr>
<tr>
<td>Cryptogenic stroke</td>
<td>A stroke in which no generally accepted cause is identified after investigation.</td>
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<tr>
<td>Carotid artery territory event</td>
<td>A stroke or TIA involving an area of brain which derives its blood supply from a branch of the internal carotid artery (ICA). This includes temporary monocular blindness or amaurosis fugax (the ophthalmic artery being a branch of the ICA). It is also known as an anterior circulation stroke/TIA.</td>
</tr>
<tr>
<td>Posterior circulation event</td>
<td>A stroke or TIA involving an area of brain which derives its blood supply from a branch of the vertebral or basilar arteries.</td>
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1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.

1.4.1 PATIENT VERSION

A patient version of this guideline has been developed in collaboration with Chest, Heart & Stroke Scotland and is available from the SIGN website, www.sign.ac.uk.

1.4.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORIZATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (product licence). This is known as “off label” use. It is not unusual for medicines to be prescribed outwith their product licence and this can be necessary for a variety of reasons.

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.

Medicines may be prescribed outwith their product licence in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose.

Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers’ professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.

Any practitioner following a SIGN recommendation and prescribing a licensed medicine outwith the product licence needs to be aware that they are responsible for this decision, and in the event of adverse outcomes, may be required to justify the actions that they have taken.

Prior to prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).

1.4.3 ADDITIONAL ADVICE TO NHSScotLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in the section on implementation.
2 Key recommendations

The following recommendations were highlighted by the guideline development group as being clinically very important. They are the key clinical recommendations that should be prioritised for implementation. The clinical importance of these recommendations is not dependent on the strength of the supporting evidence.

2.1 MANAGEMENT OF SUSPECTED STROKE OR TIA

2.1.1 SYSTEMS OF CARE

Emergency medical services should be redesigned to facilitate rapid access to specialist stroke services.

Patients with suspected stroke should have:
- ambulance priority (blue light) in appropriate cases
- rapid triage on arrival at hospital
- immediate access to specialist stroke services
- rapid brain imaging
- rapid specialist assessment.

2.2 IN-HOSPITAL CARE

Stroke patients requiring admission to hospital should be admitted to a stroke unit staffed by a coordinated multidisciplinary team with a special interest in stroke care.

2.3 ASSESSMENT, DIAGNOSIS AND INVESTIGATION

2.3.1 BRAIN IMAGING FOR SUSPECTED ACUTE STROKE OR TIA

All patients with suspected stroke should have brain imaging immediately on presentation.

2.3.2 CAROTID EVALUATION

All patients with non-disabling acute stroke syndrome/TIA in the carotid territory who are potential candidates for carotid surgery should have carotid imaging.

2.4 TREATMENT OF ISCHAEMIC STROKE

2.4.1 THROMBOLYSIS

Patients admitted with stroke within four and a half hours of definite onset of symptoms, who are considered suitable, should be treated with 0.9 mg/kg (up to maximum 90 mg) intravenous rt-PA.

2.4.2 DECOMPRESSIONAL SURGERY

For individuals aged up to 60 years who suffer an acute MCA territory ischaemic stroke complicated by massive cerebral oedema, surgical decompression by hemicraniectomy should be offered within 48 hours of stroke onset.
2.5 PREVENTING RECURRENT STROKE IN PATIENTS WITH ISCHAEMIC STROKE OR TIA

2.5.1 ANTIPLATELET AGENTS

A Low-dose aspirin (75 mg daily) and dipyridamole (200 mg modified release twice daily) should be prescribed after ischaemic stroke or TIA for secondary prevention of vascular events.

A Clopidogrel (75mg daily) monotherapy should be considered as an alternative to combination aspirin and dipyridamole after ischaemic stroke or TIA for secondary prevention of vascular events.

2.5.2 STATINS

A A statin should be prescribed to patients who have had an ischaemic stroke, irrespective of cholesterol level.

A Statin therapy after haemorrhagic stroke is not routinely recommended unless the risk of further vascular events outweighs the risk of further haemorrhage.

2.6 CAROTID INTERVENTION

2.6.1 SYMPTOMATIC CAROTID ARTERY DISEASE

A All patients with carotid artery territory stroke (without severe disability, mRS ≤ 2) or transient ischaemic attack should be considered for carotid endarterectomy as soon as possible after the index event.

A Carotid endarterectomy (on the internal carotid artery ipsilateral to the cerebrovascular event) should be considered in all:

- male patients with a carotid artery stenosis of 50-99% (by NASCET method)
- female patients with a carotid artery stenosis of 70-99%.

B For all patients, carotid endarterectomy should be performed as soon as the patient is stable and fit for surgery, ideally within two weeks of event.

2.7 PROVISION OF INFORMATION

2.7.1 PROVIDING INFORMATION AND SUPPORT

A Information should be offered to patients and carers in a variety of formats, including easy access.

A Caregivers should be offered ongoing practical information and training individualised for the needs of the person for whom they are caring.
3 Management of suspected stroke or TIA

3.1 SYSTEMS OF CARE

There is a paucity of evidence describing the best systems of care to allow efficient and rapid assessment and treatment of patients with suspected stroke. There is good evidence, however, that early assessment, diagnosis and in-hospital treatment of patients with suspected stroke reduces mortality and morbidity. The availability of effective acute treatment for stroke necessitates rapid transfer to hospital (see sections 5, 6 and 7).

Two systematic reviews and one Health Technology Assessment (HTA) identified seven barriers to timely assessment of patients with suspected stroke:11-13

- patient or family not recognising symptoms of stroke or delay seeking help11,12
- patient or family calling general practitioner (GP) first11,12
- incorrect triage11
- delays in neuroimaging11,12
- delays in following in-hospital pathways11,12
- delay in obtaining consent11
- physician unfamiliarity with recombinant tissue plasminogen activator (rt-PA) use.11

Public awareness of the symptoms of stroke should be increased.
People should be advised to contact the emergency medical services immediately if they suspect they may be having a stroke.

Interventions reported in three systematic reviews and one small non-randomised study as attempts to speed up presentation of patients with suspected stroke had more impact on in-hospital delays than out-of-hospital delays.13-16 The range of interventions described to overcome barriers was varied and included complex, multifaceted interventions, and the interventions may not be applicable to every healthcare setting.13-16 There was no clear evidence that any intervention in isolation improved clinical outcome, although multifaceted interventions may be more effective than single interventions.13 The interventions included:

- education programmes to improve the general public’s recognition of symptoms of stroke13
- training paramedics to diagnose stroke more accurately and decrease time to hospital13
- helicopter transfer13
- training emergency medical staff in acute stroke care13
- reorganisation of hospital systems13,14
- multifaceted interventions (including telemedicine systems).13,15

Emergency medical services should be redesigned to facilitate rapid access to specialist stroke services.

Patients with suspected stroke should have:
- ambulance priority (blue light) in appropriate cases
- rapid triage on arrival at hospital
- immediate access to specialist stroke services
- rapid brain imaging
- rapid specialist assessment.
3.2 PRE-HOSPITAL

3.2.1 PRE-HOSPITAL ASSESSMENT

Standard assessment scales based on face, arm and speech impairments are simple tools to improve the speed and accuracy of diagnosis in patients with suspected stroke, although there is a small risk of wrong diagnosis. The three signs most diagnostic of stroke (facial paresis, arm drift, abnormal speech) are assessed by FAST (face arm speech test, see Annex 4). The assessment scales were generally validated by clinically trained personnel, although FAST, MASS (Melbourne acute stroke scale, see Annex 5) and CPASS (Cincinnati pre-hospital stroke scale) show acceptable accuracy when used by non-medically trained people (e.g. paramedics). When used by paramedic staff indirect comparison favours the use of FAST and MASS tests over CPASS and LAPSS (Los Angeles pre-hospital stroke scale).

The positive predictive value (PPV) for suspected stroke patients assessed by paramedics using FAST was 78% (95% confidence interval, CI 72% to 84%). Twenty seven per cent of patients with confirmed stroke or TIA were admitted within one hour of onset of symptoms of stroke and 68% within three hours.

Use of MASS was associated with an increase in diagnostic accuracy from 78% to 94%, a decrease in door to doctor time from 43 to 25 minutes, a decrease in door to computerised tomography (CT) time from 187 to 127 minutes, and an increase in advanced notification to the hospital from 13% to 25% of patients. Paramedic assessment with MASS was associated with increased telephone prenotification for acute treatment from 18% to 36%. Patients admitted after prenotification had higher treatment priority (74% compared to 34%), earlier doctor assessment (15 minutes compared to 31 minutes) and earlier CT scan (94 minutes compared to 144 minutes).

No comparison of the assessment scales was identified.

C Standard assessment scales such as FAST or MASS are recommended for pre-hospital assessment to:
- increase the accuracy of the initial stroke diagnosis
- assist with more rapid diagnosis
- speed up consideration for treatment
- assist with more rapid referral to specialist services.

3.3 IN-HOSPITAL

3.3.1 IN-HOSPITAL ASSESSMENT

When used by medical or emergency department staff, the ROSIER (recognition of stroke in the emergency room) scale (see Annex 6) was superior to CPASS, LAPSS and FAST. In a study of 343 patients use of the ROSIER scale gave accurate diagnosis in 2-3 minutes. When internally validated at a cut-off score greater than zero, the ROSIER scale had a diagnostic sensitivity of 92%, specificity of 86%, PPV = 88%, and negative predictive value (NPV) of 91%. Prospective validation in 173 consecutive patients referred with suspected stroke showed sensitivity of 93% (89% to 97%), a specificity of 83% (95% CI 77% to 89%), PPV = 90% (95% CI 85% to 95%), and NPV = 88% (95% CI 83% to 93%).

C Standard assessment scales such as ROSIER are recommended for emergency department staff to:
- increase the accuracy of the initial stroke diagnosis
- assist with more rapid diagnosis.
3.3.2 IN-HOSPITAL CARE

Evidence from a large systematic review of a wide range of trials of organised stroke unit care indicates that stroke patients have better clinical outcomes in terms of survival, returning home and independence if they are managed in a stroke unit rather than admitted to a general ward or remaining at home.\(^2\) The trials included patients with a diagnosis of ischaemic stroke or PICH, although a minority of trials excluded patients with transient symptoms. The study described an effective stroke unit as a multidisciplinary team, coordinated through regular multidisciplinary meetings, providing multiple interventions.

There was insufficient evidence to assess whether acute stroke units with a short period of admission, roving stroke teams or general neurology units resulted in improved clinical outcomes for patients with suspected stroke.

A Stroke patients requiring admission to hospital should be admitted to a stroke unit staffed by a coordinated multidisciplinary team with a special interest in stroke care.

☑ Patients with TIA requiring admission to hospital should be admitted directly to a stroke unit staffed by a coordinated multidisciplinary team with a special interest in stroke care.

Evidence from three studies of very early assessment and initiation of secondary prevention therapy after TIA or minor stroke strongly suggests that early intervention (within 24 hours) reduces the risk of early stroke recurrence, although the studies do not directly address the question of admission.\(^2\) In a before and after study based on a community cohort, early active management at a daily TIA clinic was associated with an 80% drop in the risk of stroke recurrence.\(^2\) A study of a 24 hour access TIA clinic from which 74% of patients were sent home the same day showed that stroke recurrence was less than expected.\(^2\)

Assessing the risk of recurrence is covered in section 4.1.1 and Annex 7.

B Patients with TIA and minor stroke, who are at high risk of early recurrence, should undergo specialist assessment and begin treatment promptly.

3.3.3 INTEGRATED CARE PATHWAYS

A care pathway can be defined as a plan of care that aims to promote organised and efficient multidisciplinary patient care based on the best available evidence. Care pathways are complex interventions made up of a number of components, are often implemented with some form of education and usually form all or part of the patient record.\(^1\)

One systematic review of three randomised controlled trials (RCTs) and 12 observational studies found that the routine application of an integrated care pathway did not substantially improve patients’ outcomes in terms of survival or independence compared to standard multidisciplinary care. Potential benefits in preventing urinary tract infections were only seen in studies that were prone to bias.\(^1\)

The components of a multidisciplinary stroke care team and the roles of the team members have been described.\(^8\)

B The routine implementation of care pathways for acute stroke management or stroke rehabilitation is not recommended where a well organised multidisciplinary model of care exists.
3.3.4 TELEMEDICINE CONSULTATION

Scotland has a geographically scattered population and patients with suspected stroke often present to rural hospitals without a resident stroke physician. When there is no specialist available there may be a delay to diagnosis, which is relevant for thrombolysis with its narrow time window for administration of rt-PA (see section 5.1.1).

Telemedicine allows a distant stroke physician to interact with stroke patients, carers and the local doctor remotely and to view brain scans. The stroke physician can take a history, view the examination, counsel the patient and carers about the risks and benefits of thrombolysis and guide the attending doctor’s management. This interaction can occur within minutes of arrival in hospital and patients can receive thrombolysis locally.

Five observational studies of telemedicine networks for acute stroke from around the world were identified. A systematic review of five networks concluded that telemedicine systems can be feasible, acceptable and technically and diagnostically reliable in acute stroke management, and that telemedicine consultations were associated with improved delivery of rt-PA.

In areas without a local stroke specialist, telemedicine consultation should be considered to facilitate treatment in patients eligible for thrombolysis.
4 Assessment, diagnosis and investigation

4.1 CLINICAL ASSESSMENT

4.1.1 RISK OF RECURRENCE

Patients with minor stroke or TIA are at risk of recurrent stroke. Standard assessment scales can help to prioritise those patients at higher risk.

Five cohort studies demonstrated the prognostic value of age, duration of symptoms, weakness, speech problems, blood pressure and history of diabetes. The use of assessment scores (such as ABCD, based on age, blood pressure, clinical features, and duration of symptoms) in patients with mild stroke or TIA predicts early recurrence. One study of patients admitted to hospital found limited discrimination when using the ABCD score.

The revised score ABCD², which includes history of diabetes, has been extensively tested and shown to be reliable (see Annex 7).

The ABCD² score should be used to identify patients who are at highest risk of recurrent stroke to allow very rapid investigation and treatment.

4.1.2 DIAGNOSIS OF HAEMORRHAGE

Scoring tools, such as the Siriraj score, have insufficient precision to predict the presence of haemorrhage reliably. One diagnostic study found the sensitivity and specificity for predicting an infarct to be 0.78 and 0.80 respectively. By summarising seven other studies of patients with a clinical diagnosis of acute stroke, the sensitivities and specificities of the Siriraj score were found to be highly variable, ranging from around 0.4 to 0.9 and 0.7 to 0.95 respectively. Imaging is essential to exclude haemorrhage (see section 4.2).

4.1.3 ASSESSMENT OF DEGREE OF DEPENDENCY

Once a patient has been admitted, the use of standard impairment scales, such as NIHSS, short NIHSS, Guy’s Score, Canadian neurological scale (CaNS), Scandinavian stroke scale (SSS) score or the Los Angeles motor scale (LAMS), can be predictive of the degree of dependency and length of hospital stay. NIHSS is the most evaluated scale but is not clearly superior to other scales (see Annex 2).

The impairment scales are insufficiently precise on which to base individual treatment decisions. The exception is rt-PA where the use of NIHSS categories to determine suitable patients is stipulated in the licence.

Impairment scales should be considered to help discussion of likely outcomes after stroke with patients and carers.

Patients in the acute phase of stroke should not be denied treatment based on an impairment score.

The use of impairment scales may be considered for audit and benchmarking.
4.2 BRAIN IMAGING FOR SUSPECTED ACUTE STROKE OR TIA

4.2.1 WHY PERFORM IMAGING?

Brain imaging is essential to differentiate haemorrhagic from ischaemic events and to exclude stroke mimics such as tumours. Making a positive diagnosis of ischaemic stroke by identifying an ischaemic lesion and by determining both its location (for example, cortical, lacunar or posterior circulation) and its size may guide further investigations, management and predict outcome. Excluding intracranial haemorrhage influences management, particularly in patients already on antiplatelet or anticoagulant therapy.

4.2.2 TIMING OF IMAGING

An HTA explored the optimum timing of brain imaging for patients in the acute phase of stroke. A decision analysis model was developed comparing a ‘scan all patients within 48 hours’ pathway of care in acute stroke against alternative scan strategies. The most cost-effective strategy, in terms of least overall cost and most quality adjusted life years (QALYs) after adjusting for different age ranges, proportions of infarcts and accuracy of CT, was to scan all patients immediately.

A All patients with suspected stroke should have brain imaging immediately on presentation.

4.2.3 MODALITY OF IMAGING

The modality used to image an acute stroke syndrome is determined by patient factors, the purpose of the imaging and the accuracy of the modality for the suspected stroke syndrome at the time from ictus at which the patient presents.

CT is widely available, practical, quick and easy to use in ill patients. CT is highly sensitive to haemorrhage in patients in the hyperacute stage. In patients with ischaemic stroke, particularly those presenting with mild neurological deficits, CT imaging is often normal in the first few hours. The accuracy of CT for ischaemic stroke delineation improves after six hours and in the first few days but it remains less accurate than magnetic resonance imaging (MRI) in determining site and extent of ischaemic damage, particularly for small lesions and lesions in the posterior fossa. CT accuracy is reduced beyond one week after the stroke event. In particular, the discrimination between haemorrhagic and ischaemic stroke origin is impaired as blood products are absorbed.

Evidence is emerging that MRI may be superior to CT, although MRI may be contraindicated in up to a fifth of patients because they are too ill, confused, dysphasic, have an intraocular or intracerebral metallic foreign body or have a pacemaker.

MRI with diffusion weighted imaging for ischaemia and gradient echo sequences to detect haemorrhage is superior to CT scanning for accurate determination of the cause of stroke syndrome at all time points after presentation, particularly in the first few hours for ischaemia. MRI also exhibits less variability in interpretation than CT for ischaemia, including site and extent. MRI is more sensitive at detecting haemorrhage at this stage.

B CT scanning is recommended for most patients in the acute phase of stroke.

B MRI with diffusion weighted and gradient echo sequences is recommended (where available and practical) for the diagnosis of acute stroke syndromes in patients who:
- are not severely ill, especially where either neurological deficit is mild and the clinical likelihood is that the lesion is small or lies in the posterior fossa or
- present late (after one week).

The advantages and disadvantages of using CT and MRI are summarised in Annex 8.
4.2.4 BRAIN AND VASCULAR IMAGING TO INVESTIGATE THE UNDERLYING CAUSE OF INTRACEREBRAL HAEMORRHAGE

There is a lack of data on investigating the underlying causes of intracerebral haemorrhage. Generally, the underlying cause is related to age. Arteriovenous malformations are the most common cause in young patients, degenerative small vessel disease in the middle aged and amyloid angiopathy in the elderly. There is no evidence about which patients should undergo further brain or vascular imaging, which imaging modality should be used or the timing of further imaging.

In patients presenting with an intracerebral haemorrhage, where an underlying intracerebral abnormality is suspected, follow-up brain and vascular imaging may be considered in discussion with an appropriate specialist.

4.2.5 WHO SHOULDN'T INTERPRET THE BRAIN SCAN?

A meta-analysis of 15 studies of inter-observer reliability of assessing CT scans for early changes of cerebral infarction (1,281 scans, 709 readers) concluded that there was little evidence regarding who is best to read a scan. In all specialties experienced readers were more consistent and accurate than less experienced readers and training in interpreting scans improved performance. Observers were classified as expert (neuroradiologists with a major interest in stroke), experienced (radiologists or physicians with more than five years of experience in reading stroke CT scans in clinical practice), or less experienced (trainees, neurologists, physicians developing a specialisation in stroke, or radiologists learning to interpret stroke CT scans but with less than five years of experience).

Similar comparative studies for MRI interpretation do not exist.

C Unenhanced CT brain scans for detection of early changes of infarction should be interpreted by personnel trained and experienced in stroke radiology.

D Medical personnel trained and experienced in stroke radiology should interpret CT and MRI brain scans from all time frames.

4.2.6 TELERADIOLOGY

Teleradiology links allow electronic transfer of brain images to a remote reader and have been widely used for several years. One small observational study demonstrated its validity and reliability compared to reading hard copies on a view box.

Teleradiology links may be used to transfer brain images to a remote specialist.

4.3 CAROTID EVALUATION

4.3.1 CAROTID IMAGING IN PATIENTS WITH CAROTID TERRITORY TIA OR STROKE AND/OR RETINAL EVENT

A good quality meta-analysis showed that the most cost-effective diagnostic strategies for carotid stenosis are those that offer surgery to a larger proportion of patients quickly after the warning TIA/minor stroke. The benefit of performing carotid endarterectomy (CEA) diminishes with time from the event (see section 1.1), reinforcing the need for early assessment. The nearer to the time of stroke/TIA, the less important the actual degree of stenosis is in predicting benefit from CEA. The time of highest risk for recurrence of stroke/TIA is in the first hours or days after the primary warning event as stroke related to carotid bifurcation disease relates to stability of the plaque. TIA carries at least as high a risk of subsequent disabling stroke as minor stroke and its investigation and treatment should be treated with equivalent urgency. Cost-effectiveness modelling shows the best strategy is to offer surgery to a larger proportion of patients earlier than is currently the case in Scotland.
A systematic review found that Doppler ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA) or contrast-enhanced MRA (CE-MRA) all have high sensitivities and specificities for diagnosing 70-99% carotid artery stenosis (by the NASCET method, see Annex 9) in patients with ipsilateral carotid territory ischaemic symptoms. Data were too limited to provide reliable estimates of accuracy for patients with 50-69% stenosis. Non-invasive imaging avoids potential complications of invasive arteriography, but there is consistent evidence that imaging tests which produce angiographic images have better reproducibility, lower inter-observer variation and higher accuracy in assessing/quantifying carotid disease than ultrasound techniques. Of the non-invasive options contrast-enhanced magnetic resonance angiography (CE-MRA) is the most accurate modality (see Table 1). Ultrasound has high sensitivity for detecting carotid bifurcation disease and a normal ultrasound excludes disease. The poor specificity of ultrasound for degree of disease when present, high inter-observer variability and insensitivity for disease at other sites in the extracranial vasculature means that when an initial carotid duplex examination is abnormal secondary corroborative imaging is required.

Table 1: Sensitivity and specificity of non-invasive imaging for patients with 70-99% carotid artery stenosis (by the NASCET method)

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE-MRA</td>
<td>0.94</td>
<td>0.88-0.97</td>
<td>0.93</td>
<td>0.89-0.96</td>
</tr>
<tr>
<td>Doppler ultrasound</td>
<td>0.89</td>
<td>0.85-0.92</td>
<td>0.84</td>
<td>0.77-0.89</td>
</tr>
<tr>
<td>MRA</td>
<td>0.88</td>
<td>0.82-0.89</td>
<td>0.84</td>
<td>0.76-0.97</td>
</tr>
<tr>
<td>CTA</td>
<td>0.77</td>
<td>0.68-0.84</td>
<td>0.95</td>
<td>0.91-0.97</td>
</tr>
</tbody>
</table>

A. All patients with non-disabling acute stroke syndrome/TIA in the carotid territory who are potential candidates for carotid surgery should have carotid imaging.

C. Initial carotid imaging with duplex ultrasound or alternative should be performed rapidly once a diagnosis of ischaemic stroke or TIA in the carotid territory is made.

☑ Initial carotid imaging should be performed within 48 hours of presentation.

C. Corroborative imaging is recommended to confirm and more accurately grade carotid disease if duplex carotid ultrasound is abnormal.

C. Non-invasive angiographic carotid imaging (CE-MRA) should be performed and interpreted by radiologists specifically trained and with specialist interest in vascular imaging.

☑ Duplex ultrasound criteria for grading of carotid disease should be standardised and regularly audited against another modalities and surgical findings.

Criteria for carotid duplex reporting are shown in Annex 10.
4.3.2 CAROTID IMAGING IN PATIENTS SCHEDULED FOR CARDIAC SURGERY AND ASYMPTOMATIC FOR TIA/STROKE

No good quality evidence was identified to suggest whether or not screening asymptomatic patients, who are undergoing cardiac surgery, for carotid artery disease improves outcomes.

☑ Patients undergoing cardiac surgery who are asymptomatic for stroke or TIA should not be screened for carotid disease.

4.3.3 CAROTID PLAQUE MORPHOLOGY, COMPOSITION AND ACTIVITY

Ulcerated plaque and plaque activity as identified by transcranial Doppler (TCD) confers increased risk of recurrent stroke at all grades of stenosis. Carotid duplex has poor sensitivity for detection of ulceration compared to angiography, CE-MRA and CTA.58-61

No prospective trials were identified with outcomes supporting routine imaging to determine carotid plaque composition or activity and whether these should influence therapy decisions.

4.4 CARDIAC IMAGING

An HTA assessed clinical and cost effectiveness of echocardiography in stroke. The meta-analysis confirmed that there is insufficient evidence to make recommendations on the use of echocardiography in all patients with stroke.62

In the absence of significant carotid disease echocardiography may identify intracardiac thrombus in stroke patients with atrial fibrillation or evidence of recent myocardial infarction. The distinction between trans-thoracic and trans-oesophageal echocardiography is unclear. The latter has higher accuracy for intracardiac thrombus, but may be associated with increased complications in patients with acute stroke. It is also more expensive, reducing its ultimate cost effectiveness.

There is a lack of evidence to support the routine use of echocardiography to identify atrial septal abnormalities, mitral valve disease or complex aortic atheroma in patients with stroke. Pick up rates for cardiac imaging are higher in patients with a clinical suspicion of cardiac disease and in those without other risk features for stroke. Echocardiography should be considered in those patients with clinical findings and/or baseline investigations suggesting cardiac disease, and in cases of cryptogenic stroke.62

No evidence was identified regarding either the use of simple chest radiography for cardiac assessment or for the use of more sophisticated techniques such as cardiac CT and cardiac MRI specifically in stroke patients. Evidence was also lacking to support routine cardiac imaging to identify intracardiac thrombus, the prevalence of which is low in patients with stroke, particularly those with documented carotid disease (those patients already found to have a potential source of cerebral atheroembolism).62

Lack of good quality evidence to support cardiac imaging does not necessarily reflect lack of benefit.

☑ The routine use of echocardiography with contrast media for evaluation of patients with stroke is not recommended.

☑ Echocardiography should be considered in patients with:
  - clinical findings and/or baseline investigations suggesting cardiac disease
  - cryptogenic stroke.

☑ Routine chest radiography and electrocardiogram (ECG) is recommended in patients with stroke.

☑ The use of cardiac CT and MRI should be limited to secondary specialist investigations for specific problem solving where other tests are inconclusive.
4.5 Diagnostic Tests

There are good clinical arguments for performing standard haematological or biochemical tests on patients with a stroke or TIA, although few studies were found on their use or their effect on management or outcomes.

- Standard haematological and biochemical tests such as a full blood count, erythrocyte sedimentation rate, blood glucose, renal biochemistry and cholesterol level should be performed on patients with a stroke or TIA as a minimum.

Studies describing diagnostic tests for inherited thrombophilias, antiphospholipid antibodies, other auto-antibodies or measuring homocysteine levels are inconsistent. There is evidence to suggest that these tests do not help to either predict the risk of further stroke, or direct further management decisions.63,64

- The routine requesting of thrombophilia screens, antiphospholipid antibodies, other auto-antibodies or homocysteine levels is not recommended.
5 Treatment of ischaemic stroke

5.1 THROMBOLYSIS

5.1.1 INTRAVENOUS THROMBOLYSIS

A Cochrane review of intravenous (IV) thrombolysis includes data from RCTs of streptokinase and the alteplase form of rt-PA. Initial trials evaluated streptokinase, which has since been excluded from routine clinical use due to safety concerns and lack of evidence of efficacy.65

Thrombolytic therapy with rt-PA (alteplase 0.9 mg/kg up to maximum 90 mg) administered within four and a half hours of stroke onset according to protocols stated in the product licence significantly reduces death and disability at 90 days.65,66

The odds of a favourable outcome (full or nearly full recovery from stroke) are strongly related to the time to treatment and are significantly greater the earlier that treatment is delivered. The odds ratio (OR) for favourable outcome is 2.8 (95% CI 1.8 to 4.5) for 0–90 minutes, 1.6 (95% CI 1.1 to 2.2) for 91–180 minutes, and 1.4 (95% CI 1.1 to 1.9) for 181–270 minutes in favour of rt-PA treatment.67 Administration later than 4.5 hours is associated with an increased risk of mortality and the risk:benefit ratio has not been established.67

The incidence of symptomatic neurological deterioration due to intracerebral haemorrhage is increased approximately threefold to around 2% with IV alteplase.66,68,69

Selection of patients for IV alteplase treatment based on MRI protocols (diffusion-perfusion mismatch > 20% and diffusion-weighted imaging lesion volume less than 120 ml) is associated with similar proportions of favourable outcomes but reduced proportions of deaths and severe disability when compared with patients selected by CT alone within the 0-3 hour time window.70-72 Selection by the same MRI protocols was also associated with similar outcomes in the 3-6 hour window. All RCTs of IV thrombolysis, however, selected patients on the basis of CT alone.66,67,72

Patients admitted with stroke within four and a half hours of definite onset of symptoms, who are considered suitable, should be treated with 0.9 mg/kg (up to maximum 90 mg) intravenous rt-PA.

- Onset to treatment time should be minimised.
- Systems should be optimised to allow the earliest possible delivery of intravenous rt-PA within the defined time window.
- Streptokinase should not be used for treatment of patients in the acute phase of stroke.

Thrombolysis should be administered within the context of an acute stroke service.

Local protocols for the administration of thrombolytic therapy should be developed.

5.1.2 INTRA-ARTERIAL THROMBOLYSIS

The volume of evidence for intra-arterial thrombolysis is small as relatively few patients are enrolled in RCTs. Several agents have been examined including rt-PA, urokinase (UK) and recombinant pro-urokinase (r-proUK). Urokinase and recombinant pro-urokinase are not currently available in the United Kingdom.

A systematic review included 44 studies of intra-arterial thrombolysis for anterior circulation stroke, only three of which were RCTs.71 Two of the RCTs compared intra-arterial r-proUK plus heparin with placebo plus heparin (PROACT I and II, n = 220). Thirty three of the studies were case series of patients treated with urokinase (total n = 835).

A further case series of IA urokinase reported a significantly better chance of favourable outcome compared with matched historical controls.74 Reported recanalisation rates were higher than in historical control series (around 65% with super-selective administration compared to around 20%), and symptomatic intracerebral haemorrhage rates were 4-10%.
Basilar artery occlusive stroke has a high mortality (approximately 90%) without recanalisation.73

In a systematic review of case series of intravenous (n = 76) and intra-arterial (n = 344) treatment recanalisation was reported more often with IA treatment but survival rates and favourable outcomes were similar.75 Treatment was started within 12 hours of symptom onset in 73-77% of patients, but within six hours in 29%.75 One RCT of IA urokinase included only 16 patients. Four out of eight patients receiving UK had good outcome compared with only one out of eight in the control group.76 Combined IA alteplase and treatment with the glycoprotein IIb/IIIa inhibitor abciximab achieved higher recanalisation rates and a higher proportion of favourable clinical outcomes compared to a historical control series receiving IA alteplase alone, with or without stenting in either group.77

Recanalisation rates are known to be significantly poorer with certain sites of occlusion (for example, carotid “T” occlusions) and reocclusion more common with others (for example, basilar artery). Combined IV-IA treatment can be planned from the outset. Since recanalisation is the major determinant of successful outcome in stroke patients treated with IV thrombolytic therapy, and the majority of recanalisation occurs within two hours of drug administration, “rescue” IA therapy is a logical development of treatment.70

One RCT comparing IV plus IA alteplase (IV 0.6 mg/kg plus IA maximum 20 mg) with placebo plus IA alteplase, two retrospective and two prospective case series (n = 63) were included in a systematic review.73 A further prospective study of IV plus IA therapy reported a higher proportion of favourable clinical outcomes than historical controls from published IV thrombolysis RCTs with similar rates of symptomatic intracerebral haemorrhage.78

A prospective case series reported comparable outcomes in patients treated with standard IV alteplase who recanalised (as defined by ultrasound) and those who failed to recanalise after 30 minutes of IV treatment who subsequently received IA alteplase.79

B Intra-arterial thrombolysis may be considered for patients with proximal middle cerebral artery occlusion or basilar artery occlusion that presents beyond four and a half hours.

B Treatment should be delivered within six hours of symptom onset in patients with middle cerebral artery occlusion.

☑ Intra-arterial thrombolysis should be administered as soon as possible after symptom onset.
☑ Intra-arterial thrombolysis should only be carried out by an appropriately trained interventional neuroradiologist.

5.2 ANTIPLATELET AGENTS

5.2.1 ASPIRIN

A systematic review of twelve RCTs of over 40,000 patients showed that aspirin at 160 or 300 mg daily reduced death and disability, recurrent stroke, and improved the likelihood of full recovery in patients with ischaemic stroke.80 Two trials of aspirin (160 or 300 mg) given within 48 hours of stroke onset contributed 94% of the data analysed in the review. One was an open label trial and did not require a CT scan before randomisation. Exclusion criteria for these RCTs were vague and in all of the included trials mortality was lower than in the placebo arm (4-9%), suggesting that major strokes were under-represented.

A Aspirin 300 mg daily should be commenced within 48 hours of ischaemic stroke and continued for at least 14 days.

☑ In patients with dysphagia aspirin (300 mg) should be administered rectally or by enteral tube.
Guidelines are available covering the identification and management of dysphagia following stroke,\textsuperscript{7} and for administration of medication to patients with enteral feeding tubes or swallowing difficulties.\textsuperscript{81}

Standard protocols for IV and IA thrombolytic therapy presently advise avoidance of aspirin for 24 hours after thrombolytic drug treatment.\textsuperscript{80}

Aspirin for preventing recurrent stroke is discussed in section 9.1.

- Aspirin should be avoided within 24 hours of IV or IA thrombolytic therapy.

### 5.2.2 ASPIRIN PLUS CLOPIDOGREL

A small RCT of 110 patients with carotid stenosis showed that dual therapy with aspirin and clopidogrel significantly reduced the proportion of patients with embolic signals on transcranial Doppler ultrasound. The study was not powered to examine clinical end points.\textsuperscript{82} The FASTER trial randomised 392 patients with TIA or minor stroke to aspirin or aspirin plus clopidogrel for 90 days, commencing within 24 hours of symptom onset. A non-significant 3.8% absolute risk reduction (ARR) in total stroke was found for the combination therapy.\textsuperscript{25} Dual therapy with aspirin and clopidogrel given to patients within 48 hours of TIA or minor stroke was one component of several interventions in a prospective study, including early statins, antihypertensives and carotid endarterectomy. The contribution of combined aspirin and clopidogrel to the reduced stroke risk is not clear but there was no increase in the risk of intracerebral or other haemorrhage in the study group overall.\textsuperscript{24}

Insufficient evidence exists to support the routine use of the combination of aspirin and clopidogrel for treating patients in the acute phase of stroke.

### 5.3 ANTICOAGULANTS

The administration of anticoagulants is contraindicated during the first 24 hours after IV thrombolytic therapy.\textsuperscript{83} Although recanalisation may be more successful, the risk of haemorrhage increases. Evidence on adjunctive anticoagulation is limited and neither the safety nor efficacy has been established.\textsuperscript{83}

### 5.3.1 UNFRACTIONATED HEPARIN

Fixed dose unfractionated heparin (UFH) commenced within 48 hours of ischaemic stroke of any aetiology (including patients with atrial fibrillation) does not reduce the chances of death or dependence after 3-6 months and is not significantly superior to aspirin alone.\textsuperscript{84} A reduction of recurrent strokes (nine fewer for every 1,000 patients treated) was offset by nine extra symptomatic intracerebral haemorrhages for every 1,000 patients treated, and nine additional major extracranial haemorrhages for every 1,000 patients treated.

High dose UFH given within three hours of stroke onset was associated with a significant reduction in death or dependence. Patients eligible for very early heparin treatment are also likely to be candidates for thrombolysis.\textsuperscript{85}
5.3.2 LOW MOLECULAR WEIGHT HEPARINS AND HEPARINOIDS

A non-significant trend towards reduction in death and dependence at 3-6 months was seen for low molecular weight heparins (LMWH) and heparinoids when compared to control, which was a mixture of placebo, aspirin, and unfractionated heparin (OR = 0.85; 95% CI 0.66 to 1.08). In patients with atrial fibrillation, weight-adjusted high dose LMWH (dalteparin 100 IU/kg) was not superior to aspirin in preventing early stroke recurrence and carried a significantly higher risk of extracerebral haemorrhage. Symptomatic and asymptomatic venous thromboembolic events are highly significantly reduced by all heparin treatments. Deep vein thrombosis (DVT) is avoided in 281 patients for every 1,000 treated and pulmonary thromboembolisms (PTE) are avoided in four patients per 1,000 treated. LMWH and heparinoids are associated with a significantly greater reduction in DVT than UFH without any additional hazard. Enoxaparin 40 mg once daily is superior to UFH 5,000 units twice daily and is not associated with any increase in bleeding complications or difference in mortality.

5.3.3 HEPARIN PLUS ASPIRIN

Combined treatment with aspirin and UFH reduced recurrent stroke by 10 fewer per 1,000 patients treated, although a significant increase in the number of symptomatic intracranial haemorrhages was also reported (10 more per 1,000 patients). For patients in atrial fibrillation (AF) with acute ischaemic stroke aspirin reduces the risk of further stroke by 21% giving a number needed to treat (NNT) to prevent one stroke of 100 over 2-4 weeks. Any benefit of UFH in this situation is offset by the increase in haemorrhagic stroke.

5.3.4 WARFARIN

In one trial 100 patients received warfarin within two weeks of stroke onset and none had haemorrhagic worsening. Large, disabling strokes were under-represented. An arbitrary time limit of two weeks is recommended for delaying warfarin treatment for AF following acute stroke.

5.3.5 FIBRINOGEN-DEPLETING AGENTS

Fibrinogen-depleting agents did not reduce death or dependence when given within six hours of stroke onset. There was no benefit from ancrod given within six hours of stroke onset, and a significant increase in symptomatic and asymptomatic intracranial haemorrhage. When all ancrod trial results are considered, no benefit on death or dependence was evident (OR = 93; 95% CI 0.77 to 1.12, calculated from primary data).

A The routine use of anticoagulants (UFH, LMWH, heparinoids, oral anticoagulants, direct thrombin inhibitors, fibrinogen-depleting agents) is not recommended for the treatment of acute ischaemic stroke.

Anticoagulants are not recommended in patients with progressing stroke.

In patients at high risk of venous thromboembolic disease LMWH should be considered in preference to UFH.

Following administration of IV thrombolysis, heparin should not be given in any form for 24 hours.

For patients in atrial fibrillation following stroke, anticoagulation with warfarin can be introduced early in patients with minor stroke or TIA, but should be deferred for two weeks after onset in those with major stroke.
5.4 **NEUROPROTECTANTS**

Many agents have been studied for a potential neuroprotective effect in patients with stroke. There are systematic reviews of glutamate antagonists, calcium antagonists, the free radical scavenger tirilazad, vinca alkaloids, oral citicoline, the sodium antagonist lubeluzole, corticosteroids, methylxanthine derivatives (pentoxifylline, propentofylline and pentofylline), aminophylline, and piracetam and phase III RCTs of the free radical spin trap NXY 059, 5HT1a agonist repinotan, neutrophil chemotaxis inhibitors enlimomab and UK-279,276, magnesium, nalmefene, diazepam, chlomethiazole, cerebrolysin, and the free radical scavenger edaravone.

These agents have widely differing pharmacological actions. For the majority of agents, there was no evidence of benefit or harm. The exceptions are:

- **Definite harm (increase in odds of death or dependence)**
  - tirilazad (OR = 1.23; 95% CI 1.01 to 1.50)
  - enlimomab (adjusted p = 0.004 for worse distribution of Rankin grade)

- **Possible harm**
  - aptiganel hydrochloride (mortality OR = 1.32; 95% CI 0.91 to 1.93)
  - selrotel (mortality OR = 1.19; 95% CI 0.81 to 1.74)
  - corticosteroids (OR = 1.08; 95% CI 0.68 to 1.72)
  - calcium antagonists (OR 1.07 0.97 to 1.18)
  - gavestinel (mortality OR = 1.12; 95% CI 0.95 to 1.32)

- **Possible benefit (reduced odds of death or dependence)**
  - citicoline (good outcome OR = 1.38; 95% CI 1.10 to 1.72)
  - non-cortical stroke syndromes treated with magnesium (poor outcome OR = 0.75; 95% CI 0.58 to 0.97)

For other agents, there was insufficient evidence to define benefit or harm.

- Neuroprotectant agents should be used only within the context of randomised controlled trials.

5.5 **REDUCING RAISED INTRACRANIAL PRESSURE**

Stroke with symptomatic space occupying cerebral oedema affects approximately 5% of hospitalised patients with stroke.

5.5.1 **MANNITOL**

A systematic review of mannitol in acute stroke included only one RCT of 77 patients, reported in 1978. Temporary reduction in intracranial pressure (ICP) in patients with cerebral oedema in massive middle cerebral artery (MCA) infarction (malignant MCA syndrome) was reported, but there was no effect on clinical outcomes.

5.5.2 **HYPERTONIC SALINE**

Hypertonic saline (10%) reduced ICP (and elevated cerebral perfusion pressure) for up to four hours after failure of mannitol in space occupying ischaemic stroke or ICH in eight patients.
5.5.3 GLYCEROL

A systematic review of 10 RCTs (n=945) of glycerol to reduce raised ICP showed a trend towards reduced mortality within the treatment period (typically seven days, OR=0.78; 95% CI 0.58 to 1.06), which was significant when analysis was restricted to five truly randomised trials. Only two trials reported functional outcomes and there was no significant effect seen (OR=0.73; 95% CI 0.37 to 1.42). A subsequent retrospective cohort study of 442 patients found no effect on mortality, and significantly increased mortality when glycerol was co-administered with corticosteroids.

5.5.4 HEAD POSITIONING

In stable patients with MCA infarction, cerebral perfusion pressure and MCA flow velocity were significantly higher with flat head positioning compared to head elevation of 15 or 30 degrees. No effect on clinical outcomes was reported.

5.5.5 CORTICOSTEROIDS

A systematic review of seven trials of corticosteroids in acute stroke showed no evidence of benefit. In a small retrospective study of corticosteroids in acute stroke 30 day mortality was increased.

5.6 DECOMPRESSIVE SURGERY

Patients with stroke involving the MCA territory and complicated by massive cerebral oedema comprise a small proportion (3-10%) of the overall number of patients with stroke. Younger patients tend to be over-represented in this group and the untreated mortality is very high (up to 80%).

Pooled analysis of the data from three RCTs of hemicraniectomy for malignant MCA infarction found significantly reduced mortality with hemicraniectomy. Patients were eligible if they were between the ages of 18-60, were within 45 hours of symptom onset with severe MCA infarct (NIHSS >15, see section 4.1.3) and had CT scan evidence of an infarct involving >50% of the MCA territory (or MRI volume >145 cm³). Surgical hemicraniectomy and duroplasty performed within 48 hours of symptom onset increased survival to 80% compared to 28% with conservative management (ARR=50%; NNT=2). The effects of surgery are the same in patients below and above the age of 50 but have not been evaluated in those over the age of 60. The proportion of patients surviving with severe disability at three months (mRS>4, see Annex 3) was significantly increased. The proportion with severe disability, however, was less with longer follow up, consistent with delayed recovery in this younger population.

A further study examined the additive effect of mild hypothermia (35°C) with hemicraniectomy compared to hemicraniectomy alone in an RCT of 25 patients. There was no placebo group as all patients received surgical treatment and this was performed early after stroke within a mean of 15 (± 6) hours. There was a trend towards a better clinical outcome at six months with combined hypothermia and surgery but this was not significant. Hypothermia did not appear to have any additional risks associated with it as a treatment.

For individuals aged up to 60 years who suffer an acute MCA territory ischaemic stroke complicated by massive cerebral oedema, surgical decompression by hemicraniectomy should be offered within 48 hours of stroke onset.

It is uncertain whether selected patients older than 60 years will benefit from surgical decompression.
5.7 MECHANICAL REPERFUSION

5.7.1 CLOT RETRIEVAL

Mechanical clot retrieval may be an alternative to drug therapies in patients with contraindications to IV thrombolysis. It requires suitably trained and experienced interventional neuroradiologists using interventional neuroradiology facilities.

Mechanical clot retrieval with the MERCI (mechanical embolus removal in cerebral ischaemia) device is associated with a recanalisation rate of 46-54% when deployed within eight hours of symptom onset, which was higher than historical controls. Treatment with the MERCI device is associated with clinically significant procedural complications in 7-10% of patients and with a symptomatic intracerebral haemorrhage rate of 7-10%, which is comparable to that of IA thrombolysis within six hours. Half of all bleeds were subarachnoid haemorrhages resulting from vessel perforation. Recanalisation is not necessarily associated with better clinical outcomes and no RCT with concurrent controls has been undertaken.

Mechanical clot retrieval devices, when used by experienced interventional neuroradiologists, may be considered in patients:

- ineligible for thrombolytic drug therapy or
- who have failed to improve clinically or recanalise following intravenous thrombolysis.

Mechanical clot disruption (including clot maceration by guidewire, clot snaring and balloon angioplasty) may achieve recanalisation in patients with persistent MCA or ICA occlusion after standard IV or IA rt-PA. Immediate recanalisation was achieved in 38% of patients and final recanalisation in 75% compared to rates of 6% and 72% for simple clot penetration by microcatheter. Bleeding risks did not appear to be increased.

5.7.2 TRANSCRANIAL DOPPLER AND THROMBOLYSIS

The use of continuous pulsed wave TCD ultrasound at 2 MHz in patients undergoing IV rt-PA thrombolysis for middle cerebral artery occlusions (diagnosed by ultrasound) within three hours of symptom onset is associated with higher rates of early recanalisation and a trend towards more favourable clinical outcomes compared to thrombolysis alone. Forty nine per cent of patients had complete recanalisation or dramatic recovery at two hours compared to 30% of patients receiving rt-PA alone (relative risk reduction, RRR=1.6; 95% CI 1.03 to 2.6). At three months 42% of patients receiving ultrasound had better functional outcome compared to 29% of the control group (p=0.2). Similar findings were reported for transcranial colour coded sonography (TCCS) at identical frequency.

Augmentation of IV thrombolysis by continuous 2 MHz pulsed wave TCD ultrasound should be considered in the context of further clinical trials.

Using lower frequencies of ultrasound causes less heating and gives better penetration, but there is an excess risk of intracerebral haemorrhage.

TCD ultrasound at lower (kilohertz) frequencies is not recommended.
5.8 PRIOR STATIN THERAPY

Evidence from retrospective studies suggests that in addition to reducing the risk of recurrent stroke, statin pre-treatment may improve stroke outcome.

A small single centre RCT randomised 89 patients with ischaemic stroke, on prior statin therapy, to either atorvastatin 20 mg (initiated within 24 hours of symptom onset) or withdrawal of statin therapy for three days.\textsuperscript{128} Withdrawing statins increased the risk of death and dependency at 90 days (OR = 4.66; 95\% CI 1.46 to 14.91), and increased the risk of a poor clinical outcome (mRS > 2; 60\% versus 39\%; p = 0.043).

Guidelines are available covering the identification and management of dysphagia following stroke,\textsuperscript{7} and for administration of medication to patients with enteral feeding tubes or swallowing difficulties.\textsuperscript{81}

Patients with ischaemic stroke on prior statin therapy should continue treatment, via a nasogastric tube, if necessary.
6 Treatment of primary intracerebral haemorrhage

6.1 HAEMATOMA EVACUATION

The evidence for haematoma evacuation and clot lysis for primary intracerebral haemorrhage is inconsistent due to the small size and heterogeneous entry criteria of most RCTs in this area, compounded by the very long time span over which these RCTs have been conducted.

Three systematic reviews of ICH evacuation each make different judgements on data from RCTs. One systematic review of four RCTs (n = 354) included data from an RCT conducted in 1961, before use of CT to confirm diagnosis. A meta-analysis of seven RCTs and two quasi-randomised trials (total n = 1,258), also included data from non-randomised trials. There was a non-significant trend towards reduced mortality (OR = 0.84; 95% CI 0.67 to 1.07) and reduced death or dependence (OR = 0.82; 95% CI 0.63 to 1.06) for surgical intervention. One trial contributed the greatest number of patients (1,033) to this systematic review, but covered a wide range of interventions in a heterogeneous population over an extended time period.

Other analyses from STICH (Surgical Treatment for IntraCerebral Haemorrhage) indicate an extremely wide variation in the rate of surgical intervention by country. More than 75% of surgical interventions were by craniotomy.

In the single RCT published since the 2006 systematic review, with intervention within eight hours of onset, there was a non-significant reduction in death (48% versus 57%) and good functional outcome was significantly more frequent (33% versus 9%).

Minimally invasive surgical approaches such as stereotactic aspiration of haematoma after instillation of lytic drugs suggest benefit (death OR = 0.29; 95% CI 0.14 to 0.59; death or dependence OR = 0.48; 95% CI 0.24 to 0.96) but RCTs have included only 185 subjects.

A Routine surgical evacuation by craniotomy is not recommended for supratentorial primary intracerebral haematoma.

B If surgical evacuation of primary intracerebral haematoma is considered:
   - minimally invasive procedures including stereotaxy-guided evacuation should be considered as an alternative to craniotomy
   - early intervention (within eight hours of symptom onset) is recommended.

6.2 THROMBOLYSIS

Intraventricular haemorrhage (IVH) is an established independent risk factor for poor prognosis in ICH. External ventricular drain (EVD) placement allows monitoring and intracranial pressure management.

A single RCT of patients with PICH and hydrocephalus requiring EVD, randomising to urokinase (n = 7) or placebo was identified. Intraventricular urokinase speeds up radiological resolution of IVH clots. Treatment reduced the half-time of radiological resolution by a mean of 3.8 days, from 8.5 in the placebo group to 4.7 in the urokinase treated group. The trial was too small to assess the effect on functional outcomes and mortality and did not have a non-surgical control group for comparison.

Case series identified by a systematic review report more favourable outcomes than historical controls, where used, with IVH lysis either by rt-PA or urokinase administered either continuously or intermittently via an external ventricular drain. There was no reported increase in risk of haemorrhage or other adverse outcomes.
6.3 **HAEMOSTATIC THERAPIES**

RCTs of haemostatic therapy are justified on the basis of natural history studies that identify the prognostic importance of early haematoma expansion in the first four hours after symptom onset, and the association of expansion and larger haematoma volume with poor outcome.

A systematic review of four RCTs showed that, despite methodological limitations, recombinant factor VIIa significantly reduced the risk of death or dependence within 90 days of PICH.138

Preliminary results from a study of recombinant factor VIIa in acute haemorrhagic stroke treatment showed reductions in haematoma volume growth similar to previous studies but failed to show any benefits on death or dependency at 90 days with 20 mcg/kg or 80 mcg/kg of factor VIIa compared to placebo.139

- Haemostatic therapies should only be used in primary intracerebral haemorrhage within randomised controlled trials.

6.4 **REDUCING RAISED INTRACRANIAL PRESSURE**

6.4.1 **CORTICOSTEROIDS**

A systematic review of corticosteroids in primary intracerebral haemorrhage included five RCTs, all of which used dexamethasone 4-12 mg for 2-16 days.140 Two trials conducted in the 1970s did not confirm the diagnosis radiologically and in one, 28% of patients were found to have ischaemic stroke at autopsy.140

At one month, dexamethasone had no significant effect on mortality (RR = 1.14; 95% CI 0.91 to 1.42) or death or dependence (RR = 0.95; 95% CI 0.83 to 1.09). A non-significantly higher number of complications was reported in patients treated with dexamethasone.140

- Corticosteroids should not be used for treatment of primary intracerebral haemorrhage.

6.4.2 **MANNITOL**

One RCT compared IV mannitol infusions to placebo for control of raised ICP in spontaneous primary intracerebral haemorrhage.141 Four-hourly infusions of 100 ml of 20% mannitol for five days in patients with spontaneous supratentorial ICH did not affect one-month mortality (16 out of 65 mannitol-treated patients compared to 16 out of 63 untreated patients, OR = 0.96; 95% CI 0.40 to 2.31 as calculated by guideline development group) or three month death or dependence on the Barthel Index (39 out of 65 patients compared to 34 out of 63, OR = 1.28; 95% CI 0.60 to 2.74).

- Intravenous mannitol should not be used routinely for treatment of raised intracranial pressure in patients with primary intracerebral haemorrhage.

Significant benefit or harm from these interventions cannot be excluded.
7 Other causes of stroke

7.1 CEREBRAL VENOUS THROMBOSIS

Cerebral venous thrombosis (CVT) is a rare cause of stroke, affecting only two to four people per million per year, accounting for 0.5% of all strokes.\textsuperscript{142,143} Diagnosing cerebral venous thrombosis is difficult and CVT are often assumed to be ischaemic infarcts. Clinical symptoms are very variable and non-specific. CT appearances can be subtly different and other imaging such as MR or CT venography may be required. The aetiology is often multifactorial and underlying thrombophilias are found in 22% of patients.\textsuperscript{142,143}

7.1.1 ANTICOAGULANTS

Anticoagulation appears to be safe following cerebral venous thrombosis and may be associated with an improvement in outcome and reduced mortality.

A systematic review identified one poor quality and one small RCT (80 patients in total) to include in a meta-analysis. Treatment with anticoagulation (dose adjusted unfractionated heparin and the LMWH, nadroparin) commenced within 10 to 32 days of diagnosis and continued for three weeks, followed by warfarin therapy for 10 weeks, appears to be relatively safe. No new symptomatic intracerebral haemorrhages occurred during treatment with anticoagulants.\textsuperscript{144}

A case series reported the rate of ICH in patients with CVT at between 0% and 5.4%.\textsuperscript{143} Anticoagulation resulted in non-significant reductions in death or dependency at three months and non-significant reductions in death from any cause.

\begin{itemize}
\item Intravenous UFH or subcutaneous LMWH followed by warfarin therapy should be considered in patients with cerebral venous thrombosis.
\end{itemize}

Anticoagulation with warfarin (target INR 2-3) should usually be continued for 6-12 months following the recommendations for treatment of deep vein thrombosis and pulmonary thromboembolism.

7.1.2 THROMBOLYSIS

A Cochrane review of thrombolysis for cerebral venous thrombosis identified no RCTs.\textsuperscript{145}

A retrospective non-randomised study of local urokinase suggested that thrombolysis in cerebral venous thrombosis appears safe but its routine clinical use cannot be supported.\textsuperscript{146} It may be indicated in selected cases where there is ongoing clinical deterioration despite other therapy.\textsuperscript{142,147}

There is insufficient evidence to support thrombolysis for cerebral venous thrombosis.

7.2 EXTRACRANIAL CERVICAL ARTERIAL DISSECTION

Extracranial cervical arterial dissection is an uncommon cause of stroke, accounting for 2.5% of all strokes and 5-22% of strokes in young people (<45 years). The incidence of carotid artery dissections is two to three per 100,000 per year. Aetiologies include chiropractic neck manipulations and arteriopathies such as fibromuscular dysplasia and cystic medial necrosis.

Dissections of the vertebral arteries are less well defined but occur in 1 to 1.5 per 100,000 per year in a hospital population series.\textsuperscript{148} Multiple arteries are involved in 28% of patients and the vertebral arteries in around 25%. The risk of recurrence of carotid dissection is around 1% per annum. The subsequent risk of stroke was around 1% and the risk of TIA around 2% over a follow-up period of 31 months in one case series.\textsuperscript{148}

One long term follow-up study over six to seven years showed annual rates of ipsilateral stroke of 0.7% and of any stroke of 1.4% for those left with permanent carotid stenosis or occlusion. Following transient stenosis with complete or partial recovery (<50% stenosis), the annual rate of ipsilateral stroke after treated carotid dissection was 0.3% and of any stroke was 0.6%.\textsuperscript{149}
The most likely cause of stroke in cervical artery dissection is embolism from the dissection flap but some cases may be due to haemodynamic compromise from the dissection itself. It is important to be aware of the possibility of intracranial extension of the dissection resulting in subarachnoid haemorrhage. This diagnosis should be excluded in the usual way if symptoms are suggestive prior to initiating treatment with antiplatelets or anticoagulation.

7.2.1 ANTICOAGULANTS AND ANTIPLATELETS

A Cochrane review identified no RCT evidence on the treatment of extracranial cervical arterial dissection. Comparative analysis of case series found that there was no significant difference in outcomes in terms of either benefit or detriment between antiplatelet therapy and anticoagulation. Surgical treatment does not appear to be beneficial but little evidence exists to confirm this.

A Canadian multicentre prospective series of 116 patients (67 vertebral and 49 carotid dissections), found a 15% risk of recurrent TIA, stroke or death at one year of follow up. The event rate for patients on anticoagulation was not significantly different to those on aspirin.

In patients with extracranial cervical arterial dissection consider treatment with either:
- anticoagulation for three to six months or
- antiplatelet agents.

The possibility of subarachnoid haemorrhage should be excluded prior to initiating therapy if there are features suggestive of this complication.

Further imaging of the cervical arteries may be required to assess healing or progression of the vascular lesion.

7.2.2 ENDOVASCULAR STENTING

Two small case series (n = 18) demonstrated the feasibility of using endovascular stenting for carotid artery dissection. The procedures were well tolerated and only one TIA occurred following stenting. No other conclusions could be drawn.

Cervical artery pseudo-aneurysms occur following carotid artery dissection in 5-40% of cases. Follow up of patients on aspirin treatment of up to three years revealed no clinical or radiological events. Over time 5-25% resolved completely, 16-30% reduced in size and 59-65% remained unchanged.

Endovascular stenting is not routinely recommended for extracranial cervical arterial dissection or cervical artery pseudo-aneurysms.

Stenting may be considered if recurrent ischaemic events occur despite medical therapy or where traumatic dissection has occurred with a high risk of stroke.
8 Physiological monitoring and intervention

8.1 PHYSIOLOGICAL MONITORING

Little evidence was identified relating to intensity of physiological monitoring. The studies that have been done looked at different individual components of physiological monitoring. Trials addressing intensity tended to compare continuous monitoring with four to six times daily measurements for a period of 48 to 72 hours. The patients included all had ischaemic strokes. The studies did not address monitoring of conscious level or pulse rate as individual items. Patients who had received thrombolysis were not included.

A prospective study of 268 patients with ischaemic stroke comparing continuous monitoring (blood pressure, electrocardiogram, oxygen saturation, temperature) for 72 hours in a stroke unit compared to routine care (less intense monitoring) showed that more intensive care led to a 2.5 fold increase in the probability of a good outcome at discharge. This may be due to earlier detection and correction of complications.157

A small RCT (54 patients) compared a stroke care monitoring unit (SCMU) to conventional stroke unit care. Monitoring for 48 hours was associated with a lower proportion of patients who died or had a poor outcome at three months. The average length of stay was shorter for the SCMU (16 ± 5 days versus 25 ± 7 days).158

Continuous or frequent physiological monitoring in the acute phase of stroke identifies adverse physiological events that may require intervention.

- An active monitoring protocol should include frequent observations of:
  - blood pressure
  - blood glucose
  - oxygen saturation
  - temperature
  - ECG
  - respiratory rate
  - heart rate
  - pulse rate
  - conscious level.

- Monitoring should be balanced against other important aspects of stroke unit care, particularly early mobilisation and rehabilitation.

8.2 PHYSIOLOGICAL INTERVENTION

8.2.1 FLUID REPLACEMENT THERAPY

Many patients are dehydrated on admission, and this may be associated with a poorer outcome.159 Delivery of intravenous fluids is routine acute treatment in stroke, particularly in patients at risk of dehydration, such as those with reduced conscious level or swallowing impairment.

There are limited data available on the use of intravenous fluids in acute stroke. No studies were identified to determine the most effective type or volume of infusion.

Data extrapolated from evidence in patients with hyperglycaemia support avoidance of dextrose in the early post-stroke phase.160

The available evidence consistently showed no benefit from haemodilution in the acute phase of stroke, rather there was a modest trend towards harm, except in patients with polycythaemia.161 A meta-analysis of studies of haemodilution using plasma expanders (dextran, hydroxyethyl starch and albumin) compared to standard fluid replacement therapy found no evidence of benefit over standard regimens in terms of reducing mortality or improving functional outcome in survivors.161
Whilst not designed as an efficacy study, a study of the effects of hydroxyl ethyl starch showed no benefit over crystalloid solution.\(^{162}\)

The use of standard IV saline infusion was associated with a significant fall in plasma glucose within the first 24 hours after acute ischaemic stroke.\(^{160}\)

A small study of 34 stroke patients with dysphagia randomised to either intravenous or subcutaneous fluid replacement therapy suggests that the latter will satisfactorily maintain plasma osmolality within normal limits.\(^{163}\)

There are no RCTs directly comparing saline to other crystalloids.

- Early assessment of fluid balance and initiation of an appropriate IV fluid regime to maintain normal serum osmolality (or euvolaemia) should be part of routine clinical practice.

- To prevent iatrogenic hyperglycaemia, IV saline infusion is preferable to glucose containing preparations.

- Haemodilution is not recommended as a routine treatment in acute stroke with the possible exception of patients with polycythaemia.

- For patients in whom IV fluids are not appropriate, subcutaneous fluids can be used to maintain plasma osmolality within the normal range.

### 8.2.2 BLOOD PRESSURE MANAGEMENT

Patients with the highest and lowest levels of blood pressure recorded within 24 hours of an acute stroke have been shown to have early neurological decline and poorer outcome.\(^{164}\) The evidence about the relative risks or benefits of actively elevating or lowering blood pressure is inconclusive.

A systematic review showed that a variety of agents including beta blockers, calcium channel blockers (CCB), nitric oxide donors and angiotensin converting enzyme (ACE) inhibitors all lower blood pressure after acute ischaemic stroke.\(^{165}\) None of the studies found a robust association between blood pressure reduction and improved outcomes. Further systematic reviews of CCBs and nitric oxide donors failed to show any association between treatment and improved outcome.\(^{94,166}\)

Blood pressure elevation using either phenylephrine or dexamphetamine has been associated with reduction in infarct size. A small study (45 patients) suggests that blood pressure elevation with dexamphetamine may improve early outcome.\(^{167,168}\)

Small studies looking at surrogate markers of cerebral blood flow, such as SPECT, showed that both perindopril or losartan given within 2-7 days of stroke onset do not lower cerebral blood flow.\(^{169,170}\) One study of perfusion weighted MRI suggested that phenylephrine may reduce infarct size.\(^{168}\) These interventions have not been tested in RCTs with clinical end points.

Compared to placebo, candesartan given early after acute stroke appears to be associated with a reduction in further events despite a lack of effect on blood pressure.\(^{171}\) The study was underpowered and did not meet its primary end points, so no firm conclusions on BP lowering can be made.\(^{171}\)

Bendroflumethazide at 2.5 mg was shown to be ineffective at lowering blood pressure in patients with mild to moderate hypertension in the early post-stroke period.\(^{172}\)

Nimodipine has a negative effect on outcomes associated with a reduction in diastolic blood pressure but not with lowering of systolic blood pressure.\(^{169}\)

Lisinopril appears to be safe in the acute phase of stroke but its clinical benefit is uncertain. Given orally to patients with hypertension (≥ 140/≥ 90 mmHg), 5 mg within 24 hours of stroke onset significantly lowered blood pressure within four hours of administration. No difference was found in neurological or functional outcomes at 90 days.\(^{173}\)
Ongoing trials are exploring whether BP should be lowered acutely following stroke, and whether antihypertensive therapy should be continued or stopped in the first few days after stroke.\textsuperscript{174,175}

\begin{itemize}
  \item[A] Blood pressure should not be actively managed as a routine in patients in the acute phase of ischaemic stroke.
  \item[\ding{51}] Where possible, patients should be randomised into ongoing clinical trials of BP manipulation.
\end{itemize}

### BLOOD GLUCOSE MANAGEMENT

Hyperglycaemia occurs in 20% to 63% of patients admitted with ischaemic stroke and in the absence of prior diabetes.\textsuperscript{176,177} Acute post-stroke hyperglycaemia is associated with larger infarct volumes and cortical involvement,\textsuperscript{178,179} which may be associated with ischaemia of the insular cortex.\textsuperscript{180} Hyperglycaemia at any time after acute stroke is an important determinant of infarct expansion and may be associated with poorer functional outcome.\textsuperscript{178}

A meta-analysis suggests that the relative risk of death in hyperglycaemic non-diabetic stroke patients is increased by 3.3 (95% CI 2.3 to 4.6).\textsuperscript{177} Observational data suggest that over a third of patients with ischaemic stroke who have previously diagnosed type 2 diabetes may have impaired glucose tolerance or diabetes confirmed by oral glucose tolerance test (OGTT), which persists at discharge.\textsuperscript{181}

No evidence was identified to support early active treatment of mild to moderate hyperglycaemia in patients with acute ischaemic stroke. An RCT comparing a 24 hour glucose/potassium/insulin (GKI) infusion with standard intravenous saline infusion in 933 patients with a blood glucose level between 7 and 17 mmol/L was terminated early due to slow recruitment.\textsuperscript{160} There was no difference in mortality or other measured outcomes between the two groups. The GKI regimen used was labour intensive and there was a 16% risk of persisting low glucose requiring ‘rescue treatment’. There was an absolute reduction in glucose of 0.57 mmol/L compared to saline infusion. Potential confounders included an effect on blood pressure in the insulin treated group and a lack of standardisation of management after 24 hours.

\begin{itemize}
  \item[B] Routine use of insulin regimens to lower blood glucose in patients with moderate hyperglycaemia after acute stroke is not recommended.
  \item[C] Patients with hyperglycaemia (random blood glucose >7 mmol/L) should be formally assessed (by OGTT) to exclude or confirm a diagnosis of impaired glucose tolerance or diabetes.
  \item[\ding{51}] Hypoglycaemia should be corrected according to local protocols.
  \item[\ding{51}] Patients with diabetes should be treated according to local protocols.
\end{itemize}

### FEEDING

Oropharyngeal dysphagia affects a large proportion of patients in the acute phase of stroke. Swallowing difficulties can result in serious complications such as aspiration pneumonia, undernutrition, dehydration and missed medication. It is important that early screening for symptoms of dysphagia is carried out on admission and before giving food, drink or administering oral medications.

Guidelines are available on the identification and management of dysphagia following stroke,\textsuperscript{7} and for the administration of medication to patients with enteral feeding tubes or swallowing difficulties.\textsuperscript{81}

In patients who have difficulty taking food and oral medication safely due to a low consciousness level and/or the presence of dysphagia, nutrition may be provided via a nasogastric (NG) tube or a percutaneous gastrostomy (PEG) tube. There is no clear guidance on how quickly feeding should be initiated and which feeding tube is more suitable.
A multicentre RCT investigated the timing and method of enteral feeding for patients with dysphagia in the acute phase of stroke. There was no statistically significant difference between early and delayed feeding on mortality and morbidity. Early tube feeding showed a non-significant absolute risk reduction in death of 5.8% (95% CI -0.8 to 12.5; p = 0.09). There was a borderline statistically significant increase of 7.8% in the absolute risk of death or poor outcome in the use of PEG compared with NG (95% CI 0.0 to 15.5; p = 0.05). An RCT investigating the routine use of oral nutritional supplements recruited non-dysphagic patients who were adequately nourished prior to their stroke. No significant difference was identified between the study groups, although no evidence was identified for withholding the focused use of nutritional supplements in patients recognised at risk through nutritional screening.

**A** Early placement of a nasogastric feeding tube should be considered in patients identified as unable to take adequate oral intake.

**A** Routine use of nutritional supplements is not recommended.

### 8.2.5 SUPPLEMENTARY OXYGEN THERAPY

A single centre quasi-randomised study of 550 non-hypoxic patients in the acute phase of stroke compared normobaric supplemental oxygen (100%) at 3 litre/minute for 24 hours via nasal catheter to no treatment. There was no statistically significant difference in one year survival (OR = 0.82; 95% CI 0.57 to 1.19; p = 0.300) between treatment and no treatment and no statistically significant difference in neurological or disability scores at seven months. Sub-analysis found a non-significant trend towards oxygen therapy increasing mortality in the mild/moderate stroke group but being of benefit in the severe stroke group.

There is insufficient evidence to recommend routine treatment of non-hypoxic patients in the acute phase of ischaemic stroke with 100% normobaric oxygen.

Two systematic reviews of the same three RCTs of hyperbaric oxygen for acute ischaemic stroke concluded that although there was no convincing evidence that hyperbaric oxygen therapy is effective for patients with ischaemic stroke, there was no evidence that it is ineffective. A third review assessed two of the three RCTs. The RCTs included were all small (n = 106) and underpowered. Due to significant methodological differences analyses of time elapsed from stroke to treatment with hyperbaric oxygen, dose of oxygen and length of treatment course could not be performed. Only data on mortality could be pooled. There were no significant differences in mortality at six months in those receiving hyperbaric oxygen compared to control (RR = 0.61; 95% CI 0.17 to 2.2; p = 0.43).

**A** Hyperbaric oxygen therapy for patients with acute ischaemic stroke is not recommended outwith the setting of a clinical trial.

### 8.2.6 MANAGEMENT OF PYREXIA

Increased body temperature in the acute phase of stroke is associated with poor outcome and the source of any increased body temperature should be investigated.

A systematic review did not identify any evidence that either physical cooling or the use of medication to lower temperature has an effect on outcome.

Three small trials studying the effect of paracetamol (166 patients in total) and ibuprofen (24) in lowering temperature in patients with acute stroke showed the limitations of antipyretic medications in achieving normothermia for patients with fever. Treatment with a daily dose of 6,000 mg of paracetamol resulted in a small reduction in body temperature.

**C** Increased body temperature should be investigated and antipyretic medications may be administered to assist in lowering the body temperature.
8.2.7 INDUCTION OF HYPOThERMIA

No robust evidence was identified on the induction of hypothermia as a treatment for patients with ischaemic stroke.

One small RCT (n=25) of patients with malignant ischaemic stroke suitable for hemicraniectomy compared the safety and therapeutic benefit of hemicraniectomy combined with mild hypothermia (25°C) versus hemicraniectomy alone. There was no statistically significant difference between the two groups in death or clinical outcome measures (NIHSS, BI and mRS), although there was a trend in favour of hemicraniectomy plus hypothermia using NIHSS and Barthel outcome measures. The groups were not well matched as more patients in the hemicraniectomy group had right sided infarcts and more patients in the combination group had additional infarcts of cerebral arteries, which may have affected clinical outcome scores. The randomisation process and investigator blinding were also unclear.

8.2.8 EARLY MOBILISATION

A systematic review found good long term benefit from early neurological rehabilitation as part of routine stroke care. Early mobilisation and early neurorehabilitation were not clearly defined. Early was from one to three days and mobilisation was any physical activity of the body initiated either by the patient or by the environment (for example, positioning in bed, sitting on the edge of the bed, or standing up). Studies using comparisons between stroke units and general wards showed that stroke units had better outcomes, although the practice of getting patients out of bed within 24 hours in one of the studies may be confounding.

A early mobilisation, including positioning in bed, sitting on the edge of the bed, or standing up should be considered for patients within the first three days after a stroke.

8.2.9 PHYSICAL THERAPY

A systematic review of the impact of physical therapy on functional outcomes after stroke included studies with diverse interventions and flawed methodology. Insufficient evidence was identified in terms of functional outcome for traditional neurological treatment approaches.

Task orientated exercise training applied intensively and early, showed a small benefit. An observational study of 830 patients with moderate or severe strokes looked at the association between patient characteristics, the intensity and amount of therapy, and outcomes using the functional independence measure (FIM) of level of assistance in rehabilitation and functional assessment measure (FAM), and length of stay. Patients with moderate strokes did better with early participation in higher order and more challenging therapy activities aiming for shorter more intense rehabilitation. Patients with severe strokes did better with more extended rehabilitation. Neither timing nor the rehabilitation activities were clearly defined. A small study (58 patients with mild to severe stroke) monitored patient activity between 8 am and 5 pm over a period of two days and identified high levels of bed rest. At five days post stroke patients with mild stroke spent 11% of the day in active walking and 53% of the time they were resting in bed. Patients were alone for 60% of the time, spending 85.5% of their day in or beside their bed.

D Patients’ suitability for early, active rehabilitation should be considered.
- Healthcare professionals managing patients in the acute phase of stroke should consider how to actively engage patients throughout the day.
8.2.10 ACTIVE POSITIONING

A systematic review of four RCTs looking at oxygen saturation and positioning included 183 patients. There was heterogeneity in the testing positions, selection criteria, outcome measures and definition of hypoxia. Positioning did not affect oxygen saturation in patients without respiratory comorbidity. There was limited evidence that in patients with stroke who suffer from, or are at risk of, hypoxia an upright sitting position was beneficial, while being supine or side lying was shown to be detrimental.197

A small study (24 patients) of the effect of body position on arterial oxygen saturation in the first 72 hours following mild to moderate stroke found no significant differences between four lying or sitting positions.198 A larger study of 129 patients with stroke who were unable to walk without assistance and required help to change position, measured arterial oxygen saturation by pulse oximetry in five different positions maintained for 10 minutes. Sitting in a chair, if the patient was fit to do so, gave significantly higher mean arterial oxygen saturation than any other position. Lying on the left side (regardless of which side was hemiplegic) resulted in lower mean arterial oxygen saturation. The median inclusion time was 72 hours.199

Flat positioning improved middle cerebral artery mean blood flow velocity, measured by TCD ultrasound in patients in the acute phase of ischaemic stroke compared to elevating the head of the bed by 30 or 15 degrees.118 The study was small (20 patients) and inconclusive on patient outcomes.

C

- Patients should be placed in an upright sitting position, if their medical condition allows.
- Hypoxia inducing positions (on left side or slumped in a chair) should be avoided.
9 Preventing recurrent stroke in patients with ischaemic stroke or TIA

Multiple strategies for the secondary prevention of subsequent vascular events may be effective following stroke and TIA. A strategy combining three medications (aspirin, a statin and an antihypertensive) with diet and exercise may reduce recurrent vascular events in patients with cerebrovascular disease by 80% over five years in patients with an initial cerebrovascular event.200 In appropriate individuals at high risk, further benefit could be gained from carotid endarterectomy, oral anticoagulation, glycaemic control and smoking cessation.200

In an outpatient clinic rapid assessment of patients following a TIA or minor stroke and initiation of secondary prevention with antiplatelet, statin and antihypertensive therapy and urgent carotid imaging with rapid vascular surgical referral as appropriate resulted in an 80% reduction in the risk of early recurrent stroke.24

9.1 ANTIPLATELET AGENTS

See section 5.2 for additional guidance on antiplatelet treatment.

Following the initial treatment of acute ischaemic stroke with aspirin there is currently insufficient evidence to support the use of either dipyridamole or clopidogrel alone in preference to aspirin for preventing recurrent stroke.201-206

Clopidogrel was more effective than aspirin alone in reducing the combined end point of ischaemic stroke, myocardial infarction (MI) or vascular death (RRR = 8.7%; 95% CI 0.3 to 16.5; p = 0.043; ARR = 0.51%; NNT = 196 to prevent one event over a year) except in the subgroup recruited with prior stroke where there was no significant benefit of clopidogrel over aspirin (RRR = 7.3%; 95% CI -5.7 to 18.7; p = 0.26; ARR = 0.56%; NNT = 179 to prevent one event over a year).207

9.1.1 COMBINATION THERAPY

A systematic review and a subsequent RCT compared the use of aspirin in combination with dipyridamole with aspirin alone or dipyridamole alone.201, 202 The combination of aspirin and dipyridamole significantly reduced the risk of the composite end point of MI, stroke or vascular death compared with aspirin alone (OR = 0.82; 95% CI 0.74 to 0.91; ARR = 1% per year, 95% CI 0.1 to 1.8; NNT = 104; 95% CI 55 to 1006) without an increase in bleeding complications.24 Benefit from this combination was maintained for the five years duration of the trial. The two largest RCTs used a modified release preparation of dipyridamole (200 mg twice daily). Twenty six per cent of those taking dipyridamole in the ESPRIT trial discontinued it.202

Dipyridamole is commonly associated with headache. A small study (146 patients) found dose titration of dipyridamole modified release (200 mg daily for one week then 200 mg twice daily) resulted in a non-significant reduction in the incidence of headache.208

Two large RCTs evaluated the use of aspirin and clopidogrel in combination.204, 206 In the MATCH trial there was no significant benefit of aspirin and clopidogrel in combination over clopidogrel alone in a high risk population with recent ischaemic stroke or TIA for the combined end point of ischaemic stroke, myocardial infarction, vascular death, or rehospitalisation for acute ischaemia (RRR = 6.4%; 95% CI -4.6 to 16.3; p = 0.24). The rate of life threatening and major bleeding was increased in the combination group.204 In the CHARISMA trial a population of patients with multiple vascular risk factors or established vascular disease was randomised to aspirin in combination with clopidogrel or aspirin alone. There was no significant difference in the combined end point of MI, stroke or vascular death (RRR = 0.93; 95% CI 0.83 to 1.05; p = 0.22).

The rate of moderate bleeding was higher in the combination group. The combination of aspirin and clopidogrel is no more effective than aspirin or clopidogrel alone for secondary prevention of ischaemic stroke but is associated with an increase in moderate or life threatening bleeding.206
An RCT in 20,332 patients followed up for a mean of 2.5 years, compared aspirin 25 mg plus dipyridamole extended release 200 mg twice daily with clopidogrel 75 mg with the primary outcome of first recurrent stroke. The net risk of recurrent stroke did not differ between the two groups (11.7% in the aspirin/dipyridamole group compared to 11.4% in the clopidogrel group; 95% CI 0.95 to 1.11).

In patients with aspirin-related gastrointestinal intolerance there is no evidence that clopidogrel is better tolerated than aspirin or that addition of a proton pump inhibitor (PPI) improves symptoms, with the exception of those with a previously healed peptic ulcer.

Low-dose aspirin (7.5 mg daily) and dipyridamole (200 mg modified release twice daily) should be prescribed after ischaemic stroke or TIA for secondary prevention of vascular events.

Dose titration of dipyridamole may help to reduce the incidence of headache.

Clopidogrel (75 mg daily) monotherapy should be considered as an alternative to combination aspirin and dipyridamole after ischaemic stroke or TIA for secondary prevention of vascular events.

Patients with a documented aspirin hypersensitivity should receive treatment with clopidogrel monotherapy.

Patients unable to tolerate aspirin and dipyridamole combination therapy or clopidogrel monotherapy should receive treatment with aspirin or dipyridamole monotherapy.

The combination of aspirin and clopidogrel is not recommended for long term secondary prevention of ischaemic stroke or TIA.

A meta-analysis showed no significant difference between aspirin and triflusal for secondary prevention of serious vascular events, including ischaemic stroke and TIA. Two doses of triflusal were used in the included trials (600 mg and 900 mg). The confidence intervals of the meta-analysis were wide and cannot exclude the possibility that triflusal is significantly better or worse than aspirin. Triflusal was associated with a significantly lower risk of minor and major bleeding episodes but had a higher risk of non-haemorrhagic gastrointestinal episodes. A significant number of patients discontinued the study medication early for reasons other than the primary outcome.

Triflusal is not currently licensed in the UK.

There is consistent evidence from two systematic reviews and a subsequent RCT that treatment with a statin significantly reduces the relative risk of ischaemic stroke by 21% (OR = 0.79; 95% CI 0.73 to 0.85) although stroke death is not significantly reduced (OR = 0.91; 95% CI 0.76 to 1.05). The effect was seen without an associated increase in haemorrhagic stroke (OR = 0.90; 95% CI 0.65 to 1.22). The reduction in stroke risk is proportional to the lowering of low density lipoprotein (LDL) cholesterol and occurs irrespective of baseline cholesterol level.

Treatment with a statin also significantly reduces coronary events and all-cause mortality.

Atorvastatin at 80 mg daily given to patients with recent stroke or TIA reduced ischaemic stroke and cardiovascular events after TIA or ischaemic stroke. Over a median follow up of 4.9 years the absolute risk reduction in fatal or non-fatal stroke was 2.2% (95% CI 0.2 to 4.2%) giving an NNT over five years of 45 to prevent one fatal or non-fatal stroke. There were more haemorrhagic strokes in the atorvastatin group giving a hazard ratio of 1.66 (95% CI 1.08 to 2.55). The absolute risk increase was 0.9% giving a number needed to harm (NNH) of 107 over five years.
Simvastatin at 40 mg daily given to patients with prior cerebrovascular disease reduced the incidence of any major vascular event (RRR = 20%; 95% CI 8 to 29%; p = 0.01), but did not reduce the risk of subsequent stroke.\textsuperscript{215}

A systematic review pooled 8,832 individual patients with prior cerebrovascular disease treated with a statin, including simvastatin (40 mg), atorvastatin (80 mg) and pravastatin (40 mg).\textsuperscript{216} The overall relative risk reduction for any type of stroke in statin users was 0.88 (95% CI 0.78 to 0.99). The relative risk of ischaemic stroke is reduced to 0.8 (95% CI 0.70 to 0.92) but there is an increased risk of haemorrhagic stroke with a hazard ratio of 1.73 (95% CI 1.19 to 2.50).

A statin should be prescribed to patients who have had an ischaemic stroke, irrespective of cholesterol level.

Atorvastatin (80 mg) should be considered for patients with TIA or ischaemic stroke.

Other statins (such as simvastatin 40 mg) may also be considered as they reduce the risk of major vascular events.

Statin therapy for prevention of further vascular events post-haemorrhagic stroke is not recommended routinely unless the risk of further vascular events outweighs the risk of further haemorrhage.

9.3 ANTIICOAGULANTS

9.3.1 PATIENTS WITH NON-CARDIOEMBOLIC ISCHAEMIC STROKE

A systematic review comparing anticoagulants with antiplatelets in patients with non-cardioembolic ischaemic stroke looked at 4,076 patients in five trials.\textsuperscript{217} Despite the heterogeneity of the studies, there was no difference in all-cause mortality in patients treated with either antiplatelets or low (INR 1.4–2.8) or medium (INR 2.1–3.6) intensity anticoagulation. All-cause mortality was higher for intensive anticoagulation (INR 3.0–4.5) as were major bleeding complications.

The oral anticoagulant versus aspirin arm of the ESPRIT trial showed that in patients with TIA or non-disabling stroke, oral anticoagulants are no more effective than aspirin for secondary prevention of vascular events.\textsuperscript{218} Although there is possibly a protective effect against ischaemic events, this is offset by an increase in bleeding complications.

Anticoagulation is not recommended for preventing recurrent stroke in patients with non-cardioembolic ischaemic stroke.

9.3.2 PATIENTS WITH NON-RHEUMATIC ATRIAL FIBRILLATION AND ISCHAEMIC STROKE

In patients in atrial fibrillation early risk of recurrent stroke is around 5% within two weeks.\textsuperscript{89} In patients with AF treated with aspirin, the stroke risk is 10% per annum in those with a previous stroke compared to 2.7% in those without a previous stroke. This is reduced to 4% and 1.5% per annum respectively with oral anticoagulants.\textsuperscript{219}

A systematic review concluded that warfarin was more effective for prevention of all vascular events OR = 0.67 (95% CI 0.5 to 0.91) and recurrent stroke OR = 0.49 (95% CI 0.33 to 0.72), which is equivalent to 60 fewer recurrent strokes per year per 1,000 patients treated.\textsuperscript{220} Major extracranial bleeding was more frequent in patients treated with warfarin OR = 5.16 (95% CI 2.08 to 12.83) but absolute differences were small. No significant increase in intracranial bleeding was reported OR = 1.99 (95% CI 0.44 to 9.88) but the confidence intervals were wide.\textsuperscript{220}
Despite the increased incidence of AF and the higher stroke risk in the elderly (>75 years) anticoagulation is underused in this age group. One trial comparing dose-adjusted warfarin (INR 2.0-3.0) to aspirin 300 mg daily in a group of octogenarians found more adverse events in the aspirin group (33% compared to 6%, p = 0.002). Compared to aspirin 75 mg in patients aged >75 years with AF, warfarin significantly reduced the risk of stroke, arterial embolism or other ICH (21 events with warfarin, 48 events with aspirin; yearly risk 1.8% versus 3.8%; RRR = 0.48 95%, CI 0.28 to 0.8; p = 0.003; ARR = 2%; 95% CI 0.7 to 3.2; NNT = 50 over one year). This benefit takes into account any intracranial haemorrhages and occurs without any increase in the risk of extracranial haemorrhage (1.4% warfarin, 1.6% aspirin per annum).

A Patients with ischaemic stroke or TIA who are in atrial fibrillation should be offered warfarin with target INR 2.0-3.0.

B In the absence of contraindications and patient preference for alternative treatment, warfarin should be offered routinely to elderly patients (>75 years) with ischaemic stroke or TIA who are in atrial fibrillation.

No evidence was identified to support benefit from the routine use of aspirin in addition to warfarin.

9.4 ANTIHYPERTENSIVES

There is a well established link between blood pressure and stroke, and between blood pressure treatment and reduction in stroke risk.

Current guidelines for management of hypertension from the British Hypertension Society suggest systolic BP should be treated to <140 mm Hg and diastolic BP to <85 mm Hg, with a target of 130/80 mm Hg for patients with diabetes.

While many studies have included small numbers of patients with previous stroke, there have been relatively few studies looking at secondary prevention in patients presenting with ischaemic or haemorrhagic stroke.

A systematic review identified seven RCTs looking at prevention of recurrent vascular events in patients with previous stroke or TIA. Lowering BP or treating established hypertension reduced stroke (OR = 0.76; 95% CI 0.63 to 0.92), non-fatal stroke (OR = 0.79, 95% CI 0.65 to 0.95), myocardial infarction (OR = 0.79; 95% CI 0.63 to 0.98) and total vascular events (OR = 0.79; 95% CI 0.66 to 0.95). No effect was seen on vascular or all-cause mortality. There was heterogeneity in the studies due to the class of drugs used, with beta blockers having no discernible effect. Reduction in stroke was related to the difference in systolic BP between treatment and control groups (p = 0.002).

One study of patients with a history of stroke (ischaemic or haemorrhagic) looked at blood pressure lowering with perindopril (an ACE inhibitor) alone, perindopril in combination with indapamide (a thiazide) or placebo. Patients unable to tolerate the combination were excluded during run in. BP lowering with perindopril and indapamide in combination resulted in a reduction in recurrent stroke and major vascular events. Five years of treatment resulted in one less fatal or non-fatal vascular event for every 11 patients treated (95% CI 9 to 16). BP lowering with a combination of perindopril and indapamide was shown to be safe in patients who have had a stroke or TIA and who are either hypertensive or normotensive.

In an open label study comparing eprosartan and nitrendipine for secondary prevention of stroke/TIA both drugs achieved target BP reductions. The cerebrovascular and cardiovascular end points were not significantly different.

A All patients with a previous stroke or TIA should be considered for treatment with an ACE inhibitor (for example, perindopril) and thiazide (for example, indapamide) regardless of blood pressure, unless contraindicated.

D Patients with hypertension should be treated to <140/85 mm Hg (<130/80 mm Hg for patients with diabetes).
Atrial fibrillation is present in up to 17% of all patients with stroke, and in up to 25% of strokes in patients aged over 80 years. Approximately 90% of left atrial thrombi are found in the left atrial appendage (LAA). Surgical occlusion of this structure may have the potential to reduce stroke. Atrial appendage obliteration can be done surgically (such as during valve replacement surgery) or by a percutaneous implanted left atrial appendage occlusive device. A single randomised controlled pilot study of LAA occlusion randomised 77 patients with risk factors for stroke undergoing coronary artery bypass to either LAA occlusion or control. LAA occlusion rose from 43% to 87% after performing four cases (p = 0.0001). Two patients had perioperative thromboembolic events (both in the occlusion group). There were no further strokes during a 13±7 month follow-up period. A case series of 66 patients who underwent percutaneous LAA occlusion with the WATCHMAN® LAA transcatheter system found that at 45 days 93% had successful sealing of the LAA. Two devices had embolised (successfully retrieved) and the device was subsequently modified. There were two cardiac tamponades, one air embolism and one delivery wire fracture. Two patients had TIA, and two patients died from unrelated causes. A further series of six patients undergoing surgical LAA closure at the time of valve surgery showed that only one patient had complete LAA occlusion, and one patient had a stroke during follow up.

No RCTs of atrial appendage occlusion were identified that focused on outcome. Left atrial appendage occlusion should only be considered as part of a randomised controlled clinical trial.

The role of carotid endarterectomy is discussed in section 11.

Approximately 40% of patients with ischaemic stroke have no underlying cause identified. Patent foramen ovale (PFO) with right to left shunt is more common in patients with cryptogenic stroke (44–66%) compared to the general population (up to 27%). In one study of patients with cryptogenic stroke and PFO on transoesophageal echo, who were treated with aspirin, the four year rate of recurrent stroke was 2.3% for PFO alone, 15.2% for PFO and atrial septal aneurysm, and 4.2% for neither.

A single RCT comparing anticoagulant and antiplatelet therapy in patients with cryptogenic stroke, which included sub-analysis of patients with PFO (present in 39% of patients with cryptogenic stroke), randomised patients between 30 and 85 years of age to either warfarin or aspirin. The rate of recurrent stroke or death at two years was 14.3% in those with PFO, compared to 12.7% without (OR = 0.86; CI 0.41 to 1.80). There was no significant difference in event rates between patients with cryptogenic stroke and PFO treated with aspirin (17.9%, n = 56) and those treated with warfarin (9.5%, n = 42; hazard ratio, HR = 0.52; 95% CI 0.16 to 1.67; p = 0.28). As this was a substudy, it was not powered to demonstrate superiority of one therapy in patients with PFO.

Although no RCTs of closure of PFO compared to medical therapy were identified, evidence from a systematic review of case series suggests that percutaneous transcatheter closure of PFO may reduce the risk of recurrent stroke more than medical therapy alone. The review identified six studies (895 patients) looking at medical management of PFO, and 10 studies (1,355 patients) looking at transcatheter closure. Medical therapy varied by type and dose (aspirin, warfarin and clopidogrel). There was a trend towards an increased incidence of recurrent events with increasing age. With medical therapy, the incidence of stroke or TIA after one year of follow up ranged from 3.8–12%. With transcatheter closure of PFO, TIA or stroke incidence was 0-4.9%. The incidence of major or minor procedural complications was 1.45% and 7.9% respectively. Patients in the medically treated groups were at higher prevalence of risk factors for atherosclerosis.
B Patients with cryptogenic stroke and PFO should be treated with antiplatelet therapy to reduce the risk of recurrence.

D Transcatheter closure of PFO may be considered for patients with recurrent cryptogenic stroke on optimal medical management.
10 Preventing recurrent stroke in patients with primary intracerebral haemorrhage

There is little evidence on prevention of recurrent vascular events following primary intracerebral haemorrhage.

10.1 BLOOD PRESSURE REDUCTION

An RCT of secondary prevention in patients who had haemorrhagic stroke concluded that lowering blood pressure (non-acutely) following ICH using a combination therapy of ACE inhibitor and thiazide diuretic helps to prevent further vascular events.\textsuperscript{228} One group of patients received 4 mg perindopril and a second group received combination therapy of 4 mg perindopril and 2.5 mg indapamide.\textsuperscript{228} Only 10\% of the study population had haemorrhagic stroke, and these patients were younger with a mean age of 61 years compared to 64 for patients with ischaemic stroke. The risk reduction was greater for patients with (primary) haemorrhage. For ICH the RRR was 76\% (95\% CI 55 to 87) for combination therapy and 1\% (95\% CI -75 to 42) for perindopril alone compared to placebo.

A Lowering blood pressure (non-acutely) following ICH using a combination therapy of ACE inhibitor and thiazide diuretic should be considered to prevent further vascular events.

10.2 ANTIPLATELET AGENTS

A systematic review on the safety of antithrombotic agents for patients with ICH concluded that aspirin should not be used acutely when the risk of future vascular events is low. The use of aspirin in the acute phase of ICH may be justified if there is a high risk of a cardiac ischaemic event.\textsuperscript{240}

B The use of aspirin following ICH is not recommended to prevent further vascular events when the risk of recurrence is low.

C The use of aspirin following ICH may be considered when there is a high risk of cardiac ischaemic events.

10.3 ANTICOAGULANTS

No clinical trials were identified describing the use of anticoagulants after ICH. A decision analysis based on assumptions of risk of recurrent ICH and the risks associated with aspirin and warfarin therapy concluded that anticoagulation cannot be safely recommended for atrial fibrillation following either a lobar or deep ICH unless an individual is at very high risk of ischaemic stroke.\textsuperscript{241} Aspirin may be a reasonable strategy for treating those with a prior deep ICH and an intermediate or higher risk of ischaemic stroke.\textsuperscript{241}

D Anticoagulation therapy following ICH is not recommended.

In patients with a very high risk of further thrombotic or cardiac ischaemic events specialist advice should be sought.
10.4 STATINS

An RCT of statin therapy to prevent recurrent stroke included 4,731 patients, 93 of whom had haemorrhagic stroke. Forty five patients were recruited to the treatment arm and received 80 mg of atorvastatin and forty eight received placebo. Individual outcomes for these patients were not reported and the numbers were too small to be meaningful. In the treatment group there were 218 ischaemic strokes and 55 haemorrhagic strokes compared to 278 ischaemic and 33 haemorrhagic strokes in the placebo group. There were more haemorrhagic strokes in the atorvastatin group giving a hazard ratio of 1.66 (95% CI 1.08 to 2.55). The absolute risk increase was 0.9% giving an NNH of 107 over five years.

There are risks and benefits of statin treatment in this population and the potential risk of intracerebral haemorrhage should be considered (see section 9.2).

A Statin therapy after haemorrhagic stroke is not routinely recommended unless the risk of further vascular events outweighs the risk of further haemorrhage.

☑ In this group of patients, their overall vascular risk profile should be taken into account when considering the risks and benefits of statin.
11 Carotid intervention

11.1 CAROTID ENDARTERECTOMY

11.1.1 SYMPTOMATIC CAROTID ARTERY DISEASE

Meta-analysis\(^{242}\) and analysis of pooled data from three RCTs\(^{243}\) comparing best medical treatment with best medical treatment plus carotid endarterectomy in over 6,000 patients showed surgery to be highly effective in patients with severe carotid artery stenosis (≥70% by NASCET method, without near occlusion nor occlusion, see Annex 9), and modestly effective in patients with moderate stenosis (50-69% by NASCET method). These studies were performed in patients without severe disability (mRS ≤ 2; see Annex 3).

Subsequent studies also found no evidence to support the traditional view that endarterectomy should be delayed in patients with minor stroke who are neurologically stable.\(^{244, 245}\) In patients with 50-69% stenosis (by NASCET method) the only statistically significant benefit occurred if surgery was performed within two weeks of the event (see Table 2).\(^{243}\)

Table 2 Number needed to treat to prevent one ipsilateral stroke at five years in patients with ≥50% stenosis by NASCET method\(^{243}\)

<table>
<thead>
<tr>
<th>Time of surgery post primary event</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>within 2 weeks</td>
<td>5</td>
</tr>
<tr>
<td>2 to 4 weeks</td>
<td>10</td>
</tr>
<tr>
<td>4 to 12 weeks</td>
<td>18</td>
</tr>
<tr>
<td>longer than 12 weeks</td>
<td>125</td>
</tr>
</tbody>
</table>

A systematic review of operative risk in relation to timing of surgery did not demonstrate an excess risk from early surgery compared to late surgery in neurologically stable patients.\(^{246}\)

Published risks from carotid endarterectomy did not significantly change between 1985 and 2001,\(^{247}\) with a 1.4%-2.9% risk of death and a 4.2%-6.5% risk of death or stroke combined. Reported complication rates were lower in studies where non-neurologists made the postoperative assessment.

In patients with a progressing neurological deficit or stuttering stroke, there is a lack of evidence about whether surgery should be performed as an emergency and no recommendation can be made to support this.

Pooled analysis showed greater benefit of CEA in older patients (in patients with 50-99% stenosis by NASCET method).\(^{243}\) The absolute risk reduction with surgery in terms of five-year cumulative risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after surgery was 19.2% (95% CI 10.2% to 28.2%) in those aged 75 or over, 8.6% (95% CI 4.2% to 13.0%) in those aged 65-74 and 5.6% (95% CI 1.6% to 9.6%) in those less than 65 years of age. This is despite an increase in postoperative mortality in older patients.\(^{248}\)

Only 10% of patients in the analysis were over 75 years of age and very few were over 80 years.
Meta-analysis and subgroup analysis of pooled data show that women gain less benefit than men from carotid endarterectomy (for patients with 50-99% stenosis). The NNT to prevent one stroke at five years is nine for men and 36 for women. There is clear benefit in women with 70-99% stenosis but not in those with 50-69% stenosis. This is driven by a higher operative risk in women and more rapid reductions in risk of stroke recurrence on medical therapy with time in women.

A All patients with carotid artery territory stroke (without severe disability, mRS ≤ 2) or transient ischaemic attack should be considered for carotid endarterectomy as soon as possible after the index event.

A Carotid endarterectomy (on the internal carotid artery ipsilateral to the cerebrovascular event) should be considered in all:
- male patients with a carotid artery stenosis of 50-99% (by NASCET method)
- female patients with a carotid artery stenosis of 70-99%.

B For all patients, carotid endarterectomy should be performed as soon as the patient is stable and fit for surgery, ideally within two weeks of event.

B There is no justification for withholding carotid endarterectomy from older patients who are considered fit for surgery.

A All patients undergoing carotid endarterectomy should receive optimal medical therapy in addition to surgery.

☐ Surgery should be performed by specialist surgeons in centres that participate in formal audit of operative outcomes.

A proportion of patients who are severely disabled immediately following their stroke event can make rapid recovery such that they meet the criteria used in the studies (mRS ≤ 2).

☐ Patients who are severely disabled immediately following their stroke event should be considered for carotid endarterectomy if they recover sufficiently to meet the criteria for surgery.

11.1.2 ASYMPTOMATIC CAROTID ARTERY DISEASE

A systematic review of three RCTs (5,223 patients) showed that CEA for asymptomatic carotid stenosis reduces the risk of ipsilateral stroke by around 30% over three years compared to medical treatment (see Table 3). Two of the trials recruited patients with stenosis of 60% or greater reduction in diameter determined by non-invasive tests or angiogram and the third 50-99% diameter stenosis. The absolute risk reduction is small (around 1% per annum) while the rate of perioperative stroke or death is approximately 3%. Any benefit would be negated by a higher preoperative complication rate, suggesting that only operators with a complication rate less than 3% should perform CEA in patients with asymptomatic carotid stenosis. The relative risk of perioperative stroke or death or any subsequent stroke was 0.69 (95% CI 0.57 to 0.83) and the RR of perioperative stroke or death or any subsequent ipsilateral stroke was 0.71 (95% CI 0.55 to 0.90). There was a non-significant trend toward fewer events (any stroke or death) in the surgical group. Subgroup analyses comparing older and younger patients, and men and women were inconclusive, although there was a trend to less benefit in women and older patients.
Table 3 Number of patients with asymptomatic carotid artery disease needed to treat with CEA to prevent an unfavourable outcome within three years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NNT</th>
</tr>
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<tbody>
<tr>
<td>Perioperative stroke or death or ipsilateral stroke</td>
<td>59</td>
</tr>
<tr>
<td>Perioperative stroke or death or any subsequent stroke (primary outcome)</td>
<td>36</td>
</tr>
<tr>
<td>Any stroke or death</td>
<td>49*</td>
</tr>
</tbody>
</table>

*not significant

A CEA should be considered for asymptomatic patients with high grade carotid stenosis and no ipsilateral event for at least six months.

A CEA may be of more benefit for patients who:
- are < 70 years of age
- are male
- have bilateral disease.

B CEA should only be performed by operators with a low (< 3%) perioperative stroke or death rate.

11.1.3 PATIENTS WITH CAROTID DISEASE SCHEDULED FOR CARDIAC SURGERY

There is a lack of good quality evidence for surgical interventions in patients with carotid disease and asymptomatic for TIA/stroke who are scheduled for cardiac surgery.

☑ Routine carotid endarterectomy prior to coronary artery bypass graft (CABG) is not recommended in patients with asymptomatic carotid artery stenosis.

11.1.4 CAROTID SURGERY TECHNIQUE

A meta-analysis, based on seven RCTs and quasi-randomised controlled trials, involving 1,307 operations in 1,127 patients concluded that patch closure was associated with a significant reduction in all strokes (OR = 0.33), ipsilateral strokes (OR = 0.31) and combined stroke and death (OR = 0.39). There was no significant reduction in death alone, although the total number of deaths was small, only 10 deaths in the six trials with available data (10/1019, overall risk = 1.0%). It remains unclear whether patching is associated with a higher or lower perioperative mortality than primary closure (OR = 0.73; 95% CI 0.20 to 2.60; p = 0.6).

A Patch angioplasty should be used as the closure method in all carotid endarterectomies performed by conventional methods.

A well conducted meta-analysis of five RCTs comparing conventional carotid endarterectomy with eversion method in 2,465 patients (2,589 arteries) concluded that there was no significant difference in perioperative stroke or death rate and stroke during follow up.

A Changing surgical technique from conventional carotid endarterectomy to eversion method is not recommended.
A meta-analysis of seven RCTs (554 operations) and 41 non-randomised controlled trials (25,622 operations) found no reliable evidence to guide the choice between local or general anaesthesia for patients undergoing carotid surgery.252

The choice of anaesthetic technique for patients undergoing surgery should be made by the individual operator/anaesthetist.

A systematic review found no data to support or refute the use of routine shunting over selective shunting in CEA. 253

11.2 CAROTID ANGIOPLASTY AND STENTING

A Cochrane review of carotid angioplasty and stenting (CAS) included seven RCTs (involving 941 patients) comparing endovascular treatment with carotid endarterectomy or medical therapy, and a further five RCTs (involving 2,286 patients) comparing CAS with surgery, which were stopped early.254 Not all studies were included in each analysis due to differing methods and reporting of results. Some studies included symptomatic and asymptomatic patients. Meta-analysis used fixed-effect and random-effects models.

There was a statistically significant excess of deaths or strokes within 30 days of treatment with CAS compared to CEA (OR = 1.39; 95% CI 1.05 to 1.84; p = 0.02) using the fixed-effects model. This result lost statistical significance using the random-effects model (OR = 1.44; 95% CI 0.91 to 2.26; p = 0.12). There was no statistical difference between treatments for the end points of 30-day stroke, myocardial infarction or death or stroke during long term follow up. Follow-up data to a maximum of 36 months were available for CAS. Endovascular therapy significantly reduced the risk of cranial nerve injury, OR = 0.07 (95% CI 0.03 to 0.20; p < 0.00001). only two of the seven studies included data on cerebral protection devices and found no significant difference in risk of death or stroke at 30 days between endovascular treatment with or without a cerebral protection device (OR = 0.77; 95% CI 0.41 to 1.46; p = 0.43, with significant heterogeneity). No significant difference was found comparing endovascular treatment and surgery in asymptomatic patients (OR = 1.06; 95% CI 0.16 to 6.94; p = 0.96), although only two trials were available, one of which recorded no deaths or strokes at 30 days. Two small studies comparing endovascular with medical treatment, in patients considered unfit for surgery, failed to show any significant difference in risk of stroke or death at 30 days (OR = 0.39; 95% CI 0.14 to 1.14; p = 0.09).

Carotid angioplasty and stenting is not recommended outwith ongoing randomised controlled trials.

Angioplasty and stenting may be considered for patients with high risk of stroke recurrence and a “hostile surgical neck” (for example, previous radical neck dissection or radiotherapy).

11.3 PERIPROCEDURAL ANTIPLATELET OR ANTITHROMBOTIC THERAPY

A systematic review suggested that antiplatelet treatment given after CEA reduces the rate of stroke, but not of death.255 Antiplatelet treatment was started before CEA in four of the six RCTs reviewed, but five days and up to three months after CEA in the other two studies. The individual study results do not conclusively show that one regimen is superior to the other.

Antiplatelet treatment is described in section 5.2 and antiplatelet therapy to prevent recurrent stroke is discussed in section 9.1.

Standard antiplatelet treatment should be given after CEA.
12 Promoting lifestyle changes

Patients often have numerous risk factors for recurrent stroke. Reducing the risk of recurrent stroke may require the patient to make significant lifestyle changes. A combination of three strategies for preventing recurrent stroke (dietary modification, exercise, aspirin, a statin and an antihypertensive) may result in a cumulative RR reduction of 80%.

12.1 INTERVENTIONS TO PROMOTE LIFESTYLE CHANGE

Patients with stroke may find it challenging to change their lifestyle especially if they are trying to reduce several risk factors. Patients not only need advice about lifestyle changes but support from healthcare professionals to make changes.

An observational study of 60 patients in a population of people at risk of stroke compared simple advice or motivational interviewing with behavioural change against a control group. Most success was achieved when patients chose which risk factor to focus on, when milestones were set and when one change was made at a time. The model used was FRAMES (see Table 4) together with the identification of stages of readiness to change; pre-contemplation, contemplation, preparation, action and maintenance. The patients had to show a readiness to change for the intervention to be successful. Although the study was designed to investigate risk of stroke it is reasonable to extrapolate the evidence to secondary prevention.

Table 4 The FRAMES model of behavioural change

| Feedback                                      | patient receives information about current status |
| Responsibility                                | patient assumes responsibility for change       |
| Advice                                       | patient receives suggestions that will help him or her in the change process |
| Menu                                         | patient receives a number of alternative strategies for modifying the problem behaviour |
| Empathy                                      | patient receives warm support and respect        |
| Self efficacy                                | patient develops an “I can do this” attitude     |

Patients should be encouraged to take responsibility for their own health and be supported to identify, prioritise, and manage their risk factors.

12.2 ALTERING DIETARY FAT INTAKE

12.2.1 SATURATED FAT

A Cochrane review of 27 trials (18,196 participants) examined the effect of reduction or modification of dietary fats for at least six months on reducing serum cholesterol levels and on total and cardiovascular mortality and morbidity. The review included trials of high- (seven), moderate- (six) and low-risk (14) participants. Trials involving high-risk participants included men only. There was no significant effect on total mortality (rate ratio of 0.98; 95% CI 0.86 to 1.12), a trend towards protection from cardiovascular mortality (rate ratio of 0.91; 95% CI 0.77 to 1.07), and significant protection from cardiovascular events (rate ratio of 0.84; 95% CI 0.72 to 0.99). This effect was non-significant if studies at high risk of bias were removed. Trials with at least two years of follow up provided stronger evidence of protection against cardiovascular events (rate ratio of 0.76; 95% CI 0.65 to 0.90). The reviewers concluded that there is a small but potentially important reduction in cardiovascular risk with a reduction or modification of dietary fat intake, seen particularly in trials of longer duration.

Diets low in total and saturated fats should be recommended to all for the reduction of cardiovascular risk.
12.2.2 OMEGA-3 FATS

There is conflicting evidence from two systematic reviews on the benefits associated with increased consumption of omega-3 fats for the prevention of cardiovascular or stroke disease.\textsuperscript{257,258} It is not clear that dietary or supplemental omega-3 fats change total mortality, cardiovascular events or cancer in people with, or at risk of, cardiovascular disease.\textsuperscript{257}

For secondary prevention most trials reported that fish oil significantly reduced all-cause mortality, MI, cardiac and sudden death, and stroke. Effects on stroke were inconsistent, and the evidence suggests that increased consumption of omega-3 fats from fish or fish oil, but not of α-linolenic acid (ALA, found in certain vegetable oils, such as flax seed, soybean, walnuts, canola) may be beneficial. The review also stated that five cohort studies provided no evidence to support the hypothesis that fish consumption reduces the risk of stroke.\textsuperscript{258}

In view of this uncertain effect and in order to avoid conflicting dietary advice, no change is recommended in the current dietary guidelines (two 140 g portions of fish, one of which should be a fatty fish, per week).\textsuperscript{259}

- All individuals should eat at least two portions of fish per week, one of which should be a fatty fish.

No evidence was identified to advise people to stop taking supplemental omega-3 fats.

12.3 REDUCING DIETARY SALT

A meta-analysis of 28 trials on the effect of moderate salt reduction on blood pressure demonstrated that a modest reduction in salt intake for four or more weeks has a significant effect on blood pressure in both hypertensive and normotensive individuals. The pooled estimates of blood pressure fall were 4.96/2.73 ± 0.40/0.24 mm Hg in hypertensive patients (p<0.001 for both systolic and diastolic) and 2.03/0.97 ± 0.27/0.21 mm Hg in normotensive individuals (p<0.001 for both systolic and diastolic). A reduction of salt intake of 6 g per day (100 mmol or 2.3 g sodium per day) predicted a fall in blood pressure of 7.11/3.88 mm Hg (p<0.001 for both systolic and diastolic) in hypertensive patients and 3.57/1.66 mm Hg in normotensive individuals (systolic: p<0.001; diastolic: p<0.05).\textsuperscript{260}

A Cochrane review of advice to reduce salt intake lasting at least six months also reported small but significant benefits to blood pressure. Long term maintenance of low sodium diets was difficult for individuals, even with considerable advice, support and encouragement.\textsuperscript{261}

The Food Standards Agency has recommended that adults should consume no more than 6 g of salt per day (approximately equivalent to one teaspoonful).\textsuperscript{262}

- People with hypertension should be advised to reduce their salt intake as much as possible to lower blood pressure.
- All individuals should aim to consume less than 6 g of salt per day.
12.4 FRUIT AND VEGETABLE CONSUMPTION

A meta-analysis of cohort studies addressing primary prevention of all cerebrovascular events including ischaemic stroke, haemorrhagic stroke and TIA showed that the risk of stroke decreased in a dose-responsive fashion as fruit and vegetable consumption increased. The risk of stroke was decreased by 11% (RR = 0.89; 95% CI 0.85 to 0.93) for each additional portion per day of fruit, by 5% (RR = 0.95; 95% CI 0.92 to 1.97) for fruit and vegetables and by 3% (RR = 0.97, 0.92 to 1.02, which was non-significant) for vegetables.

Many observational studies of fruit consumption correlate with healthy behaviours and lifestyle in general, for example smoking less, exercising more and having a higher level of education.

Increasing fruit and vegetable consumption is recommended to reduce risk of stroke or TIA.

12.5 VITAMIN SUPPLEMENTS

An association between hyperhomocysteinaemia and vascular disease including stroke has been demonstrated in epidemiological studies. There is a twofold greater risk of stroke associated with hyperhomocysteinaemia.

A trial of vitamin B_{12} and folate in patients with stroke found that lowering total homocysteine by 2 mmol/L (0.27 mg/l) with high-dose B-multivitamin therapy did not prevent recurrent stroke in patients with recent ischaemic stroke. There is insufficient evidence to make a recommendation about vitamin therapy to prevent recurrent stroke. A study of vitamins B_{12}, B_{6} and folic acid therapy in patients with previous stroke or TIA is ongoing.

Vitamin supplementation is not recommended in patients following ischaemic stroke.

12.6 WEIGHT REDUCTION

One systematic review of RCTs of diet to reduce weight, which evaluated the effect on blood pressure, was identified. Only small numbers of patients were included in the trials (six trials including 361 participants). Dietary interventions to reduce weight were moderately effective at reducing blood pressure. Diets producing weight loss in the range of 3% to 9% body weight were partially associated with blood pressure reductions of about 3 mm Hg systolic and diastolic. The review was underpowered to detect differences in morbidity or mortality outcomes.

Patients and individuals at risk of cardiovascular disease, who are overweight, should be targeted with interventions designed to reduce weight, and to maintain this reduction.

12.7 SMOKING

Tobacco smoking is strongly and dose-dependently associated with all cardiovascular events, including coronary heart disease (CHD), stroke, peripheral arterial disease (PAD) and cardiovascular death. Smoking cessation reduces these risks substantially, although the decrease is dependent on the duration of cessation.

All people who smoke should be advised to stop and offered support to help facilitate this in order to minimise cardiovascular and general health risks.

12.8 ALCOHOL

When giving advice to patients with stroke, the current general advice of no more than two to three units of alcohol per day for women and no more than three to four units of alcohol per day for men, with at least two drink-free days per week for both men and women, should be recommended.
12.9 **EXERCISE**

Physical activity is an important aspect of lifestyle that patients at risk of recurrent stroke can modify. A meta-analysis of epidemiological data from large observational studies looking at primary prevention (not stroke specific) indicated that physical activity may reduce the risk of stroke. Increased occupational activity was associated with a lower risk of ischaemic stroke compared to a moderate or inactive occupation. Overall moderate occupational activity gave a 15% lower risk in total stroke compared to inactive people. The majority of these studies were carried out at least six months, and in some cases up to 12 years post stroke and involved participants who were ambulatory. It may be reasonable to extrapolate this information to secondary prevention.

There may be many reasons why older people do not participate in physical activities.

- lack of interest
- lack of access to a car
- shortness of breath
- joint pain
- dislike of going out alone
- perceived lack of fitness
- lack of energy
- doubting that exercise can lengthen life.

A systematic review of physical fitness training after stroke identified 12 trials (289 patients) with an intervention to improve either muscle strength with or without cardiorespiratory fitness. Many of the trials had participants who volunteered and were ambulatory. Trial quality was varied and outcome measures were very diverse. The benefits of physical fitness training appeared to be short term only. Consequently, few conclusions can be drawn about the impact of physical fitness training. A second systematic review of the same data showed no evidence of effect rather than evidence of no effect. Individual studies showed an increase in quality of life and reduction in the level of impairment. Secondary prevention was not an outcome but positive effects from cardiovascular training on gait speed, stair climbing, human activity profile, motor function, workload and exercise time were reported. A study comparing three 40 minute sessions of treadmill training a week for six months with a programme of common components of conventional rehabilitation showed that treadmill training was superior at improving cardiovascular fitness. In a small study (13 participants) patients in a water-based programme of three one hour sessions per week for eight weeks showed significant improvement in cardiovascular fitness over the control group at least one year post stroke.

An observational study of 25 patients one to 12 years post stroke taking part in an exercise group demonstrated that improvement in balance and functional activity could be acquired well after the initial stroke episode and improvement was retained at least one month after the programme stopped. The benefits of physical exercise, in terms of function and quality of life, tend to be lost after the formal programme of exercise stops.

Nationally recognised recommendations state that all adults should accumulate 30 minutes of moderate activity on most days of the week. National guidance is available on the most effective way to promote physical activity.

- **B** Lifelong participation in programmes of exercise after stroke should be encouraged.
- **☑** Exercise programmes should ideally be delivered by exercise instructors with knowledge and training in exercise and stroke.

Many stroke patients are more disabled than those included in these studies, have language and cognitive problems, coexisting physical disease and are elderly. There is a paucity of data on more disabled patients.
13 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing the acute phase of stroke with patients and carers and in guiding the production of locally produced information materials.

13.1 PROVIDING INFORMATION AND SUPPORT

13.1.1 INFORMATION NEEDS OF PATIENTS AND CARERS IN THE ACUTE PHASE OF STROKE

The information needs of patients with stroke change over time.

The overall effectiveness of information provision has not been conclusively demonstrated. Evaluation of structured information provision and the strategies used to provide it are sparse.\textsuperscript{286} Verbal and written information may be more effective than either format alone and information individualised to the patient rather than general information more beneficial. No conclusive evidence was identified on how to tailor information.\textsuperscript{286}

A systematic review suggested that information provision and educational sessions are more effective than provision of a leaflet alone.\textsuperscript{286} Success can be limited if strategies of information provision are unacceptable. In one study, 58% of patients failed to attend three or more outpatient educational sessions, although the reason for non-attendance was not detailed.

One study showed that younger patients required more medical information as well as having questions concerning exercise and post-stroke sexual activities. Women ranked receiving information on post-stroke management higher than men.\textsuperscript{287} Carers’ information requirements also differ with age and sex.\textsuperscript{288} Female relatives place more importance on information. Relatives with higher educational level place less importance on counselling.

In hospital 77% of patients and carers wanted information on preventing further strokes, 65% on where to obtain further information, 65% on causes of stroke, 61% on risk factors for stroke, 60% on recovery, 54% on what a stroke is and 53% on stroke-related medications.\textsuperscript{286} Seventy five per cent of carers wanted information on the emotional or psychological effects of stroke.\textsuperscript{289} At six months the most frequently desired topic by both patients and carers was prevention of further strokes (67% of people surveyed), where to obtain more information (33%) and the cognitive effects of stroke (33%).\textsuperscript{289}

In one study patients were given a guide on discharge, which they could use as a reference tool. Patients and carers suggested topics for the guide. The patients were all younger with few disabilities and had healthy carers. The study showed that 59% of patients and caregivers wanted to receive information once or twice, 22% three to six times or more frequently, 19-59% would like to receive information within 24 hours and 22% on day one to two weeks after the event. The preferred information was medical information about the course of the disease, its cause, consequences and treatment (see Table 5).\textsuperscript{290} At six months patients and carers still require information and in a self reporting study some people may have forgotten between discharge and six months that they had received information.\textsuperscript{289} A questionnaire of knowledge of stroke showed that family members do not retain information offered concluding that information should be given frequently.\textsuperscript{291}

In one study 119 out of 252 patients responded to a questionnaire about the usefulness of a patient-held record. Twenty seven per cent had lost it, only 59% read it and two thirds said that they had difficulty in getting staff to record in it. Half of patients thought it was more trouble than benefit.\textsuperscript{292}

Material given to patients and carers may not be suitable. One study showed that the readability and accessibility of material was equivalent to 11th grade (UK equivalent of fourth year at secondary school, age 15). The average ability of the carers was 9th grade (second year at secondary school, age 13) and the patients 7-8th grade (primary 7-first year at secondary school, age 11-12).\textsuperscript{289}
Table 5 The five most important issues identified by patients and carers looking for information

<table>
<thead>
<tr>
<th>Issue</th>
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<tbody>
<tr>
<td>Medical Information</td>
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<tr>
<td>Consequences of stroke</td>
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<tr>
<td>Experiences of other patients and caregivers</td>
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<tr>
<td>Home recovery</td>
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<tr>
<td>Advice for the partner and the social circle</td>
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</tbody>
</table>

- Each patient should be individually assessed on his or her readiness to receive information.
- Healthcare professionals should take a patient’s age, gender, educational status and communication support needs into account when assessing their need for information.
- Information should be offered to patients and carers in a variety of formats, including easy access.
- Information should be tailored to the phase of the patient’s journey.
- Information should be repeated and re-offered at appropriate intervals.
- Information giving should be documented to allow consistency.

13.1.2 SUPPORT NEEDS OF CARERS IN THE ACUTE PHASE OF STROKE

No evidence was identified about structured support for carers.

Fifty per cent of family members in one study were overly optimistic about the functional ability of the patient at discharge. In a study of 14 patients, semistructured interviews showed that carers are unprepared for the impact of caring for someone who has had a stroke.

Relatives’ needs are reported as information, counselling (communication and support) and accessibility to staff. They often find the first three days of hospitalisation very emotional and tiring. In this period most relatives focus on the patient and their illness rather than their own needs. Carers may have to adapt to altered or additional roles (for example, driving) and their relationship with the patient may change.

Carers can feel that they lack knowledge and are unable to help or cope. They often require information that they feel may not have been provided to them by staff. The carer’s burden is lessened when they are able to care for the person with stroke in hospital.

A systematic review of intervention studies for caregivers of people after a stroke studied four types of support programmes targeted at caregivers’ problems and needs:

- providing specialist services
- (psycho) education
- counselling
- social support by peers.

Counselling programmes appeared to have most positive outcomes in terms of health related quality of life, satisfaction, confidence and knowledge, problem solving skills, emotional state, burden and caregiver preparedness. The aim of counselling was to teach caregivers coping strategies to reduce stress. Counselling was more effective than education alone. Up to three years after counselling confidence and knowledge about patient care and use of active coping strategies were increased. Counselling is a time consuming intervention with around about eight hours of individual counselling given. More research is required taking into account the needs of caregivers.
Training caregivers in basic skills reduces the burden of care and improves quality of life for patients and carers. Three to five 30-40 minute sessions of training defined by the needs of the patient were effective. The type of training offered in the study is shown in Table 6. At three and 12 months patients whose caregivers had received training reported significantly improved quality of life and mood outcomes and burden of care was reduced and quality of life and mood outcomes were improved in caregivers. The study was biased towards middle class, fit participants and may not be applicable to all patients with stroke and their carers. There were no data on which type of training was most useful. The study was in the rehabilitation setting but the results may be extrapolated to the acute setting.

Table 6 Caregiver training provided by healthcare professionals

<table>
<thead>
<tr>
<th>Instruction on common stroke-related problems</th>
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<tbody>
<tr>
<td>positioning</td>
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<tr>
<td>prevention of bed sores</td>
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<tr>
<td>continence</td>
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<tr>
<td>nutrition</td>
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<tr>
<td>gait facilitation</td>
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<tr>
<td>advice on benefits and local services</td>
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</table>

<table>
<thead>
<tr>
<th>Hands on training tailored to the needs of the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>moving and handling</td>
</tr>
<tr>
<td>activities of daily living and communication</td>
</tr>
<tr>
<td>mobilisation</td>
</tr>
</tbody>
</table>

Healthcare professionals should discuss the caring role and its implications with relatives.

Healthcare professionals should actively involve carers and find out what support they need.

Caregivers should be offered ongoing practical information and training individualised for the needs of the person for whom they are caring.

Carers should be given advice about where to seek support (for example, GP, voluntary organisations, etc).

Carers’ support needs should be addressed prior to patient discharge.

A named healthcare professional should be responsible for coordinating discharge.

13.2 SOURCES OF FURTHER INFORMATION

13.2.1 NATIONAL ORGANISATIONS SPECIFIC TO STROKE

Chest, Heart & Stroke Scotland
65 North Castle Street, Edinburgh, EH2 3LT
Tel: 0131 225 6963 • Fax: 0131 220 6313 • Advice Line: 0845 077 6000
www.chss.org.uk • Email: admin@chss.org.uk

Offers rehabilitation and support to people affected by stroke through the Volunteer Stroke Service (VSS). The CHSS Advice Line offers confidential, professional advice from trained nurses on all aspects of chest, heart and stroke illness, backed up by free booklets, fact sheets, DVDs and videos.
Connect
16-18 Marshalsea Road, London, SE1 1HL
Tel: 020 7367 0840 www.ukconnect.org

Works to promote effective services, new opportunities and a better quality of life for people living with aphasia. Useful publications for people with aphasia and carers of people with aphasia are available.

Different Strokes (Scotland)
53 Elmore Avenue, Glasgow, G44 5BH
Tel: 0141 569 3200 www.differentstrokes.co.uk • Email: glasgow@differentstrokes.co.uk

Helps stroke survivors of working age to optimise their recovery, take control of their own lives and regain as much independence as possible by providing a national network of weekly exercise classes, practical, easy to use information, newsletters, interactive website and ‘StrokeLine’ telephone service.

DIPEX. Personal experiences of health and illness
www.dipex.org/stroke

The High Blood Pressure Foundation
Department of Medical Sciences, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU
Tel: 0131 332 9211

Speakability
1 Royal Street, London SE1 7LL
Helpline: 080 8808 9572 www.speakability.org.uk

Offers impartial information and support for people with aphasia and their carers through its helpline, website and training courses, and distributes its own fact sheets, low-cost publications and videos.

The Stroke Association
Links House, 15 Links Place, Edinburgh EH6 7EZ
Tel: 0131 555 7240 • Fax: 0131 555 7259 • National Stroke Helpline: 0845 30 33 100 www.stroke.org.uk • Email: scotland@stroke.org.uk

Funds research into prevention, treatment and better methods of rehabilitation, and helps stroke patients and their families directly through its Rehabilitation and Support Services. It also produces publications including patient leaflets, Stroke News (a quarterly magazine) and information for health professionals.

strokeinfoplus
www.strokeinfoplus.scot.nhs.uk

Provides access to stroke patient leaflets, and information on stroke support groups, social security benefits, medicines and treatment, and the evidence and clinical trials on which treatment is based.

13.2.2 LOCAL ORGANISATIONS SPECIFIC TO STROKE

Inverclyde Centre for Independent living Stroke Rehabilitation Group
10-16 Gibshill Road, Greenock, Inverclyde, PA15 2UP
Tel: 01475 714350

Together Opening Doors
Marjorie Hall, Millgreen House Millgreen, Dumfries, DG2 7QY

The Way Head Group
Corona Marshall, 52 Campsie Drive, Milngavie, East Dumbartonshire, G62 8HX
Tel: 0141 570 2869
13.2.3 NATIONAL ORGANISATIONS

DVLA
Drivers Medical Group, DVLA, Swansea, SA99 1TU
Tel: 0870 600 0301 (Monday to Friday, 8.00 am to 5.30 pm and Saturday, 8.00am to 1.00pm) • Fax: 0845 850 0095
www.dvla.gov.uk/medical.aspx • Email: eftd@dvla.gsi.gov.uk

Completed medical questionnaires can be returned by post, FAX, or email. Details of the specific medical condition can be noted by telephone, along with full name, date of birth and/or driver number (if known).
14 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

14.1 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

A National Clinical and Resource Impact Assessment based on recommendations identified by the guideline development group likely to have major resource implications will be available from the Scottish Health Technologies Group (www.nhshealthquality.org) in 2009. The assessment will summarise the likely resources required and the associated costs of implementing the guideline, with the objective of facilitating more rapid implementation.

14.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

14.2.1 MANDATORY CORE DATA SET

The clinically led Scottish Stroke Care Audit aims to improve the quality of care provided by the hospitals in all NHS Boards by collating and reporting upon data collected by the Managed Clinical Networks (MCNs). The system collects a mandatory core data set for each episode which leads a patient to be referred to a hospital. A minimum dataset has been defined which has the mandatory core data at its centre but which aims to provide information to reflect the quality of the stroke service. This dataset includes six variables which describe case mix and allows correction of case fatality and functional outcome data. This minimum dataset will provide information on:

- patient demographics
- the process of care and its appropriateness, and
- the performance of services in relation to the national clinical standards.

14.2.2 NATIONAL TIME-LIMITED AUDITS OF SPECIFIC ASPECTS OF STROKE SERVICE

Although the minimum dataset reflects aspects of stroke services for which there is very robust evidence that compliance will influence patient outcomes, the quality of many other aspects of stroke care also needs to be addressed. This can be achieved by defining an extended data set to be collected for each patient for a set period of time.
14.2.3 KEY POINTS TO AUDIT

In addition the guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- time to assessment of acute stroke patient
- time to assessment of TIA patient
- time to access proper multidisciplinary stroke unit
- time to brain imaging
- time to carotid assessment with duplex
- the performance of carotid duplex examinations when compared to other tests (usually CE-MRA)
- carotid endarterectomy outcomes compared between centres
- has recommended medication initiation occurred, where appropriate, prior to discharge from hospital (e.g., antiplatelet, statin, ACE inhibitor, diuretic).

14.3 ADDITIONAL ADVICE TO NHSScotLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

In February 2004 the Scottish Medicines Consortium (SMC) advised that alteplase (rt-PA) (Actilyse) is accepted for restricted use within NHSScotland for the treatment of acute ischaemic stroke (www.scottishmedicines.org.uk/smc/files/Alteplase.pdf).

The NHS QIS validated NICE (Single) Technology Appraisal Guidance No 122: Alteplase for the treatment of acute ischaemic stroke does not differ materially from the SMC recommendation.

The NICE Technology Appraisal Guidance No. 94: Statins for the prevention of cardiovascular events has been considered by NHS QIS. No important differences were identified and NHS QIS advises that it is as valid for Scotland as for England and Wales.
15 The evidence base

15.1 SYSTEMATIC LITERATURE REVIEW
The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO, and the Cochrane Library. The year range covered was 2000-2007. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

15.1.1 LITERATURE SEARCH FOR ECONOMIC ISSUES
A SIGN Information Officer conducted a literature search of the NHS Economics Evaluations Database (NEED) for studies that highlighted economic issues related to management of acute stroke.

15.1.2 LITERATURE SEARCH FOR PATIENT ISSUES
At the start of the guideline development process, a SIGN Information Officer conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to the acute phase of stroke. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group. A copy of the Medline version of the patient search strategy is available on the SIGN website.

15.2 RECOMMENDATIONS FOR RESEARCH
The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research have been identified:

15.2.1 MANAGEMENT OF SUSPECTED STROKE OR TIA
The most accurate methods of identification and early assessment of TIA and minor stroke in patients who need to be seen within 24 hours.

15.2.2 ASSESSMENT, DIAGNOSIS AND INVESTIGATION
The role of CT perfusion and MRI perfusion imaging as potential complementary modalities to guide thrombolysis therapy.

The role of single photon emission computed tomography (SPECT) and positron emission tomography (PET) for aiding diagnosis of stroke.

Assessment of computed tomography angiography accuracy compared with other standards for carotid imaging in patients with carotid territory TIA or stroke and/or retinal event.

Prospective trials of routine carotid imaging to determine whether carotid plaque composition or activity can influence therapy decisions.
15.2.3 TREATMENT OF ISCHAEMIC STROKE
Evaluation of the safety and efficacy of r-tPA in some patient groups, such as the very elderly (over 80 years) and those with rapidly improving symptoms.
Evaluation of imaging-based protocols for selection of patients suitable for r-tPa therapy.
Comparison of IV and IA thrombolysis for treatment of all types of stroke are required.
Randomised controlled trials of IA therapy in patients who fail to recanalise after routine IV thrombolysis.
Evaluation of dual therapies for the treatment of acute stroke and TIA.
Further evaluation of the use of mannitol and hypertonic saline in ischaemic stroke associated with raised intracranial pressure.
Assessment of horizontal head positioning in patients with acute ischaemic stroke.
Mechanical clot retrieval devices should be further evaluated in randomised controlled trials.
RCTs to investigate the clinical outcomes and the safety of administration of microbubble ultrasound contrast agents to increase recanalisation rates.

15.2.4 TREATMENT OF PRIMARY INTRACEREBRAL HAEMORRHAGE
Further RCTs to assess the efficacy of surgical interventions for acute primary intracerebral haemorrhage, addressing in particular:
- early surgical evacuation (for example, six hour time window) versus conservative treatment
- minimally invasive surgery including aspiration via burr hole or stereotaxy, with and without instillation of thrombolytic drugs, versus medical therapy and/or craniotomy
- standardised medical management of patients in both arms of future trials.
RCTs evaluating the thrombolysis in patients with PICH.
Evaluation of the efficacy of mannitol or other interventions to reduce raised ICP perioperatively in patients undergoing surgical evacuation.

15.2.5 OTHER CAUSES OF STROKE
Evaluation of endovascular stenting to treat extracranial cervical arterial dissection or cervical artery pseudo-aneurysms.
A comparison of the efficacy of anticoagulation with antiplatelet therapy for treating extracranial artery dissection.

15.2.6 PHYSIOLOGICAL MONITORING AND INTERVENTION
The role of continuous compared to frequent monitoring in the acute phase of stroke.
Further evaluation of the benefits and risks of blood pressure lowering in the acute phase of stroke.
Further assessment of the benefit of mobilising patients.
Evaluation of active positioning in the acute phase of stroke, including RCTs to assess the effect on cerebral blood flow of placing patients flat (0° head of the bed elevation).

15.2.7 PREVENTING RECURRENT STROKE IN PATIENTS WITH ISCHAEMIC STROKE
Transcatheter closure of PFO should be considered as part of an RCT for patients with a first cryptogenic stroke and PFO with right to left shunt.
15.2.8 CAROTID INTERVENTION
An RCT of surgical interventions, such as CEA in patients with carotid disease who are asymptomatic for TIA/stroke and are scheduled for cardiac surgery.

15.2.9 PROVISION OF INFORMATION
What information patients and carers need, how patients and carers are given information (verbal, written etc) and in what format (easy access etc).

15.2.10 PROMOTING LIFESTYLE CHANGES
Further research is required on:
- people who are more disabled by stroke
- exercise programmes beginning sooner after stroke
- how to motivate people to participate in lifelong exercise.

15.3 REVIEW AND UPDATING
This guideline was issued in 2008 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk.
16 Development of the guideline

16.1 INTRODUCTION
SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

16.2 THE GUIDELINE DEVELOPMENT GROUP

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
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<tr>
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</tr>
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<td>Dr Paul Neary</td>
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<tr>
<td>Mr Tony Scanlon</td>
<td>Lay representative, Glasgow</td>
</tr>
<tr>
<td>Dr Tim Shallcross</td>
<td>Consultant Physician, Caithness General Hospital</td>
</tr>
</tbody>
</table>
Mr Peter Stonebridge  Consultant in Vascular Surgery, Ninewells Hospital, Dundee
Mr Paul Teenan  Consultant Vascular Surgeon, Glasgow Royal Infirmary
Mrs Amanda Wong  Site Lead Physiotherapist, Queen Margaret Hospital, Dunfermline

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

16.2.1 PATIENT INVOLVEMENT

In addition to the identification of relevant patient issues from a broad literature search, SIGN involves patients and carers throughout the guideline development process in several ways. SIGN recruits a minimum of two patient representatives to guideline development groups by inviting nominations from the relevant “umbrella”, national and/or local patient focused organisations in Scotland. Where organisations are unable to nominate, patient representatives are sought via other means, for example, from consultation with health board public involvement staff.

Further patient and public participation in guideline development was achieved by involving patients, carers and voluntary organisation representatives at the National open Meeting (see section 16.3.1). Patient representatives were invited to take part in the peer review stage of the guideline and specific guidance for lay reviewers was circulated. Members of the SIGN patient network were also invited to comment on the draft guideline section on provision of information.

16.2.2 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group.

Dr Niall Campbell  General Practitioner, Hawick
Dr Judith Keighley  General Practitioner, Strathbrock Partnership Centre, Broxburn
Ms Avril Kerr  Nurse Practitioner, Strathbrock Partnership Centre, Broxburn
Dr Hamish MacRitchie  Consultant Radiologist, Borders General Hospital, Melrose
Dr Ron MacWalter  Consultant Physician of General and Acute Stroke Medicine, Ninewells Hospital and Medical School, Dundee
Ms Claire Ritchie  Occupational Therapist, Southern General Hospital, Glasgow
16.3 CONSULTATION AND PEER REVIEW

16.3.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 26th June 2007 and was attended by 317 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

16.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Malcolm Alexander  
Associate Medical Director, NHS 24

Dr Rodney Burnham  
Registrar, Royal College of Physicians, London

Ms Annette Cameron  
Speech and Language Therapist, Aberdeen

Dr George Crookes  
Clinical Director/Chief Operating Officer, NHS 24 and Interim Medical Director for the Scottish Ambulance Service

Dr Carol Davidson  
Director of Public Health, Ayrshire and Arran

Dr Katherine Henderson  
Emergency Department Consultant, St Thomas' Hospital, London

Dr Christine McAlpine  
British Geriatrics Society, London

Mr David Paul  
Lay Representative, Glasgow

16.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr Keith Brown  
Chair of SIGN; Co-Editor

Professor Tracey Howe  
Allied Health Professions

Dr Rajan Madhok  
The Royal College of Physicians and Surgeons of Glasgow

Ms Clare Mayo  
The Royal College of Nursing

Mrs Fiona McMillan  
Royal Pharmaceutical Society of Great Britain

Dr Safia Qureshi  
SIGN Programme Director; Co-Editor

Dr Graeme Simpson  
The Royal College of Physicians of Edinburgh

Dr Sara Twaddle  
Director of SIGN; Co-Editor

Dr Christine Walker  
The Royal College of Radiologists, Faculty of Radiology
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD/ABCD²</td>
<td>age, blood pressure, clinical features, and duration of symptoms</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin converting enzyme</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>ALA</td>
<td>α-linolenic acid</td>
</tr>
<tr>
<td>ARR</td>
<td>absolute risk reduction</td>
</tr>
<tr>
<td>BI</td>
<td>Barthel index</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CaNS</td>
<td>Canadian neurological scale</td>
</tr>
<tr>
<td>CAS</td>
<td>carotid angioplasty and stenting</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blockers</td>
</tr>
<tr>
<td>CC</td>
<td>common carotid</td>
</tr>
<tr>
<td>CCA</td>
<td>common carotid artery</td>
</tr>
<tr>
<td>CEA</td>
<td>carotid endarterectomy</td>
</tr>
<tr>
<td>CE-MRA</td>
<td>contrast-enhanced MRA</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CPASS</td>
<td>Cincinnati pre-hospital stroke scale</td>
</tr>
<tr>
<td>CT</td>
<td>computerised tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomography angiography</td>
</tr>
<tr>
<td>CVT</td>
<td>cerebral venous thrombosis</td>
</tr>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion weighted imaging</td>
</tr>
<tr>
<td>EDV</td>
<td>end diastolic velocity</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ECST</td>
<td>European Carotid Surgery Trial</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>European/Australasian Stroke Prevention in Reversible Ischaemia Trial</td>
</tr>
<tr>
<td>EVD</td>
<td>external ventricular drain</td>
</tr>
<tr>
<td>FAST</td>
<td>face arm speech test</td>
</tr>
<tr>
<td>FASTER</td>
<td>Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence</td>
</tr>
<tr>
<td>FAM</td>
<td>functional assessment measure</td>
</tr>
<tr>
<td>FES</td>
<td>first-ever-in-a-lifetime stroke</td>
</tr>
<tr>
<td>Acronym</td>
<td>Term</td>
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<tr>
<td>---------</td>
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</tr>
<tr>
<td>FIM</td>
<td>functional independence measure</td>
</tr>
<tr>
<td>FRAMES</td>
<td>feedback, responsibility, advice, menu, empathy, self efficacy</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow coma scale</td>
</tr>
<tr>
<td>GKI</td>
<td>glucose/potassium/insulin</td>
</tr>
<tr>
<td>GP</td>
<td>general practitioner</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>IA</td>
<td>intra-arterial</td>
</tr>
<tr>
<td>ICA</td>
<td>internal carotid artery</td>
</tr>
<tr>
<td>ICH</td>
<td>intracerebral haemorrhage</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>IU</td>
<td>international units</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVH</td>
<td>intraventricular haemorrhage</td>
</tr>
<tr>
<td>LAA</td>
<td>left atrial appendage</td>
</tr>
<tr>
<td>LAMS</td>
<td>Los Angeles motor scale</td>
</tr>
<tr>
<td>LAPSS</td>
<td>Los Angeles pre-hospital stroke scale</td>
</tr>
<tr>
<td>LDL</td>
<td>low density lipoprotein</td>
</tr>
<tr>
<td>LMWH</td>
<td>low molecular weight heparin</td>
</tr>
<tr>
<td>MASS</td>
<td>Melbourne acute stroke scale</td>
</tr>
<tr>
<td>MATCH</td>
<td>Management of Atherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischaemic stroke</td>
</tr>
<tr>
<td>MCA</td>
<td>middle cerebral artery</td>
</tr>
<tr>
<td>MCN</td>
<td>Managed Clinical Network</td>
</tr>
<tr>
<td>MERCI</td>
<td>mechanical embolus removal in cerebral ischaemia</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MRA</td>
<td>magnetic resonance angiography</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>mRS</td>
<td>modified Rankin scale</td>
</tr>
<tr>
<td>MTA</td>
<td>multiple technology assessment</td>
</tr>
<tr>
<td>NASCET</td>
<td>North American Symptomatic Carotid Endarterectomy Trial</td>
</tr>
<tr>
<td>NEED</td>
<td>NHS Economics Evaluations Database</td>
</tr>
<tr>
<td>NG</td>
<td>nasogastric</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institutes of Health stroke scale</td>
</tr>
<tr>
<td>NNH</td>
<td>number needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>NPV</td>
<td>negative predictive value</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
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<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>OGTT</td>
<td>oral glucose tolerance test</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PAD</td>
<td>peripheral arterial disease</td>
</tr>
<tr>
<td>PEG</td>
<td>percutaneous gastrostomy</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFO</td>
<td>patent foramen ovale</td>
</tr>
<tr>
<td>PICH</td>
<td>primary intracerebral haemorrhage</td>
</tr>
<tr>
<td>PPI</td>
<td>proton pump inhibitor</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>PROACT</td>
<td>Prolyse in Acute Cerebral Thromboembolism</td>
</tr>
<tr>
<td>PSV</td>
<td>peak systolic velocity</td>
</tr>
<tr>
<td>PTE</td>
<td>pulmonary thromboembolism</td>
</tr>
<tr>
<td>QALY</td>
<td>quality adjusted life year</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>ROSIER</td>
<td>recognition of stroke in the emergency room</td>
</tr>
<tr>
<td>r-proUK</td>
<td>recombinant pro-urokinase</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>RRR</td>
<td>relative risk reduction</td>
</tr>
<tr>
<td>rt-PA</td>
<td>recombinant tissue plasminogen activator</td>
</tr>
<tr>
<td>SCMU</td>
<td>stroke care monitoring unit</td>
</tr>
<tr>
<td>SMC</td>
<td>Scottish Medicines Consortium</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
</tr>
<tr>
<td>SSS</td>
<td>Scandinavian stroke scale</td>
</tr>
<tr>
<td>STICH</td>
<td>Surgical Treatment for IntraCerebral Haemorrhage</td>
</tr>
<tr>
<td>SWI</td>
<td>susceptibility weighted imaging</td>
</tr>
<tr>
<td>TCD</td>
<td>transcranial Doppler</td>
</tr>
<tr>
<td>TCCS</td>
<td>transcranial colour coded sonography</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
</tr>
<tr>
<td>UK</td>
<td>urokinase</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
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</table>
Annex 1
Key questions used to develop the guideline

### MANAGEMENT OF SUSPECTED STROKE OR TIA

<table>
<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> In patients suspected of stroke or TIA do out-of-hospital systems of care improve the number of patients referred, the speed of referral and the implementation of acute interventions? Consider: a. emergency department protocols b. ambulance protocols c. NHS 24 protocols d. telemedicine services.</td>
<td>3.1, 3.3.4</td>
</tr>
<tr>
<td><strong>2.</strong> In patients with symptoms suggestive of acute stroke or TIA does the use of a standard assessment scale/method/tool compared to a standard history and examination, improve: a. accuracy, sensitivity, specificity of diagnosis b. speed of referral to specialist services c. time to diagnosis and treatment? Consider: ambulance service, accident and emergency, nursing, primary care and general practice.</td>
<td>3.2, 3.3.1</td>
</tr>
<tr>
<td><strong>3.</strong> In patients with suspected stroke or TIA which form of hospital care reduces death or dependency? a. general ward vs home b. stroke unit vs home c. stroke unit vs general ward d. stroke team vs general ward e. acute stroke unit vs general ward f. neurology unit vs general ward. Consider: medical receiving units, acute medical units and high dependency units</td>
<td>3.3.2</td>
</tr>
<tr>
<td><strong>4.</strong> In patients with suspected stroke or TIA does implementation of an integrated care pathway reduce complications, death, dependency or length of hospital stay? Consider: primary and secondary care</td>
<td>3.3.3</td>
</tr>
<tr>
<td><strong>5.</strong> In people with previous stroke or TIA what strategies improve the control of risk factors, eg drug compliance/concordance, smoking cessation, BP control, HbA1C levels? a. education programmes b. mini intervention programmes from health professionals (eg nurse, doctor) c. prompts to healthcare professionals regarding patient education. Consider: physician/doctor advice and nurse advice.</td>
<td>3.3.3</td>
</tr>
</tbody>
</table>
ASSESSMENT, DIAGNOSIS AND INVESTIGATION

**Key question**

<p>| | |</p>
<table>
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</thead>
</table>
| 6. | In patients with suspected stroke or TIA does the use of assessment tools identify those at low risk of:  
|   | a. early stroke recurrence  
|   | b. significant dependency  
|   | c. requiring hyper acute treatment such as thrombolysis  
|   | d. cerebral haemorrhage?  
|   | Consider: ambulance service, Accident and Emergency, nursing, primary care and general practice |
|   | **See guideline section** |
|   | 4.1.1-4.1.3 |
| 7. | In patients with likely acute stroke or TIA what is the evidence that brain imaging (CT, MRI) results in change of management, is cost effectiveness and reduces disability or death?  
|   | Consider: no imaging, early, late (< 3, < 6, < 14, < 48 hours, < 1 week, > 1 week) |
|   | **4.2.2** |
| 8. | In patients with likely acute stroke or TIA what is the evidence that brain imaging within 3, 6, 24, 48, > 48 hours results in a change of management, increased diagnostic accuracy in terms of differentiation of infarct from haemorrhage (sensitivity and specificity for infarct AND haemorrhage)?  
|   | Consider: CT, CT perfusion, MRI perfusion, MRI diffusion |
|   | **4.2.3** |
| 9. | In patients with confirmed diagnosis of primary intracerebral haemorrhage which modality of brain imaging (no imaging, MRI, MRA, cerebral angiography, CTA) affects management, diagnostic accuracy and diagnosis of underlying cause of stroke?  
|   | Consider: intracranial aneurysm, cavernoma, ICVM |
|   | **4.2.4** |
| 10. | In patients with likely acute stroke or TIA who have undergone brain imaging with CT or MRI how does interpretation of imaging by interpreters with different levels of expertise, including radiographer, general physician, stroke physician, general radiologist, neuroradiologist (with or without use of scoring system eg ASPECT) change management and affect diagnostic accuracy eg detection of early infarction? |
|   | **4.2.5** |
| 11. | In patients with likely acute stroke or TIA does the use of remote diagnostic aids such as teleradiology or telemedicine change management, diagnostic accuracy, time to diagnosis, disability, death, use of thrombolysis, time to treatment or use of surgery? |
|   | **4.2.6** |
12. In patients with carotid territory TIA or stroke and/or retinal event (including amaurosis fugax, transient monocular blindness and retinal artery occlusion) does carotid imaging improve accuracy of diagnosis for carotid disease on the symptomatic side (sensitivity, specificity, accuracy, NPV & PPV) for the following outcomes?
   a. plaque burden
   b. plaque composition
   c. plaque morphology
   d. stenosis degree
   e. stenosis extent
   f. tandem disease (ipsilateral at site other than carotid bifurcation/carotid bulb/internal carotid origin).

Consider:
   a. ultrasound (greyscale)
   b. duplex/Doppler ultrasound
   c. contrast-enhanced ultrasound
   d. CT angiography
   e. MR angiography
   f. contrast-enhanced MR angiography
   g. angiography/arteriography
   h. rotational angiography/arteriography.

13. In patients scheduled for cardiac surgery and who are asymptomatic for TIA/stroke which modality of carotid imaging is most effective for improving the outcomes of recurrent stroke/dependency/death?
   a. duplex ultrasound
   b. CT angiography
   c. MR angiography
   d. contrast-enhanced MR angiography
   e. angiography/arteriography
   f. rotational angiography.

Consider:
   a. coronary artery bypass grafting (CABG)
   b. valve replacement (aortic and/or mitral valves, with/without CABG)
   c. left ventricular aneurysmectomy (with/without CABG)
   d. thoracic aortic aneurysm repair.

14. In patients with confirmed stroke or TIA does imaging of the heart change management?

Consider:
   a. trans-thoracic echo
   b. trans-oesophageal echo (TOE, TEE)
   c. contrast-enhanced echo
   d. trans-cranial Doppler
   e. cardiac CT
   f. cardiac MRI.
15. In patients with confirmed stroke or TIA which diagnostic tests change management/treatment?
   a. thrombophilia screen (anti-thrombin, protein C, protein S, APC resistance, Factor V Leiden genotyping, prothrombin 20210 mutation)
   b. auto-antibody screen
   c. rheumatoid factor
   d. anti-nuclear factor
   e. ANCA
   f. anti-DNA
   g. anti-cardiolipin antibodies
   h. lupus anticoagulant
   i. genetic testing
   j. coagulation screen
   k. serum protein electrophoresis
   l. immunoglobulin levels
   m. homocysteine levels
   n. syphilis serology
   o. sickle cell screen.

TREATMENT OF ISCHAEMIC STROKE

<table>
<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Which therapeutic interventions in acute ischaemic stroke patients reduce death or dependence, compared with placebo/standard management?</td>
<td>5.1-5.7</td>
</tr>
<tr>
<td>a. thrombolysis (IV) vs placebo</td>
<td></td>
</tr>
<tr>
<td>b. thrombolysis (IA) vs IV thrombolysis or vs placebo</td>
<td></td>
</tr>
<tr>
<td>c. general (‘anterior circulation’)</td>
<td></td>
</tr>
<tr>
<td>d. basilar artery occlusion</td>
<td></td>
</tr>
<tr>
<td>e. antiplatelet agents vs control/placebo</td>
<td></td>
</tr>
<tr>
<td>f. heparin (UF or LMWT): heparin vs control or UF vs LMWT</td>
<td></td>
</tr>
<tr>
<td>g. neuroprotectants vs placebo</td>
<td></td>
</tr>
<tr>
<td>h. reducing raised ICP (positioning, hyperventilation, mannitol, hypertonic saline, glycerol vs control)</td>
<td></td>
</tr>
<tr>
<td>i. decompressive surgery</td>
<td></td>
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<tr>
<td>j. hemicraniectomy vs control</td>
<td></td>
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<tr>
<td>k. post fossa decompression vs control</td>
<td></td>
</tr>
<tr>
<td>l. post fossa decompression vs EVD</td>
<td></td>
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<tr>
<td>m. EVD vs control</td>
<td></td>
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<tr>
<td>n. mechanical reperfusion vs control</td>
<td></td>
</tr>
<tr>
<td>– clot retrieval</td>
<td></td>
</tr>
<tr>
<td>– transcranial Doppler plus thrombolysis vs thrombolysis only</td>
<td></td>
</tr>
<tr>
<td>– microbubbles.</td>
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</tr>
<tr>
<td>17. In patients with acute ischaemic stroke, does temporary withdrawal of intervention reduce death or dependence?</td>
<td>5.8</td>
</tr>
<tr>
<td>Consider:</td>
<td></td>
</tr>
<tr>
<td>a. antiplatelet agents (aspirin, clopidogrel, dipyridamole)</td>
<td></td>
</tr>
<tr>
<td>b. warfarin</td>
<td></td>
</tr>
<tr>
<td>c. antihypertensive therapy (beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II antagonists, alpha blockers, centrally acting agents)</td>
<td></td>
</tr>
<tr>
<td>d. statins.</td>
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</table>
### TREATMENT OF PRIMARY INTRACEREBRAL HAEMORRHAGE

<table>
<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
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</thead>
<tbody>
<tr>
<td>18. Which interventions reduce death or dependence in patients with PICH (primary intracerebral haemorrhage)?</td>
<td>6.1-6.4</td>
</tr>
<tr>
<td>a. haematoma evacuation, immediate vs delayed vs none</td>
<td></td>
</tr>
<tr>
<td>b. neuroprotective agents vs placebo</td>
<td></td>
</tr>
<tr>
<td>c. thrombolysis vs placebo</td>
<td></td>
</tr>
<tr>
<td>d. recombinant factor VIIa vs placebo</td>
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<tr>
<td>e. acute blood pressure lowering vs no blood pressure lowering</td>
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<tr>
<td>f. vitamin K or fresh frozen plasma or concentrated clotting factors vs placebo</td>
<td></td>
</tr>
<tr>
<td>g. interventions to reduce raised intracranial pressure (mannitol etc vs placebo).</td>
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</tbody>
</table>

### OTHER CAUSES OF STROKE

<table>
<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>19. In patients with cerebral venous sinus thrombosis which interventions reduce death or dependence vs control?</td>
<td>7.1</td>
</tr>
<tr>
<td>a. anticoagulation (warfarin or heparin) vs placebo</td>
<td></td>
</tr>
<tr>
<td>b. anticoagulation vs antiplatelet agents</td>
<td></td>
</tr>
<tr>
<td>c. antiplatelet agents vs placebo</td>
<td></td>
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<tr>
<td>d. thrombolysis vs above therapies.</td>
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</table>

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<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
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</thead>
<tbody>
<tr>
<td>20. In patients with extracranial arterial dissection, which interventions reduce death or dependency vs control?</td>
<td>7.2</td>
</tr>
<tr>
<td>a. warfarin vs aspirin</td>
<td></td>
</tr>
<tr>
<td>b. stenting vs control.</td>
<td></td>
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</tbody>
</table>

### PHYSIOLOGICAL MONITORING AND INTERVENTION

<table>
<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. In patients with acute stroke does the intensity (more vs less) of physiological monitoring (heart rate, blood pressure, temperature, oxygen saturation) in conjunction with a management protocol reduce death and dependence?</td>
<td>8.1</td>
</tr>
<tr>
<td>a. blood glucose</td>
<td></td>
</tr>
<tr>
<td>b. blood pressure</td>
<td></td>
</tr>
<tr>
<td>c. temperature</td>
<td></td>
</tr>
<tr>
<td>d. oxygen saturation.</td>
<td></td>
</tr>
</tbody>
</table>
22. In patients with acute stroke, which interventions vs control reduces death or dependence?

   a. intravenous fluids
      - IV fluids vs oral fluids
      - saline vs other (dextrose, Ringer’s, Hartmann’s)
      - high vs standard volume (>2 litres/24 hours vs <2 litres/24 hours)

   b. blood pressure management
      - active lowering vs control
      - active elevating (sympathomimetic agents or plasma expanders vs control)
      - withdrawing antihypertensive drugs vs continuing

   c. lowering blood glucose (insulin vs control)

   d. feeding (early vs deferred feeding, NG, PEG, supplementary feeding)

   e. supplementary oxygen therapy vs standard, normobaric vs hyperbaric

   f. management of pyrexia (antipyretics vs control)

   g. early mobilisation

   h. active positioning

   i. induction of hypothermia vs control.
### PREVENTING RECURRENT STROKE IN PATIENTS WITH ISCHAEMIC STROKE OR TIA

<table>
<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. In patients with ischaemic stroke (or TIA) which therapies are proven to reduce the incidence of recurrent stroke or cardiovascular events (non-fatal MI, vascular death, non-fatal recurrent stroke)?</td>
<td>9.1-9.5, 11.1, 12.2.5</td>
</tr>
<tr>
<td>a. antiplatelet agents</td>
<td></td>
</tr>
<tr>
<td>- aspirin vs placebo, vs others in list, high dose &gt; 300mg vs low dose (&lt; 300mg ), immediate vs deferred, aspirin vs aspirin plus dipyridamole</td>
<td></td>
</tr>
<tr>
<td>- clopidogrel vs placebo, vs aspirin, vs aspirin plus clopidogrel, vs dipyridamole plus aspirin</td>
<td></td>
</tr>
<tr>
<td>- dipyridamole vs placebo, vs aspirin, vs aspirin plus dipyridamole, standard vs modified release</td>
<td></td>
</tr>
<tr>
<td>- triflusal vs aspirin</td>
<td></td>
</tr>
<tr>
<td>- combinations of these.</td>
<td></td>
</tr>
<tr>
<td>b. statins</td>
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</tr>
<tr>
<td>- statins vs placebo</td>
<td></td>
</tr>
<tr>
<td>- statin vs statin (different drugs)</td>
<td></td>
</tr>
<tr>
<td>- statin vs other lipid-lowering interventions (fibrates, ezetemibe, nicotinamide, cholestyramine, surgical)</td>
<td></td>
</tr>
<tr>
<td>- immediate vs delayed statin therapy.</td>
<td></td>
</tr>
<tr>
<td>- statin treatment to cholesterol target vs treatment irrespective of cholesterol level.</td>
<td></td>
</tr>
<tr>
<td>c. anticoagulation</td>
<td></td>
</tr>
<tr>
<td>- in patients in AF. Warfarin vs placebo, warfarin vs aspirin or clopidogrel/ aspirin, or warfarin plus aspirin. Immediate vs delayed.</td>
<td></td>
</tr>
<tr>
<td>- which INR?</td>
<td></td>
</tr>
<tr>
<td>- other stroke aetiologies (warfarin vs placebo, warfarin vs aspirin, warfarin vs clopidogrel or combinations)</td>
<td></td>
</tr>
<tr>
<td>d. antihypertensives</td>
<td></td>
</tr>
<tr>
<td>- specific agents vs placebo</td>
<td></td>
</tr>
<tr>
<td>- specific agents vs each other, and also combinations.</td>
<td></td>
</tr>
<tr>
<td>- immediate v deferred treatment</td>
<td></td>
</tr>
<tr>
<td>- blood pressure target vs treatment irrespective of blood pressure</td>
<td></td>
</tr>
<tr>
<td>e. vitamins, minerals, dietary supplements/nutraceuticals vs placebo</td>
<td></td>
</tr>
<tr>
<td>f. carotid endarterectomy</td>
<td></td>
</tr>
<tr>
<td>g. atrial appendage occlusion.</td>
<td></td>
</tr>
<tr>
<td>24. In patients with patent foramen ovale and cryptogenic stroke, which interventions reduce recurrent stroke or cardiovascular events?</td>
<td>9.7</td>
</tr>
<tr>
<td>a. antiplatelet vs warfarin</td>
<td></td>
</tr>
<tr>
<td>b. closure vs medical therapy (antiplatelets or warfarin).</td>
<td></td>
</tr>
</tbody>
</table>
PREVENTING RECURRENT STROKE IN PATIENTS WITH PRIMARY INTRACEREBRAL HAEMORRHAGE

### Key question

25. In patients with PICH what interventions prevent recurrent vascular events (recurrent stroke or cardiovascular events (non-fatal MI, vascular death, non-fatal recurrent stroke)?
   - a. blood pressure reduction
   - b. antiplatelet agents
   - c. anticoagulation
   - d. statins.

26. In patients with haemorrhagic transformation of an ischaemic infarction does withdrawal of antiplatelet agent (aspirin/clopidogrel/dipyridamole) or anticoagulant (warfarin, heparin) affect death or disability?

### CAROTID INTERVENTION

#### Key question

27. In patients with carotid territory TIA or stroke and/or retinal event (including amaurosis fugax, transient monocular blindness and retinal artery occlusion) does carotid intervention reduce recurrent stroke/dependency/death?
   - a. surgical carotid endarterectomy
   - b. carotid angioplasty and stent
   - c. carotid angioplasty and stent with cerebral protection.

28. Patients with carotid disease who are asymptomatic in that (ipsilateral) carotid territory does carotid intervention reduce recurrent stroke/dependency/death?
   - a. surgical carotid endarterectomy
   - b. carotid angioplasty and stent
   - c. carotid angioplasty and stent with cerebral protection.

29. In patients scheduled for cardiac surgery with carotid disease and who are asymptomatic for TIA/stroke which carotid intervention reduces recurrent stroke/dependency/death?
   - a. surgical carotid endarterectomy
   - b. carotid angioplasty and stent
   - c. carotid angioplasty and stent with cerebral protection.
   
   **Consider:**
   - a. coronary artery bypass grafting (CABG)
   - b. valve replacement (aortic and/or mitral valves, with/without CABG)
   - c. left ventricular aneurysmectomy (with/without CABG)
   - d. thoracic aortic aneurysm repair.

30. In patients undergoing surgical carotid endarterectomy which carotid surgery techniques reduces recurrent stroke/dependency/death?
   - a. local versus general anaesthetic
   - b. shunt or no shunt
   - c. patch or no patch
   - d. monitor with transcranial Doppler vs none
   - e. monitor with EEG vs none
   - f. monitor with infra-red spectroscopy vs none.
31. In patients undergoing surgical carotid endarterectomy or carotid angioplasty/stent does periprocedural antiplatelet or antithrombotic therapy (aspirin, dipyridamole, clopidogrel, ticlopidine and abciximab) reduce stroke/dependency/death/bleeding (haemorrhage)?

32. In patients presenting with stroke, TIA, ‘crescendo’ TIA or ‘stuttering’ stroke and/or retinal events (amaurosis fugax, transient monocular blindness and retinal artery occlusion) and carotid disease suitable for intervention does early intervention reduce recurrent stroke/dependency/death compared to delayed intervention or late intervention?

<table>
<thead>
<tr>
<th>Key question</th>
<th>See guideline section</th>
</tr>
</thead>
<tbody>
<tr>
<td>33. What evidence is there for when and how patients with suspected stroke/TIA and carers should be offered information?</td>
<td>12.1.1</td>
</tr>
<tr>
<td>34. What evidence is there that individualised information for patients with suspected stroke/TIA and carers is more beneficial than generic information? Consider: literacy, age, ethnicity, risk factors, format (visually impaired, aphasia, dysphasia.)</td>
<td>12.1.1</td>
</tr>
<tr>
<td>35. What information do patients with stroke want? a. Why have I had a stroke? b. Will I have another stroke? c. What caused the stroke?</td>
<td>12.1.1</td>
</tr>
<tr>
<td>36. What practical information can be given to carers about the day-to-day living of a patient with acute stroke? Consider: clothing, food and drink, eating, texture, dysphagia, impact of stroke on lifestyle, mood, personality.</td>
<td>12.1.2</td>
</tr>
<tr>
<td>37. What early and ongoing support do carers need to help them cope with caring for a patient with stroke? Consider: who should be their contact (practically and emotionally), methods of support</td>
<td>12.1.2</td>
</tr>
<tr>
<td>38. What evidence is there that encouraging independence in patients with stroke is beneficial? Consider: reducing dependence, self help, taking responsibility, patient centred goal setting, informed decision making</td>
<td>12.2.1</td>
</tr>
<tr>
<td>39. What is the evidence that changing lifestyle prevents secondary stroke (secondary prevention)? Consider: obesity, exercise, smoking, diet (lower fat, lower salt, higher fruit and vegetable.</td>
<td>12.2.2-12.2.8</td>
</tr>
</tbody>
</table>
40. What are the best ways of motivating people to continue exercising after discharge and are there any exercise programmes that link physiotherapist led exercise and gym?
Consider: education, transition

41. What are the symptoms of stroke and who should the patient contact under which circumstances?

42. How acceptable is telemedicine for patients with suspected stroke/TIA and their carer/family?
Consider: specialist opinion, rural locations, communication between healthcare professional and patient/carer

43. What factors influence drug compliance for secondary prevention in patients with (acute) stroke?
Consider: cost (if not on free prescription), poor information, lack of understanding of benefits vs harms, patients ability (physical and mental), lack of support
Annex 2

NIH stroke scale

The NIH stroke scale (NIHSS) is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extra-ocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patient’s ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal, and there is an allowance for untestable items. The single patient assessment requires less than 10 minutes to complete.

A free educational website presented by the International Electronic Education Network® provides tutorials, assessment and accreditation on the use of the NIHSS. The target audiences for this programme are first responders, physicians, neurologists, nurses, clinical raters and medical students (www.nihstrokescale.org).
Annex 2 (continued)

NIH Stroke Scale

<table>
<thead>
<tr>
<th>Interval</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1 am</td>
</tr>
<tr>
<td>2 hours post treatment</td>
<td>2 pm</td>
</tr>
<tr>
<td>7-10 days</td>
<td>3 am</td>
</tr>
<tr>
<td>3 months</td>
<td>4 pm</td>
</tr>
<tr>
<td>24 hours post onset of symptoms</td>
<td>5 am</td>
</tr>
<tr>
<td>6 minutes</td>
<td>6 pm</td>
</tr>
</tbody>
</table>

The NINDS tPA Stroke Trial No. __________________________ __________
Pt. Date of Birth _______ / _______ / _______
Hospital __________________________ ( _______ / _______ / _______ )
Date of Exam _______ / _______ / _______

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

IF ANY ITEM IS LEFT UNTESTED, A DETAILED EXPLANATION MUST BE CLEARLY WRITTEN ON THE FORM. ALL UNTESTED ITEMS WILL BE REVIEWED BY THE MEDICAL MONITOR, AND DISCUSSED WITH THE EXAMINER BY TELEPHONE.

<table>
<thead>
<tr>
<th>Instructions</th>
<th>Scale Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</td>
<td>0 = Alert, keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.</td>
<td></td>
</tr>
<tr>
<td>1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct — there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not “help” the patient with verbal or non-verbal cues.</td>
<td>0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.</td>
<td></td>
</tr>
<tr>
<td>1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.</td>
<td>0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly</td>
<td></td>
</tr>
</tbody>
</table>
### Annex 2 (continued)

#### NIH Stroke Scale

The NINDS tPA Stroke Trial No.

Pt. Date of Birth __ / __ / __

Hospital ________________ ( __ / __ / __ )

Date of Exam __ / __ / __

| Interval | Baseline | 2 hours post treatment | 7–10 days | 3 months | 24 hours post onset of symptoms | 6 months | Other
|----------|----------|------------------------|-----------|----------|-------------------------------|----------|-------|

#### Instructions

**2. Best Gaze:** Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.

**3. Visual:** Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or uncinate, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to answer question 11.

**4. Facial Palsy:** Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.

#### Scale Definition

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present.</td>
</tr>
<tr>
<td>2</td>
<td>Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.</td>
</tr>
<tr>
<td>0</td>
<td>No visual loss</td>
</tr>
<tr>
<td>1</td>
<td>Partial hemianopia</td>
</tr>
<tr>
<td>2</td>
<td>Complete hemianopia</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral hemianopia (blind including cortical blindness)</td>
</tr>
<tr>
<td>0</td>
<td>Normal symmetrical movement</td>
</tr>
<tr>
<td>1</td>
<td>Minor paralysis (flattened nasolabial fold, asymmetry on smiling)</td>
</tr>
<tr>
<td>2</td>
<td>Partial paralysis (total or near total paralysis of lower face)</td>
</tr>
<tr>
<td>3</td>
<td>Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)</td>
</tr>
</tbody>
</table>
Annex 2 (continued)

NIH Stroke Scale

The NINDS tPA Stroke Trial No. 

Pt. Date of Birth / / ___ / ___

Hospital ______________________ ( ___ ___ - ___ ___ )

Date of Exam / / ___ / ___

Interval: 1 Baseline 2  2 hours post treatment 3  24 hours post onset of symptoms 6 minutes 4  7–10 days 5  3 months 6  Other ______________________ ( ___ ___ )

<table>
<thead>
<tr>
<th>Instructions</th>
<th>Scale Definition</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>5 &amp; 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pannomine but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be &quot;9&quot; and the examiner must clearly write the explanation for scoring as a &quot;9.&quot;</td>
<td>0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift, limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement 9 = Amputation, joint fusion explain:</td>
<td></td>
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</table>

5a. Left Arm   5b. Right Arm

0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion explain: |

6a. Left Leg   6b. Right Leg

<p>| | |</p>
<table>
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<tbody>
<tr>
<td>5a. Left Arm</td>
<td></td>
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<tr>
<td>5b. Right Arm</td>
<td></td>
</tr>
<tr>
<td>6a. Left Leg</td>
<td></td>
</tr>
<tr>
<td>6b. Right Leg</td>
<td></td>
</tr>
</tbody>
</table>
### NIH Stroke Scale

The NINDS tPA Stroke Trial No. __ __ __ __ __ __ __ __ __

Pt. Date of Birth __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __.__
Annex 2 (continued)

NIH Stroke Scale

The NINDS tPA Stroke Trial No. _______ • _______ • _______ • _______
Pt. Date of Birth _______ / _______ / _______
Hospital ________________________ ( _______ • _______ )
Date of Exam _______ / _______ / _______

Interval:
1    Baseline
2    2 hours post treatment
4    7–10 days
5    3 months
6    Other ________________________ ( _______ )

<table>
<thead>
<tr>
<th>Instructions</th>
<th>Scale Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech may the item be scored “9,” and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.</td>
<td>0 = Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty.</td>
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<tr>
<td></td>
<td>2 = Severe; patient’s speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.</td>
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</tr>
<tr>
<td></td>
<td>9 = Intubated or other physical barrier, explain</td>
<td></td>
</tr>
</tbody>
</table>

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.

<table>
<thead>
<tr>
<th>Instructions</th>
<th>Scale Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 = No abnormality.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.</td>
<td></td>
</tr>
</tbody>
</table>

Additional item, not a part of the NIH Stroke Scale score.

A. Distal Motor Function: The patient’s hand is held up at the forearm by the examiner and patient is asked to extend his/her fingers as much as possible. If the patient can’t or doesn’t extend the fingers, the examiner places the fingers in full extension and observes for any flexion movement for 5 seconds. Only the patient’s first attempts are graded. Repetition of the instructions or of the testing is prohibited.

<table>
<thead>
<tr>
<th>Instructions</th>
<th>Scale Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 = Normal (No flexion after 5 seconds)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 = At least some extension after 5 seconds, but not fully extended. Any movement of the fingers which is not upon command is not scored.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 = No voluntary extension after 5 seconds. Movements of the fingers at another time are not scored.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Left Arm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Right Arm</td>
<td></td>
</tr>
</tbody>
</table>

12. ________________________ ( _______ )

Person Administering Scale

Code
Annex 2 (continued)
Annex 2 (continued)

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.
Annex 2 (continued)
Annex 2 (continued)

MAMA
TIP-TOP
FIFTY-FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER
Annex 3
Modified Rankin score²⁹⁸

A record of the functional outcome after an event based upon the extent of any disability or disabling symptoms experienced by the patient following the event, measured using the modified Rankin score (mRS) tool.

<table>
<thead>
<tr>
<th>Score</th>
<th>Symptoms</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
<td>No symptoms at all. Score of 0</td>
</tr>
<tr>
<td>1</td>
<td>No significant disabling symptoms</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities. Score of 1</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability</td>
<td>Unable to carry out all previous activities but able to look after their own affairs without assistance. Score of 2</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability</td>
<td>Requiring some help but able to walk without assistance. Score of 3</td>
</tr>
<tr>
<td>4</td>
<td>Moderate/severe disability</td>
<td>Unable to walk without assistance and unable to attend to own bodily needs without assistance. Score of 4</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability</td>
<td>Bedridden, incontinent and requiring constant nursing care and attention. Score of 5</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
<td>Score of 6</td>
</tr>
</tbody>
</table>
Annex 4
Face arm speech test (FAST) and instructions

Adapted from Harbison et al and reproduced by kind permission of Lippincott, Williams and Wilkins, Baltimore

<table>
<thead>
<tr>
<th>STROKE (FACE ARM SPEECH TEST)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SPEECH IMPAIRMENT</td>
<td>YES</td>
<td>NO</td>
<td>?</td>
</tr>
<tr>
<td>FACIAL PALSY</td>
<td>YES</td>
<td>NO</td>
<td>?</td>
</tr>
<tr>
<td>AFFECTED SIDE</td>
<td>L</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>ARM WEAKNESS</td>
<td>YES</td>
<td>NO</td>
<td>?</td>
</tr>
<tr>
<td>AFFECTED SIDE</td>
<td>L</td>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

FACIAL MOVEMENTS
Ask patient to smile or show teeth
- Look for NEW lack of symmetry - Tick the YES box if there is an unequal smile or grimace or obvious facial asymmetry
- Note which side does not move well, and mark on the form whether it is the patient’s right or left side

ARM MOVEMENTS
- Lift the patient’s arms together to 90° if sitting, 45° if supine and ask them to hold the position for 5 seconds then let go
- Does one arm drift down or fall rapidly?
- If one arm drifts down or falls, note whether it is the patient’s left or right arm

SPEECH
If the patient attempts a conversation
- Look for NEW disturbance of speech
- Check with companion
- Look for slurred speech
- Look for word-finding difficulties. This can be confirmed by asking the patient to name commonplace objects that may be nearby, such as a cup, chair, table keys, pen
- If there is a severe visual disturbance, place an object in the patient’s hand and ask him/her to name it
Annex 5
MASS Test

Adapted from Bray et al and reproduced by kind permission of S. Karger AG, Basel.22

<table>
<thead>
<tr>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History items</strong></td>
</tr>
<tr>
<td>Age &gt; 45 years</td>
</tr>
<tr>
<td>Absent history of seizure or epilepsy</td>
</tr>
<tr>
<td>At baseline not wheelchair bound or bedridden</td>
</tr>
<tr>
<td>Blood glucose level between 2.8 and 22.2 mmol/L</td>
</tr>
<tr>
<td><strong>Physical assessment items</strong> (normal and abnormal outcomes)</td>
</tr>
<tr>
<td>Facial droop</td>
</tr>
<tr>
<td>Patient smiles or shows teeth</td>
</tr>
<tr>
<td>(both sides move equally, one side does not move)</td>
</tr>
<tr>
<td>Arm drift</td>
</tr>
<tr>
<td>Patient closes eyes and extends both arms out for 10 seconds</td>
</tr>
<tr>
<td>(both arms move/both arms do not move, one arm does not move/one arm drifts compared to the other)</td>
</tr>
<tr>
<td>Hand grip</td>
</tr>
<tr>
<td>Place a hand in each hand of the patient and ask him/her to squeeze hands</td>
</tr>
<tr>
<td>(both grip equally/not at all, unilateral weak/no grip)</td>
</tr>
<tr>
<td>Speech</td>
</tr>
<tr>
<td>Repeats a sentence</td>
</tr>
<tr>
<td>(normal, slurred/incorrect words, unable to speak)</td>
</tr>
<tr>
<td><strong>Criteria for identifying stroke</strong></td>
</tr>
<tr>
<td>Presence of any physical assessment item</td>
</tr>
<tr>
<td>All history items answered yes</td>
</tr>
</tbody>
</table>
Annex 6
ROSIER scale proforma


<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPTOM ONSET</td>
<td>Date</td>
<td>Time</td>
</tr>
</tbody>
</table>

GCS  E= ☐  M= ☐  V= ☐  BP ☐ ☐  *BM ☐

*If BM < 3.5mmol/L treat urgently and reassess once blood glucose normal

Has there been loss of consciousness or syncope?  Y (-1) ☐  N (0) ☐

Has there been seizure activity?  Y (-1) ☐  N (0) ☐

Is there a NEW ACUTE onset (or on awakening from sleep)

I. Asymmetric facial weakness  Y (+1) ☐  N (0) ☐

II. Asymmetric arm weakness  Y (+1) ☐  N (0) ☐

III. Asymmetric leg weakness  Y (+1) ☐  N (0) ☐

IV. Speech disturbance  Y (+1) ☐  N (0) ☐

V. Visual field defect  Y (+1) ☐  N (0) ☐

*Total Score________ (−2 to + 5)

Provisional diagnosis
☐ Stroke  ☐ Non-stroke (specify)________________________________________

* Stroke is unlikely but not completely excluded if total scores are ≤0.

BM blood glucose, BP blood pressure (mmHg), GCS Glasgow coma scale, E eye, M motor, V verbal
Annex 7

ABCD/ABCD²

Reprinted from The Lancet, 366 (9479), Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, Mehta Z. A, A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack, 29-36, Copyright (2005), with permission from Elsevier.34, 299

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Age of patient</td>
<td>Age ≥ 60</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 60</td>
<td>0</td>
</tr>
<tr>
<td>B Blood pressure at</td>
<td>140 mm Hg systolic or &gt;90 mm Hg diastolic</td>
<td>1</td>
</tr>
<tr>
<td>assessment</td>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>C Clinical features</td>
<td>Unilateral weakness</td>
<td>2</td>
</tr>
<tr>
<td>at presentation</td>
<td>Speech disturbance (no weakness)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>D Duration of TIA</td>
<td>≥60 minutes</td>
<td>2</td>
</tr>
<tr>
<td>symptoms</td>
<td>10-59 minutes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;10 minutes</td>
<td>0</td>
</tr>
<tr>
<td>D Diabetes</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

Early risk of stroke after TIA:
- Scores 0-3: low risk
- Scores 4-5: moderate risk
- Scores 6-7: high risk
Annex 8
Brain imaging for stroke

The choice of imaging of the brain in the acute phase of stroke is between CT and MRI (see section 4.2.3). It is difficult to recommend which modality to use exclusively, as this will depend upon individual patient circumstances. The strengths and weaknesses of both modalities are shown in the table below to help inform choice. For the purposes of this table CT brain imaging is unenhanced (without contrast) and MRI while also unenhanced is assumed to include diffusion weighted imaging (DWI) and some form of susceptibility weighted imaging (SWI) sequences.

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Geographic availability</strong></td>
<td>Widely available throughout Scotland including some island locations.</td>
<td>Increasing availability in Scotland but still mainly confined to the larger centres.</td>
</tr>
<tr>
<td><strong>Out-of-hours availability</strong></td>
<td>Generally available out-of-hours.</td>
<td>Still very limited availability out-of-hours in Scotland.</td>
</tr>
<tr>
<td><strong>Imaging unwell patients</strong></td>
<td>Images rapidly acquired and suitable for imaging acutely unwell or obtunded patients.</td>
<td>May present difficulties in unwell or confused patients, longer examination times than CT. Some patients ineligible for MRI due to contraindications such as for those patients dependent upon pacemakers.</td>
</tr>
<tr>
<td><strong>Sensitivity for ischaemia</strong></td>
<td>Insensitive in first few hours with poor inter-observer agreement for early ischaemic changes. Increasing accuracy with time and size of infarct. Relatively insensitive for small infarcts, especially in posterior fossa structures.</td>
<td>Highly sensitive for ischaemia at all time points and in all brain regions.</td>
</tr>
<tr>
<td><strong>Sensitivity for haemorrhage</strong></td>
<td>Highly sensitive for haemorrhage in first hours and days but this decreases with time from ictus.</td>
<td>Sensitive for parenchymal haemorrhage at all time points following stroke.</td>
</tr>
</tbody>
</table>

The high sensitivity of CT for haemorrhage, its rapid acquisition and applicability in unwell patients allows diagnostic decision making in many of those presenting with acute stroke syndrome, especially where a substantial territory of brain is likely to be involved. For patients presenting at later time points (days) MRI has advantage in differentiating haemorrhage from ischaemia. Patients presenting with limited or unusual neurology (NIHSS ≤3), especially brainstem syndromes, may also be better served by MRI as the first imaging investigation. MRI is also useful after initial negative CT scan, where there is diagnostic doubt or the definitive depiction of ischaemic damage will aid future management.
Annex 9

Carotid stenosis

A misconception engendered by the concentration on stenosis measurement is that stenosis causes stroke when in fact it is not stenosis in itself (luminal narrowing impeding blood flow) that is the main cause of stroke, rather in the context of carotid disease stroke is usually caused by atheroembolism. At the time of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) the only imaging methodology available to visualise carotid atheromatous disease burden was conventional selective carotid angiography using cut film. The sole means by which these images could be analysed for disease quantification was to measure stenosis. In NASCET the stenosis was measured with the luminal diameter of the normal appearing internal carotid artery distal to the site of stenosis as the denominator. A potential limitation of this is that at higher grades of narrowing when the normal vessel beyond a stenosis becomes depressurised this intrinsically affects the calculation. As a small vessel the potential errors in measurement of the internal carotid are relatively greater than in a larger artery such as the common carotid. The European Carotid Surgery Trial also used angiographic measurement but did not demand selective arteriograms and used a different method for stenosis calculation using the perceived normal diameter of the vessel at the site of disease (usually the carotid bulb) as the denominator. This normal diameter is not actually delineated on arteriography and it is likely that this measurement was judged by extrapolation of the common carotid artery diameter proximal to the disease. It has been proposed that the denominator should be the common carotid artery, unaffected by post-stenotic pressure phenomena and better inter-observer diameter estimation, however, the NASCET criterion has become the accepted standard.

The figure below shows a comparison of the methods used to measure carotid stenosis as assessed by diameter reduction shown on angiography. There is also a diagrammatic representation of ulcerated plaque for which simple stenosis assessment would underestimate the degree of pathology and potential for atheroembolism.

<table>
<thead>
<tr>
<th>Method</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECST</td>
<td>( \frac{C-A}{C} \times 100% ) stenosis</td>
</tr>
<tr>
<td>NASCET</td>
<td>( \frac{B-A}{B} \times 100% ) stenosis</td>
</tr>
<tr>
<td>CC</td>
<td>( \frac{D-A}{D} \times 100% ) stenosis</td>
</tr>
<tr>
<td>NASCET % stenosis</td>
<td>( \frac{\text{ECST or CC stenosis} \times 40}{0.6} )</td>
</tr>
</tbody>
</table>
Annex 10
Carotid Duplex Reporting

The degree of internal carotid artery stenosis as found with carotid duplex ultrasound should be reported in broad categories. Attempts to grade carotid stenosis to more precise degrees by ultrasound are inappropriate. The grade of stenosis reported should be based on a combination of parameters and not just one variable. The report should state the velocity measurements and also the gray-scale and colour Doppler findings. A degree of stenosis >50% should be corroborated by a second imaging modality.300

<table>
<thead>
<tr>
<th>Degree of stenosis (%)</th>
<th>ICA PSV (cm/sec)</th>
<th>Plaque estimate (%)</th>
<th>ICA/CCA PSV ratio</th>
<th>ICA EDV (cm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;125</td>
<td>None</td>
<td>&lt;2.0</td>
<td>&lt;40</td>
</tr>
<tr>
<td>&lt;50</td>
<td>&gt;125</td>
<td>≤50</td>
<td>&lt;2.0</td>
<td>&lt;40</td>
</tr>
<tr>
<td>50-69</td>
<td>125-230</td>
<td>≥50</td>
<td>2.0-4.0</td>
<td>40-100</td>
</tr>
<tr>
<td>≥70 but less than near occlusion</td>
<td>&gt;230</td>
<td>≥50</td>
<td>&gt;4.0</td>
<td>≥100</td>
</tr>
<tr>
<td>Near occlusion</td>
<td>High, low or undetectable</td>
<td>Visible</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>Undetectable</td>
<td>Visible, no detectable lumen</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

*ICA* internal carotid artery, *PSV* peak systolic velocity, *CCA* common carotid artery, *EDV* end diastolic velocity

References


92. Muir KW, lees KR. Excitatory amino acid antagonists for acute ischaemic stroke. The Cochrane Library 2005; (ID #CD001924).


279. Saunders DH, Greig CA, Young A, Mead GE. Physical fitness training for stroke patients. The Cochrane Library 2005; 2005:


