
*The National Collaborating Centre
for Chronic Conditions*

Funded to produce guidelines for the NHS by NICE

STROKE

National clinical guideline for diagnosis
and initial management of acute stroke and
transient ischaemic attack (TIA)

Published by



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National Collaborating Centre for Chronic Conditions

The National Collaborating Centre for Chronic Conditions (NCC-CC) is a collaborative, multiprofessional centre undertaking commissions to develop clinical guidance for the National Health Service (NHS) in England and Wales. The NCC-CC was established in 2001. It is an independent body, housed within the Clinical Standards Department at the Royal College of Physicians of London. The NCC-CC is funded by the National Institute for Health and Clinical Excellence (NICE) to undertake commissions for national clinical guidelines on an annual rolling programme.

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Guideline Development Group Members

Dr Pippa Tyrrell

Clinical Advisor/Senior Lecturer/Honorary Consultant Stroke Medicine,
Salford Royal NHS Foundation Trust/University of Manchester

Dr Anthony Rudd

GDG Chair/Consultant Stroke Physician, Guy's and St Thomas' NHS Foundation Trust

Mrs Katherine Cullen

Health Economist until September 2007, NCC-CC

Mrs Alison Richards

Information Scientist, NCC-CC

Dr Sharon Swain

Research Fellow, NCC-CC

Miss Claire Turner

Senior Project Manager, NCC-CC

Mr David Wonderling

Senior Health Economist from September 2007, NCC-CC

Mr Alan Bowmaster

Patient/Carer Representative

Ms Diana Day

Stroke Specialist Research Nurse, Addenbrookes Hospital NHS Trust

Professor Gary Ford

Professor of Pharmacology of Old Age,
Newcastle Upon Tyne Hospitals NHS Foundation Trust

Mr Steve Hatton

Paramedic/Emergency Care Practitioner, Yorkshire Ambulance Service NHS Trust

Mr Joe Korner

Patient/Carer Representative, The Stroke Association

Dr Richard McManus

Clinical Senior Lecturer in Primary Care and General Practitioner, University of Birmingham

Dr Andy Molyneux

Consultant Neuroradiologist, Oxford Radcliffe Hospitals NHS Trust

Professor John Potter

Professor in Geriatrics and Stroke Medicine, University of East Anglia

Ms Rhoda Allison

Invited expert, Consultant Therapist in Stroke, Teignbridge PCT
(GDG1, 2 and 9)

Mrs Julie Barker

Invited expert, Senior Dietitian, United Bristol Healthcare Trust

Mr Peter Kirkpatrick

Invited expert, Consultant Neurosurgeon, Addenbrookes NHS Trust
(GDG10)

Mr Peter Lamont

Invited expert, Consultant Vascular Surgeon, United Bristol Healthcare Trust
(GDG1, 2, 5, 6 and 10)

Ms Mariane Morse

Invited expert, Principal Speech and Language Therapist, Newcastle PCT
(GDG7 and 9)

Professor Peter Rothwell

Invited expert, Consultant Neurologist, Oxford Radcliffe Hospitals NHS Trust
(GDG 4, 5 and 12)

Dr Neil Baldwin (deputy for John Potter)

Consultant in Stroke Medicine, North Bristol Healthcare Trust
(GDG12)

Mr Sam Willis (deputy for Steve Hatton)

Paramedic Lecturer Practitioner,
London Ambulance Service and Greenwich University
(GDG2)

Preface

As a newly qualified doctor, I remember feeling a sense of uselessness whenever I admitted a patient with a stroke. Here was one of the commonest of medical admissions, yet I had embarrassingly little to offer them. Today on acute takes, when a patient with a suspected stroke appears I am ushered aside by a specialist team eager to waste no time in assessing the patient, initiating appropriate treatment, considering their suitability for trials. This change in attitude is one of the most striking, and most welcome, I have seen in my medical lifetime.

I am perhaps fortunate in working in a hospital which was an early developer of the acute stroke team. The potential benefits of stroke medicine as an active discipline are obvious, and it is encouraging to see large research projects taking place in what was once such a neglected area. However, all this activity brings with it a new challenge. We need to ensure that the benefits of this specialist expertise are available to all patients across the UK. This guideline in acute stroke and transient ischaemic attack (TIA) management has been commissioned by NICE to address that challenge.

The guideline concerns itself with the earliest phases of the presentation of stroke. The keynote is the avoidance, or minimisation, of damage to the ischaemic brain, i.e. in the first hours of a cerebrovascular accident (CVA) or through active management of a TIA. Accurate but swift assessment is critical, and one of the priority recommendations is the more widespread use of a validated tool for the pre-hospital diagnosis of stroke and TIA. For patients with a TIA, identification and aggressive management of those at significant risk of progression to stroke is highlighted. For those who have already sustained a stroke, rapid availability of appropriate imaging and access to a specialist acute stroke team are recommendations which are emphasised. The guideline recognises that not all patients need the most aggressive management, but that it is vital to identify swiftly those who may benefit.

Although this guideline concentrates on TIA and acute stroke, the development group (GDG) are fully aware of the importance of good management continuing throughout recovery. The decision not to address the later stages within this guideline was taken partly because this would increase the size of the task, but mainly because we knew that the Intercollegiate Stroke Working Party were updating their own excellent guideline which covers the later part of the patient pathway. The two guideline groups have collaborated extensively throughout development, and their separate pieces of guidance complement each other.

We at the NCC-CC are extremely grateful to the GDG for the hard work they have put in over the course of development. They have been a pleasure to work with, both knowledgeable and committed, and I believe they have produced an excellent guideline. Stroke medicine is now such an active field that there will doubtless be further improvements to add in the near future. For the moment however, implementing this guideline across the country should be of real and immediate benefit to all patients with this once neglected problem.

Bernard Higgins MD FRCP

Director, National Collaborating Centre for Chronic Conditions

DEVELOPMENT OF THE GUIDELINE

1 Introduction

1.1 Background

Stroke is a preventable and treatable disease. It can present with the sudden onset of any neurological disturbance, including limb weakness or numbness, speech disturbance, visual loss or disturbance of balance. Over the last two decades, a growing body of evidence has overturned the traditional perception that stroke is simply a consequence of aging which inevitably results in death or severe disability. Evidence is accumulating for more effective primary and secondary prevention strategies, better recognition of people at highest risk and thus most in need of active intervention, interventions that are effective soon after the onset of symptoms, and an understanding of the processes of care that contribute to a better outcome. In addition, there is now good evidence to support interventions and care processes in stroke rehabilitation. In the UK, the National Sentinel Stroke Audits^{2,3} have documented changes in secondary care provision over the last 10 years, with increasing numbers of patients being treated in stroke units, more evidence-based practice, and reductions in mortality and length of stay. In order for evidence from research studies to improve outcomes for patients, it needs to be put into practice. National guidelines provide clinicians, managers and service users with summaries of evidence and recommendations for clinical practice. Implementation of guidelines in practice, supported by regular audit, improves the processes of care and clinical outcome.

This guideline covers interventions in the acute stage of a stroke ('acute stroke') or transient ischaemic attack (TIA). Most of the evidence considered relates to interventions in the first 48 hours after onset of symptoms, although some interventions of up to 2 weeks are covered as well. This guideline is a stand-alone document, but is designed to be read alongside the Intercollegiate Stroke Working Party guideline 'National clinical guideline for stroke'* which considers evidence for interventions from the acute stage into rehabilitation and life after stroke. The Intercollegiate Stroke Working Party guideline is an update of the 2004 2nd edition and includes all the recommendations contained within this guideline. This acute stroke and TIA guideline is also designed to be read alongside the Department of Health's (DH) 'National stroke strategy' (NSS).⁴ Where there are differences between the recommendations made within this acute stroke and TIA guideline and the NSS, the Guideline Development Group (GDG) members feel that their recommendations are derived from systematic methodology to identify all of the relevant literature.

Stroke has a sudden and sometimes devastating impact on the patient and their family who need continuing information and support. Clinicians dealing with acute care need to be mindful of the rehabilitation and secondary care needs of patients with stroke to ensure a seamless transition across the different phases of care. All aspects of care must be patient-centred and where possible based on full discussion with the patient and/or carer, for example some aspects of the guideline may not be appropriate for patients who are dying or who have other severe comorbidities. Healthcare professionals should also follow a code of practice accompanying the Mental Capacity Act 2005 (summary available from www.dca.gov.uk/menincap/bill-summary.htm).

* Intercollegiate Stroke Working Party. 'National clinical guideline for stroke', 3rd edition. London: RCP, 2008.

1.2 Incidence and prevalence

Stroke is a major health problem in the UK. It accounted for over 56,000 deaths in England and Wales in 1999, which represent 11% of all deaths.⁵ Most people survive a first stroke, but often have significant morbidity. Each year in England, approximately 110,000 people have a first or recurrent stroke and a further 20,000 people have a TIA. More than 900,000 people in England are living with the effects of stroke, with half of these being dependent on other people for help with everyday activities.⁶

1.3 Health and resource burden

In England, stroke is estimated to cost the economy around £7 billion per year. This comprises direct costs to the NHS of £2.8 billion, costs of informal care of £2.4 billion and costs because of lost productivity and disability of £1.8 billion.⁶

Until recently, stroke was not perceived as a high priority within the NHS. However, following the publication of the National Audit Office report in 2005, a National Stroke Strategy was developed by the DH in 2007.⁴ This outlines an ambition for the diagnosis, treatment and management of stroke, including all aspects of care from emergency response to life after stroke.

1.4 Definition

Stroke is defined by the World Health Organization⁷ as ‘a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin.’ A transient ischaemic attack (TIA) is defined as stroke symptoms and signs that resolve within 24 hours. There are limitations to these definitions. The symptoms of a TIA usually resolve within minutes or a few hours at most and anyone with continuing neurological signs when first assessed should be assumed to have had a stroke. ‘Brain Attack’ is sometimes used to describe any neurovascular event and may be a clearer and less ambiguous term to use.

2 Methodology

2.1 Aim

The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- offers best clinical advice for the diagnosis and acute management of stroke and TIA
- is based on best published clinical and economic evidence, alongside expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of NHS care provision for the management of acute stroke and TIA
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences.

2.2 Scope

The guideline was developed in accordance with a scope, which detailed the remit of the guideline originating from the DH and specified the aspects of diagnosis and the management of acute stroke and TIA care to be included and excluded.

Prior to guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by National Institute for Health and Clinical Excellence (NICE).¹ The full scope is shown in Appendix B, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250

2.3 Audience

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with acute stroke or TIA and their carers
- patient support groups
- commissioning organisations
- service providers.

2.4 Involvement of people with stroke and TIA

The NCC-CC was keen to ensure the views and preferences of people with stroke and TIA and their carers were informed at all stages of the guideline. This was achieved by:

- having two people with experience of stroke and TIA as patient representatives on the guideline development group

- consulting the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline project
- the inclusion of patient groups as registered stakeholders for the guideline.

2.5 Guideline limitations

These include:

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the DH).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- Where a meta-analysis was available, generally the individual papers contained within were not appraised.
- It is not possible in the development of a clinical guideline to complete extensive systematic literature review of all pharmacological toxicity. NICE advises that the guidelines are read alongside the summaries of product characteristics (SPCs).
- Overall, the evidence review identified very few randomised controlled trials (RCTs) or high-quality case-control or cohort studies. Many of the studies had a small sample size and were consequently statistically under-powered. Also, some studies relied on retrospective data collection or post-hoc analysis. Furthermore, the different diagnostic tests, interventions and outcomes often precluded any meaningful comparison across studies.

2.6 Other work relevant to the guideline

Related NICE guidance:

- 'Alteplase for the treatment of acute ischaemic stroke', *NICE technology appraisal* no. TA122 (2007). Available from www.nice.org.uk/TA122
- 'Vascular disease – clopidogrel and dipyridamole', *NICE technology appraisal* no. TA90 (2005). Available from www.nice.org.uk/TA90
- 'Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition', *NICE clinical guideline* CG32 (2006). Available from www.nice.org.uk/CG32
- 'Hypertension: management of hypertension in adults in primary care', *NICE clinical guideline* CG34 (2006). Available from www.nice.org.uk/CG34
- 'Diagnosis and management of Type 1 diabetes in children, young people and adults', *NICE clinical guideline* CG15 (2004). Available from www.nice.org.uk/CG15
- 'Lipid modification guideline', *NICE clinical guideline* CG67 (2008). Available from www.nice.org.uk/CG67

2.7 Methodological background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE's 'Guideline development methods manual'¹ and the methodology pack⁸ specifically developed by the NCC-CC for each chronic condition guideline. The developers' role and remit is summarised in table 2.1 below.

Table 2.1 Role and remit of the developers

National Collaborating Centre for Chronic Conditions (NCC-CC)	<p>The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from NICE.</p> <p>A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCC-CC.</p>
NCC-CC technical team	<p>The technical team met approximately two weeks before each GDG meeting and comprised the following members:</p> <ul style="list-style-type: none"> GDG Chair GDG Clinical Adviser Information Scientist Research Fellow Health Economist Project Manager.
Guideline Development Group (GDG)	<p>The GDG met monthly (November 2006 to November 2007) and comprised a multidisciplinary team of professionals and people with experience of acute stroke or TIA who were supported by the technical team.</p> <p>The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.</p>
Guideline Project Executive (PE)	<p>The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.</p> <p>The PE comprised of:</p> <ul style="list-style-type: none"> NCC-CC Director NCC-CC Assistant Director NCC-CC Manager NICE Commissioning Manager Technical Team.
Formal consensus	<p>At the end of the guideline development process, the GDG met to review and agree the guideline recommendations.</p>

Members of the GDG declared any interests in accordance with the NICE technical manual.¹ A register is given in Appendix D, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250

2.8 The process of guideline development

The basic steps in the process of producing a guideline are:

- 1 developing clinical evidence-based questions
- 2 systematically searching for the evidence
- 3 critically appraising the evidence
- 4 incorporating health economic evidence
- 5 distilling and synthesising the evidence and writing recommendations
- 6 grading the evidence statements
- 7 agreeing the recommendations
- 8 structuring and writing the guideline
- 9 updating the guideline.

▷ 1 Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, which are shown in Appendix A, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250

▷ 2 Searching for the evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. In addition, the health economist searched for additional papers providing economic evidence or to inform detailed health economic work (for example, modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists, generated for each question together with the rationale for the exclusion, were presented to the GDG. Full papers were obtained where relevant. See Appendix A, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250 for literature search details.

▷ 3 Appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors. However, there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the ‘Guideline development methods – information for national collaborating centres and guideline developers’ manual’ 2007.¹
- NCC-CC quality assurance document and systematic review chart available at www.rcplondon.ac.uk/college/NCC-CC

▷ 4 Health economic evidence

Areas for health economic modelling were agreed by the GDG after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

▷ 5 Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations. The criteria for grading evidence are shown in table 2.2.

Evidence tables are available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250

▷ 6 Grading the evidence statements

Table 2.2 Grading the evidence statements NICE 2007¹

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.*
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.*
3	Non-analytic studies (for example case reports, case series).
4	Expert opinion, formal consensus.
*Studies with a level of evidence '–' are not used as a basis for making a recommendation. RCT, randomised controlled trial	

▷ 7 Agreeing the recommendations

The GDG employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations

- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The GDG also reached agreement on the following:

- six recommendations as key priorities for implementation
- six key research recommendations
- algorithms.

In prioritising key recommendations for implementation, the GDG took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

Audit criteria for this guideline will be produced by NICE, following publication, in order to provide suggestions of areas for audit in line with the key recommendations for implementation.

▷ 8 Structuring and writing the guideline

The guideline is divided into sections for ease of reading. For each section, the layout is similar and contains:

- *Clinical introduction* sets a succinct background and describes the current clinical context.
- *Methodological introduction* describes any issues or limitations that were apparent when reading the evidence base. Point estimates (PE) and confidence intervals (CI) are provided for all outcomes in the evidence tables, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250. In addition, within the guideline PE and CI are cited in summary tables. In the absence of a summary table, PE and CI should be provided in the narrative text when the outcome adds something to the text and to make a particular point. These may be primary or secondary outcomes that were of particular importance to the GDG when discussing the recommendations. The rationale for not citing *all* statistical outcomes in the text is to try to provide a 'user friendly' readable guideline balanced with statistical evidence where this is thought to be of interest to the reader.
- *Evidence statements* provides a synthesis of the evidence base and usually describes what the evidence showed in relation to the outcomes of interest.
- *Health economics* presents, where appropriate, an overview of the cost effectiveness of evidence base, or any economic modelling.
- *From evidence to recommendations* this section sets out the GDG decision-making rationale, providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.
- *Recommendations* provides stand alone, action-orientated recommendations.
- *Evidence tables* the evidence tables are not published as part of the full guideline but are made publicly available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250. These describe comprehensive details of the primary evidence that was considered during the writing of each section including all statistical outcomes.

▷ 9 Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accord with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website, www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

Table 2.3 Versions of this guideline

Full version	Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCC-CC. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250
NICE version	Documents the recommendations without any supporting evidence. Available at www.nice.org.uk/CG68
‘Quick reference guide’	An abridged version. Available at www.nice.org.uk/CG68
‘Understanding NICE guidance’	A lay version of the guideline recommendations. Available at www.nice.org.uk/CG68

▷ Updating the guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 31 October 2007 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will ask a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be considered for update approximately four years after publication.

2.9 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.10 Funding

The NCC-CC was commissioned by the NICE to undertake the work on this guideline.

3 Key messages of the guideline

3.1 Key priorities for implementation

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

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

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

People with crescendo TIA (two or more TIAs in a week) should be treated as being at high risk of stroke (as described in recommendation 5), even though they may have an ABCD² score of 3 or below.

All people with suspected stroke should be admitted directly to a specialist acute stroke unit following initial assessment either from the community or accident & emergency (A&E) department.

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

- indications for thrombolysis or early anticoagulation treatment (see sections 8.1 and 8.2)
- on anticoagulant treatment
- a known bleeding tendency
- a depressed level of consciousness (Glasgow Coma Score (GCS) below 13)
- unexplained progressive or fluctuating symptoms
- papilloedema, neck stiffness or fever
- severe headache at onset of stroke symptoms.

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

* The GDG felt that immediately was defined as 'ideally the next slot and definitely within 1 hour, whichever is sooner' in line with the National Stroke Strategy.⁴

3.2 Algorithms

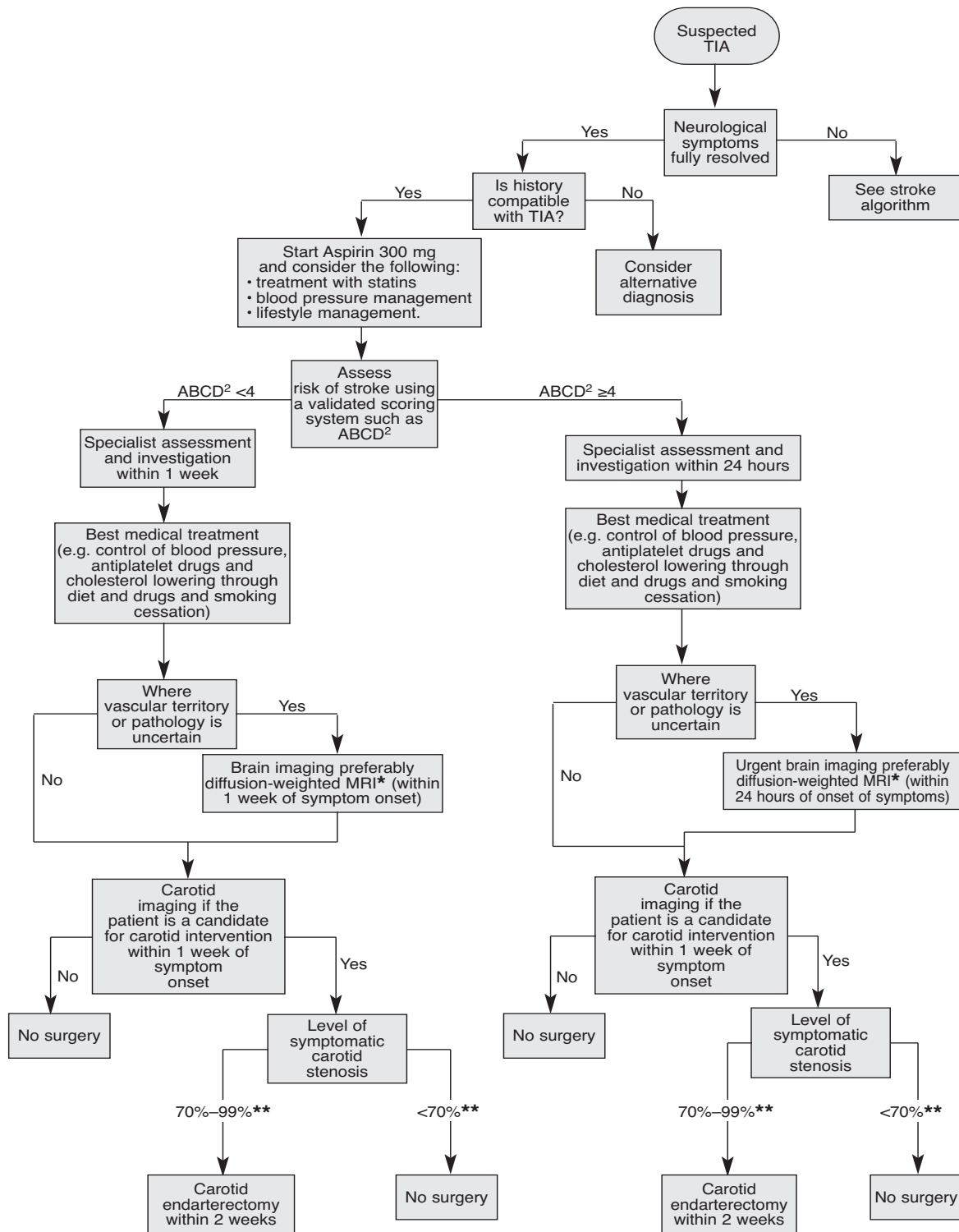
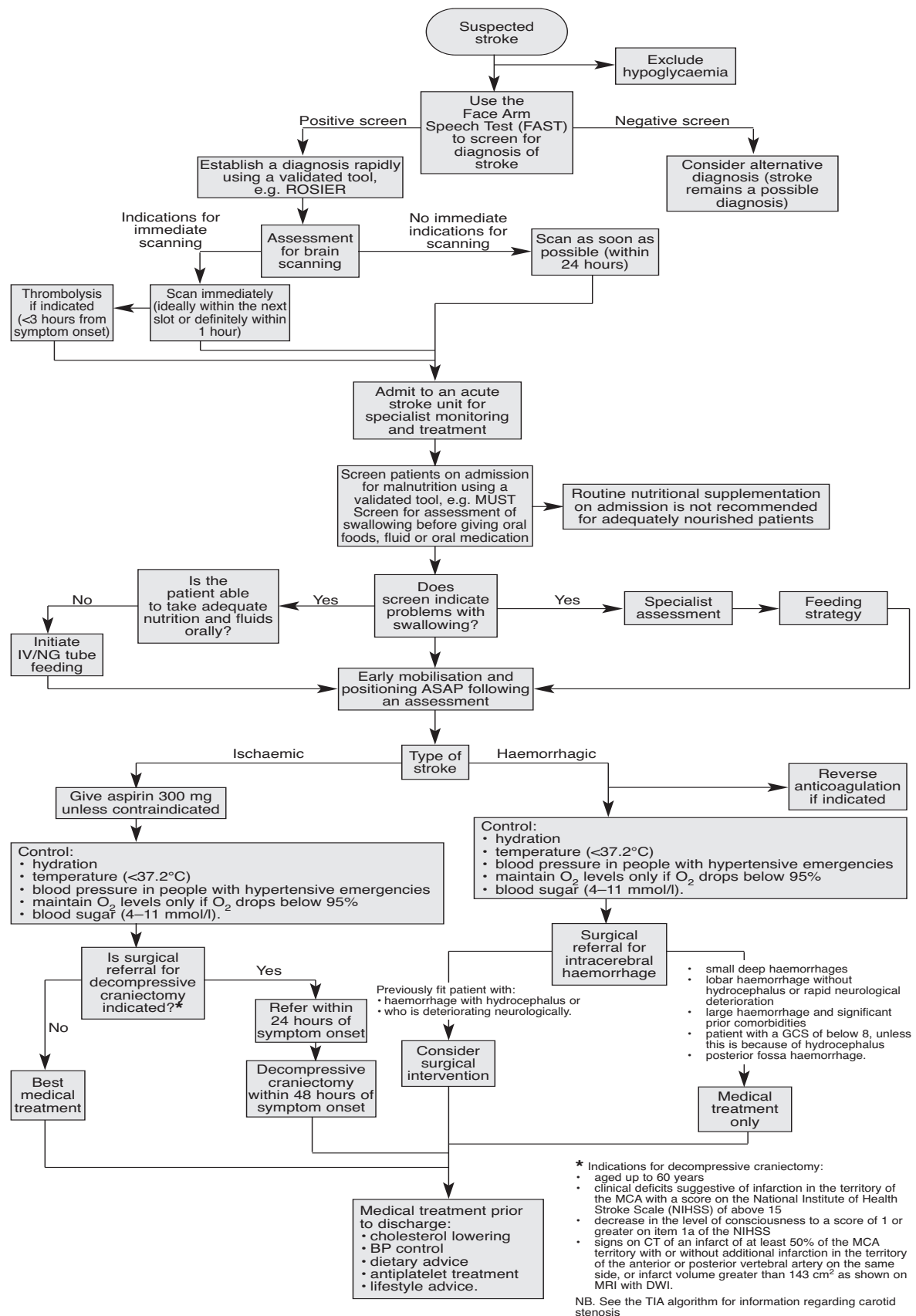


Figure 3.1 Transient ischaemic attack (TIA) algorithm

*except where contraindicated, in which case computed tomography (CT) should be used

**according to the European Carotid Surgery Trial (ECST) criteria



4 Glossary and definitions

ABCD and ABCD²	Prognostic score to identify people at high risk of stroke after a TIA. It is calculated based on: A – age (≥ 60 years, 1 point) B – blood pressure at presentation ($\geq 140/90$ mmHg, 1 point) C – clinical features (unilateral weakness, 2 points or speech disturbance without weakness, 1 point) D – duration of symptoms (≥ 60 minutes, 2 points or 10–59 minutes, 1 point). The calculation of ABCD ² also includes the presence of diabetes (1 point). Total scores range from 0 (low risk) to 7 (high risk).
Alteplase	A drug used for thrombolysis.
Anticoagulants	A group of drugs used to reduce the risk of clots forming by thinning the blood.
Antiphospholipid syndrome	Sometimes called ‘sticky blood syndrome’ because the blood clots too quickly due to antibodies that form against the body’s phospholipids.
Antiplatelets	A group of drugs used to prevent the formation of clots by stopping platelets in the blood sticking together.
Arterial dissection	This is caused as a result of a small tear forming in the tunica intima lining of the arterial wall.
Barthel Index	Scale measuring daily functioning specifically relating to the activities of daily living or mobility. Scores range from 0 to 100.
Bedside swallowing assessment	A term covering a range of techniques.
BMI	Body mass index – an index of body weight corrected for height.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Carotid artery	Main arteries in the neck supplying oxygenated blood to the brain.
Carotid endarterectomy (CEA)	A surgical procedure used to clear the inside of the carotid artery of atheroma.
Carotid stenosis	The narrowing of the carotid arteries in the neck.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure

	to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Confidence interval (CI)	The probability of the observed data (or data showing a departure more extreme from the null hypothesis) when the null hypothesis is accepted.
Cochrane review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
CT	Computed tomography – an X-ray technique used to examine the brain.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality adjusted life years (QALYs).
Decompressive craniectomy	A surgical procedure for the treatment of raised intracranial pressure. A piece of the skull is removed to allow the swelling brain to expand.
DVT	Deep vein thrombosis.
Diagnostic accuracy	The degree to which a diagnostic (or screening) tool or procedure is able to distinguish between cases and non-cases. See also ‘sensitivity’, ‘specificity’, ‘negative predictive value’ and ‘positive predictive value’.
Dysphagia	A difficulty in swallowing.
Endarterectomy	The surgical removal of plaque from a blocked artery to restore blood flow.
FAST	Face Arm Speech Test – used to screen for the diagnosis of stroke or TIA.
FEES	Fibreoptic Endoscopic Evaluation of Swallowing. A flexible nasendoscope is inserted through the nose to the throat to observe swallowing.
FFP	Fresh frozen plasma.
GDG	Guideline Development Group.
GUSS	Gugging Swallowing Screen. A screen designed to identify patients with dysphagia and reduce the risk of aspiration.
Haemorrhage	Bleeding caused by blood escaping into the tissues.
Hydrocephalus	Raised pressure within the skull.
HTA	Health Technology Assessment, funded by the NHS Research and Development Directorate.
Incremental cost	The cost of one alternative less the cost of another.

Incremental cost effectiveness ratio (ICER)	The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.
Independent predictor	A variable whose value predicts the occurrence of an event independent of the values of other variables.
Infarct	An area of cell death due to the result of a deprived blood supply.
INR	International normalised ratio. A measure of the clotting ability of blood, usually following use of anticoagulant drugs. It is calculated as the ratio of the length of time it takes blood to clot over the time it would take the blood of a normal subject to clot.
Intracranial haemorrhage	A bleed in the brain as a result of a ruptured or bleeding blood vessel.
MCA	Middle cerebral artery.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.
Methodological limitations	Features of the design or reporting of a clinical study which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.
Modified Rankin Scale (mRS)	Six-point scale with 0 for no symptoms and 6 for death measuring the degree of disability or dependence in daily activities.
MRI	Magnetic resonance imaging – a non-invasive imaging technique allowing detailed examination of the brain.
MRI with DWI	Magnetic resonance imaging with diffusion-weighted imaging.
MUST	Malnutrition Universal Screening Tool. A screening tool comprising 5 steps which help identify which adults are malnourished or at risk of malnourishment.
Northern American Symptomatic Carotid Endarterectomy Trial (NASCET)	The NASCET and ECST (see below) methods both indicate the degree of stenosis as a percentage reduction in vessel diameter. The minimum diameter of the arteries caused by stenosis (which is the maximum point of blood constriction) is compared to another diameter that represents the normal diameter of the carotid arteries when the patient is healthy. NASCET includes a measurement taken along a point of the internal carotid artery in a healthy area well beyond an area of the bulb that was caused by stenosis.
European Carotid Surgery Trial (ECST)	The ECST formula includes the estimated normal lumen diameter at the site of the lesion, based on a visual impression of where the normal artery wall was before development of the stenosis.
NCC-CC	The National Collaborating Centre for Chronic Conditions, set up in 2000 to undertake commissions from the NICE to develop clinical guidelines for the NHS.

Negative predictive value (NPV)	The proportion of individuals with a negative test result who do not have the disease.
NG feeding	Nasogastric intubation using a nasogastric tube which is inserted through the nose, past the throat and down into the stomach for the purposes of feeding.
NHS	National Health Service. This guideline is written for the NHS in England and Wales.
NICE	National Institute for Health and Clinical Excellence – a special health authority set up within the NHS to develop appropriate and consistent advice on healthcare technologies, and to commission evidence-based guidelines.
Non-significant (NS)	See ‘statistical significance’.
NSF	National Service Framework – a nationwide initiative designed to improve delivery of care for a related group of conditions.
Null hypothesis	The ‘no difference’ or ‘no association’ hypothesis that can be tested against an alternative hypothesis that postulates a difference or association that is non-zero.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups, for example cohort studies and case-control studies.
Odds ratio (OR)	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The ‘odds’ is the ratio of non-events to events.
Open-label study	In the context of study design, a study in which the physicians or investigators are not blinded to which patients are allocated to which treatment arm.
PE	Pulmonary embolism – a blood clot in the lungs.
PEG/PEJ	Percutaneous endoscopic gastrostomy/jejunostomy used for feeding. A gastroscope is used to insert a tube through the wall of the abdomen into the stomach.
PCC	Prothrombin complex concentrate.
Positive predictive value (PPV)	The proportion of individuals with a positive test result who actually have the disease.
p values	The probability that an observed difference could have occurred by chance. A p value of less than 0.05 is conventionally considered to be ‘statistically significant’.
Quality of life	Refers to the level of comfort, enjoyment and ability to pursue daily activities.

Quality of life-adjusted year (QALY)	A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.
RCT	Randomised controlled trial. A trial in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. Such trial designs help minimise experimental bias.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A, divided by the risk of the event in group B).
ROSIER	Recognition of Stroke in the Emergency Room – used to establish the diagnosis of stroke or TIA.
Sensitivity	The proportion of individuals classified as positive by the gold or reference standard, who are correctly identified by the study test.
Sensitivity analysis	A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.
Side effect	An adverse event that occurs because of a therapeutic intervention.
Specialist	A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.
Specificity	The proportion of individuals classified as negative by the gold (or reference) standard, who are correctly identified by the study test.
Stakeholder	Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.
Statistical significance	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Stenosis	Abnormal narrowing of a blood vessel.
Stenting	A metal mesh tube is placed in an artery or blood vessel to increase blood flow to an area blocked by stenosis.
Stroke	The damaging or killing of brain cells starved of oxygen as a result of the blood supply to part of the brain being cut off. Types of stroke include Ischaemic stroke caused by blood clots to the brain or haemorrhagic stroke caused by bleeding into/of the brain.

Stroke mimics	A term used to describe other clinical conditions which can mimic a stroke and confound diagnosis. Examples of these include brain tumours, epilepsy or subdural haematomas. Neurologic abnormalities similar to a stroke can also be the result of imbalances of glucose, sodium and calcium.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Technology appraisal	Formal ascertainment and review of the evidence surrounding a health technology, restricted in the current document to appraisals undertaken by NICE.
TIA	Transient ischaemic attack – a stroke which recovers within 24 hours of onset of symptoms.
Thrombosis	A formation of a blood clot.
Thrombolysis	The use of drugs to break up a blood clot. Two examples of thrombolysis drugs are tPA and Alteplase.
tPA	Tissue plasminogen activator – a drug used for thrombolysis.
Venous stroke	The formation of a blood clot in the intracerebral veins and venous sinuses.
Videofluoroscopy	Videofluoroscopy is a test for assessing the integrity of the oral and pharyngeal stages of the swallowing process. It involves videotaping fluoroscopic images as the patient swallows a bolus of barium.
WHO	World Health Organization.

THE GUIDELINE

5 The rapid recognition of symptoms and diagnosis

5.1 Pre-hospital prompt recognition of symptoms of TIA and stroke symptoms

5.1.1 Clinical introduction

People who present with acute stroke or TIA need immediate clinical assessment and treatment. Few people have much awareness of the symptoms of stroke, and may delay seeking help as a result; hence the need for the UK Stroke Association's Act FAST campaign.⁹ A number of tools have been designed to help paramedics and other healthcare professionals recognise symptoms in the community. Other tools have been developed to improve the speed of diagnosis on arrival in the A&E department to avoid delay in the delivery of specialist assessment and management. It should be noted that some strokes (e.g. those affecting purely balance or cognition) may not be picked up by clinical assessment tools.

The clinical question addressed is whether emergency health professionals are able to use a clinical assessment tool to accurately identify those patients who have had a suspected stroke or TIA.

5.1.2 Clinical methodological introduction

A number of different pre-hospital 'assessment tools' were identified for use by paramedics, namely the Face Arm Speech Test (FAST),^{10,11} Los Angeles Prehospital Stroke Screen (LAPSS),¹² Cincinnati Prehospital Stroke Scale (CPSS)¹³ and Melbourne Ambulance Stroke Screen (MASS).^{14,15} In addition one assessment tool, Recognition of Stroke in the Emergency Room (ROSIER)¹⁶ has been developed for use by ER (A&E department) hospital personnel. Level 2+

Studies varied considerably with respect to patient selection, setting (e.g. hospital versus field study) and outcomes. Table 5.1 below outlines the different pre-admission and emergency assessment tools.

Table 5.1 Pre-admission and emergency assessment tools

Study	Assessment tool	Administered by	Number of patients/ assessments	Description
Harbison et al. (2003), Mohd Nor et al. (2004)	Face Arm Speech Test (FAST) (modified from the Cincinnati Prehospital Stroke Scale (CPSS) – see below)	Paramedics	Harbison et al. N=487 Smith et al. N=446 Mohd Nor et al. N=278	Physical assessment: facial weakness, arm weakness and speech disturbance. Training in FAST is an integral component of the paramedic training module.

continued

Table 5.1 Pre-admission and emergency assessment tools – *continued*

Study	Assessment tool	Administered by	Number of patients/ assessments	Description
Kidwell et al. (2000)	Los Angeles Prehospital Stroke Screen (LAPSS)	Paramedics	N=171	History items: age >45 yrs, seizures history, at baseline patient is not wheelchair bound or bedridden and blood glucose. Physical assessment: facial asymmetry, hand grip and arm weakness.
Kothari et al. (1999)	Cincinnati Prehospital Stroke Scale (CPSS)	Paramedics and emergency medical technicians	N=74	History items: none. Physical assessment: facial palsy, arm weakness and speech abnormalities.
Bray et al. (2005a, 2005b)	Melbourne Ambulance Stroke Screen (MASS)	Paramedics	N=100 (a) N=210 (b)	History items: age >45 yrs, seizure history, at baseline wheelchair bound or bedridden and blood glucose. Physical assessment: facial droop, hand grip, arm drift and speech abnormalities.
Mohd Nor et al. (2005)	Recognition of Stroke in the Emergency Room (ROSIER)	ER physicians	N=343	Demographic details, blood pressure and blood glucose concentrations. Items on loss of consciousness and seizure activity. Physical assessment: facial weakness, arm weakness, leg weakness, speech disturbance and visual field defects.

5.1.3 Health economic methodological introduction

No studies were identified.

5.1.4 Clinical evidence statements

▷ 1.0 Face Arm Speech Test (FAST)

Two studies evaluated the diagnostic accuracy of FAST by paramedics.^{10,11} **Level 1b+**

One study prospectively compared the characteristics and the accuracy of referrals to the acute stroke unit from ambulance staff using the FAST instrument with those of primary care doctors (PCDs) and ER doctors.¹⁰ **Level 1b+**

The positive predictive value (PPV) for ambulance staff was 78% (95%CI 72 to 84%). A stroke/TIA detection rate (diagnostic accuracy) was estimated for the ambulance paramedics by assuming all strokes/TIAs that were taken by ambulance to the ER were referred to the acute stroke unit. This gave an upper estimation of sensitivity of 79%.^{*10} There were no significant differences between the ambulance paramedics, PCDs and ER personnel on the number of non-stroke cases referred to the stroke service (NS). Overall, the ambulance paramedic diagnosis of stroke was as accurate as that of PCDs or ER doctors, although the strokes they admitted tended to be more severe and may have therefore been easier to diagnose.¹⁰ **Level 1b+**

* It was not possible to calculate an accurate diagnostic sensitivity in any referring group because non-referrals to the acute stroke unit were not reviewed.

A further 'in the field' study reported acceptable interobserver agreement between neurological signs recorded in the FAST by paramedics and stroke physicians after admission.¹¹ **Level 1b+**

▷ 1.1 The Cincinnati Prehospital Stroke Scale (CPSS)

This study prospectively validated the CPSS used by pre-hospital care providers (paramedics and emergency medical technicians (EMTs)).¹⁷ **Level 2+**

There was high reproducibility among pre-hospital care providers for total score and for each scale item (arm weakness, speech and facial droop). There was a high correlation between the physicians' total scores and the pre-hospital providers. Agreement on scoring on specific items between physicians and pre-hospital personnel was high for all three items. A single abnormality on the CPSS had a sensitivity of 66% and a specificity of 87% in identifying a patient with stroke when scored by a physician and 59% and 89% respectively, when scored by a pre-hospital provider.¹⁷ **Level 2+**

▷ 1.2 Los Angeles Prehospital Stroke Screen (LAPSS)

The diagnostic accuracy of paramedics using LAPSS in the field was compared with that of emergency department and final hospital discharge diagnoses.¹² **Level 2+**

In patients with completed LAPSS forms (corrected for documentation error) the sensitivity was 91% (95%CI 76 to 98%); specificity 97% (93 to 99%); PPV 97% (84 to 99%); and negative predictive value (NPV) 98% (95 to 99%).¹² **Level 2+**

▷ 1.3 Melbourne Ambulance Stroke Screen (MASS)

Two studies were identified for this assessment scale.^{14,15} **Level 2+**

One study reported that accuracy of paramedics at identifying stroke significantly improved after stroke education and training on the use of the MASS tool from 78% (95%CI 63 to 88%) to 94% (95%CI 86 to 98%). For the MASS paramedics the sensitivity of stroke diagnosis was significantly greater when the MASS tool was used compared with strokes for which there was no documented assessment (95 vs 70%).¹⁴ **Level 2+**

Another study performed an in-field validation of the MASS (N=100 assessments). The MASS showed equivalent levels of sensitivity compared to the CPSS (NS) but was significantly superior to that of the LAPSS (90 vs 78% (95%CI 67 to 87)). The specificity of the MASS was equivalent to that of the LAPSS (NS) but was significantly superior to that of the CPSS (74 vs 56% (36 to 74)).¹⁵ The PPV of MASS, LAPSS and CPSS were 90 (95%CI 81 to 96), 93 (95%CI 83 to 98) and 85 (95%CI 75 to 92) per cent respectively, the NPV for MASS, LAPSS and CPSS were 74 (95%CI 53 to 88), 59 (95%CI 42 to 74) and 79 (95%CI 54 to 93) per cent respectively. **Level 2+**

▷ 1.4 Recognition of Stroke in the Emergency Room (ROSIER)

One study prospectively validated the ROSIER in stroke/TIA patients used by ER physicians.¹⁶ **Level 1b+**

For a stroke cut-off rating of 1+ or above, the ROSIER scale had a sensitivity of 93%. The ROSIER scale incorrectly diagnosed 17/160 (10%; 10 false positive, 7 false negative). The

diagnostic performance of ROSIER compared with CPSS, FAST and LAPSS in the patients described in this study is presented in table 5.2 below. FAST scores were completed for 49 of 91 (54%) stroke patients taken to ER by ambulance paramedics. For these patients, ROSIER was superior to FAST (sensitivity 92 vs 54%, specificity 96 vs 91%, PPV 96 vs 88%, NPV 92 vs 64%).¹⁶ **Level 1b+**

Table 5.2 The diagnostic performance of ROSIER compared to CPSS, FAST and LAPSS

	ROSIER % (95%CI)	CPSS % (95%CI)	FAST % (95%CI)	LAPSS % (95%CI)
Sensitivity	93 (89–97)	85 (80–90)	82 (76–88)	59 (52–66)
Specificity	83 (77–89)	79 (73–85)	83 (77–89)	85 (80–90)
Positive Predictive Value	90 (85–95)	88 (83–93)	89 (84–94)	87 (82–92)
Negative Predictive Value	88 (83–93)	75 (68–82)	73 (66–80)	55 (48–62)

5.1.5 From evidence to recommendations

The use of a validated tool to identify the symptoms and signs of suspected stroke and TIA increases diagnostic accuracy. The GDG noted that a study of ambulance paramedics, A&E and PCDs using the FAST assessment demonstrated a high PPV for accurate diagnosis of stroke and TIA. Immediate diagnosis improves the speed of access to specialist care.

The GDG noted that one study using the MASS validated tool compared the diagnostic accuracy of untrained versus trained paramedics and found that training improved the accuracy of diagnosis.

The ROSIER assessment is validated for use in A&E. It is more detailed than the FAST assessment (it includes blood sugar, visual field assessment and documentation of a history of seizures or loss of consciousness). It is more accurate than CPSS, FAST or LAPSS. The GDG reviewed the evidence and concurred that while a pre-hospital assessment including blood glucose is essential to ensure rapid admission to specialist care, a more detailed assessment tool is required in A&E to exclude common stroke mimics such as hypoglycaemia or Todd's paresis.

5.1.6 RECOMMENDATIONS

- R1** In people with sudden onset of neurological symptoms a validated tool, such as Face Arm Speech Test (FAST), should be used outside hospital to screen for a diagnosis of stroke or TIA.
- R2** In people with sudden onset of neurological symptoms, hypoglycaemia should be excluded as the cause of these symptoms.
- R3** People who are admitted to accident & emergency (A&E) with a suspected stroke or TIA should have the diagnosis established rapidly using a validated tool, such as Recognition of Stroke in the Emergency Room (ROSIER).

5.2 Early versus late assessment of people with TIA, and identifying those at high risk of stroke

5.2.1 Clinical introduction

Patients with transient neurological symptoms may underestimate their significance. They delay seeking specialist care or may wait days to see a general practitioner (GP). The Inter-collegiate Working Party Guidelines in 2001¹⁸ set a standard for a time to specialist assessment in a rapid access TIA clinic of 14 days, a target that was widely seen at the time as difficult to achieve. By 2004, this target was 1 week. The National Sentinel Audit in 2006³ showed that while 78% of Trusts had a designated neurovascular clinic, the average waiting time for a clinic appointment remained high at 12 days (IQR 7–17). Recent data from the Oxford Vascular Study (OXVASC) demonstrate that some patients are at high risk from completed stroke long before this time.

A systematic review of the risk of stroke within 7 days of TIA identified 18 independent cohorts (N=10,126 patients). The outcomes of 15 people were reported at 2 days after TIA and 17 at 7 days. The pooled risk of stroke at 2 days was 3.1% (95%CI 2.0 to 4.1) and at 7 days 5.2% (3.9 to 6.5). Significant heterogeneity was reported between the studies ($p < 0.0001$) reflecting the different study methodologies and clinical characteristics of the patient population.¹⁹

Simple clinical scoring systems can identify patients at particularly high risk who require immediate investigation and management. Specialist assessment involves confirmation of the diagnosis of TIA (around 40–50% of all TIA clinic referrals may, after specialist assessment, be diagnosed as non-neurovascular) and its vascular territory, appropriate investigations (including brain and carotid imaging), and assessment and management of vascular risk factors. A number of models of specialist assessment have been developed including ‘rapid access’ TIA clinics, daily in some cases, a 24-hour clinic, and day-case admission to hospital.

The clinical question addressed is whether scoring systems can accurately predict those patients with suspected TIA who need urgent referral for specialist assessment, and whether this early (immediate) assessment improves outcome.

5.2.2 Clinical methodological introduction

▷ Early vs late assessment

One prospective cohort study (EXPRESS)²⁰ and one observational study (SOS-TIA)²¹ were identified that looked at outcomes in patients with TIA who had undergone urgent assessment and treatment.

One study was a prospective population-based sequential comparison study (EXPRESS) of patients referred to an appointment-based TIA clinic that made treatment recommendations to primary care physicians (April 2002 to September 2004, phase one) (N=310) with a TIA clinic that did not require an appointment and at which treatment was initiated immediately if the diagnosis was confirmed (October 2004 onwards, phase two) (N=281). The mode of access and time of treatment initiation changed but the referral criteria remained consistent throughout. Treatment initiated in the second phase included aspirin 300 mg taken in the clinic, together with a 4-week prescription for any other medication prescribed by the clinic. In addition,

clopidogrel 300 mg loading dose was given to all patients initiated on aspirin. In contrast, in phase one, primary care physicians were generally recommended to prescribe aspirin or clopidogrel if the former was contraindicated.²⁰ Level 2++

A prospective observational study (SOS-TIA) (N=1,085) evaluated the impact of a 24-hour rapid assessment clinic for patients with suspected TIA. Clinical assessment occurred within 4 hours of admission. Patients with minor stroke, definite or possible TIA were prescribed antithrombotic medication immediately. The study reported on the risk of recurrent stroke in patients treated in a rapid access clinic compared with that predicted on the basis of signs and symptoms of admission (ABCD²).²¹ Level 3

▷ Scoring systems

Five studies were identified, all evaluated the accuracy of the one scoring system, namely the ABCD or a derivation of this (ABCD² score), to predict early stroke risk after TIA.^{22–25} One study was excluded due to methodological limitations.²⁶

5.2.3 Health economic methodological introduction

No papers were identified. An original cost-effectiveness analysis was conducted for this guideline. Detailed methods are presented in Appendix C, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250.

▷ Aim of the cost-effectiveness model

To evaluate the relative cost effectiveness of assessing patients identified by a GP with a suspected TIA:

- immediately at a specialist stroke unit, or
- within 7 days at a weekly specialist stroke unit clinic.

For comparison, we also included a strategy of follow-up by the GP without referral for specialist assessment.

We assessed cost effectiveness of each strategy for all patients combined but also compared the strategies for each ABCD² score group.

▷ General methods

The cost effectiveness of the different strategies was estimated using a simple decision analysis. The NICE reference case was followed. For example:

- Costs are measured from the perspective of the NHS and personal social services (PSS) including the long-term care costs for stroke patients.
- Health outcome is measured from the perspective of the patient (not carer or family members).
- Health outcome is measured in terms of quality adjusted life years (QALYs).
- A 3.5% discount rate was applied to both costs and effects.

Where appropriate, we have used data and assumptions from the HTA report on the effectiveness and cost effectiveness of carotid artery assessment by Wardlaw et al.²⁷

▷ The model

The decision model sought to capture the following effects:

- Patients seen at a specialist clinic are more likely to be given appropriate medication and therefore will have strokes averted (in the first 90 days).
- Patients seen immediately will receive this medication sooner and therefore will have more strokes averted than those seen at weekly clinics.
- Patients seen at a specialist clinic will receive carotid artery ultrasound imaging (and subsequent carotid endarterectomy if stenosis $\geq 50\%$), which will reduce the incidence of stroke (over 5 years). Whereas patients followed up by their GP do not receive imaging or surgery.
- Patients seen at a specialist clinic immediately will be more likely to receive endarterectomy within 2 weeks, when it is more effective, compared with patients who are seen at a weekly clinic. Furthermore, more patients will have a stroke before they have surgery.
- Carotid artery imaging is not perfectly accurate.
- Endarterectomy confers a risk of death in the short term.
- Specialist clinics are more costly than GP assessment. Costs of drugs over the lifetime will be increased. But these costs will be at least partly offset by cost savings from reduced stroke treatment over the lifetime.

The effect of different treatment strategies is first modelled in terms of effect on stroke incidence. Patients are then divided into whether or not the stroke was fatal and whether or not the stroke left them dependent. Long-term quality adjusted life expectancy was estimated for each group and for the patients who do not experience a stroke. Similarly, lifetime healthcare costs are measured for each stroke outcome.

Patients in lower ABCD² score groups have a lower baseline risk of stroke and therefore have fewer strokes averted compared with patients in higher ABCD² score groups.

5.2.4 Clinical evidence statements

▷ Early vs late assessment

The EXPRESS study reported a highly significant reduction in the 90-day recurrent stroke rate in phase two compared with phase one for patients referred to the study clinic (12.4 vs 4.4%; $p < 0.0015$).²⁰ **Level 2++**

At one month a significantly higher proportion of patients referred to the study clinic in phase two compared with phase one were prescribed antiplatelet agents or anticoagulant therapy, aspirin and a 30-day course of clopidogrel, one or more blood pressure lowering drugs. Similarly, a significantly higher proportion were referred to carotid surgery within 7 days or less or 30 days or less.²⁰ **Level 2++**

There was no significant difference in the delay from the presenting event to seeking medical attention in patients subsequently referred to the study clinic between the two study phases (NS). However, there was a significantly longer delay in seeking medical attention from primary care to assessment in clinic in phase one (median 3 days) compared with phase two (median less than 1 day). A significantly higher proportion of patients were seen within 6 hours or less

from first call to medical attention to assessment in the study clinic in phase two than in phase one. Consequently, there were significantly fewer recurrent strokes after presentation to primary care but before assessment in clinic in phase two than in phase one. Median time from seeking medical attention to first prescription of one or the other treatments recommended in the faxed letter from the study clinic to primary care was significantly longer in phase one than in phase two (20 vs 1 day).²⁰ **Level 2++**

The 90-day risk of recurrent stroke in referrals to the study clinic was significantly greater in phase one than in phase two for patients presenting with TIA, stroke, both men and women and for all age groups (statistical analysis not reported).²⁰ **Level 2++**

Early treatment (phase two) did not increase the 30-day risk of bleeding events requiring medical attention (NS). No symptomatic intracerebral or other intracerebral haemorrhages were identified in either phase of the study and there was no symptomatic haemorrhagic transformation of infarction (NS).²⁰ **Level 2++**

The prospective observational study evaluating the impact of a 24-hour rapid assessment clinic for patients with suspected TIA reported:²¹

- 701/1085 (65%) patients assessed in the clinic had confirmed TIA or minor stroke. 277/1085 (26%) of patients were admitted to a stroke unit and remainder were discharged home on the day of the examination at the clinic.
- 824/845 (98%) patients with minor stroke, definite or probable TIA received antithrombotic medication immediately.
- 44/51 (86%) patients with atrial fibrillation (AF) and definite TIA were prescribed oral anticoagulants.
- 129 (24%) patients with definite TIA and no evidence of brain tissue damage, and 46 (43%) patients with definite TIA and evidence of brain tissue damage, were started on medication to lower blood pressure or had their medication modified. **Level 3**

Table 5.3 below reports the 90-day stroke risk (95%CI) recorded in patients attending the rapid assessment clinic compared with that expected on the basis of the ABCD² score.²¹

Table 5.3 90-day stroke risk recorded in patients attending the rapid assessment clinic compared with that expected on the basis of the ABCD² score

Patients	Number of strokes	90-day stroke risk	
		Reported (95%CI)	Predicted
All (N=1,052)	13	1.24 (0.72 to 2.12)	5.96
Definite TIA + no brain lesion (N=524)	7	1.34 (0.64 to 2.78)	6.13
Definite TIA + new brain lesion (N=105)	7	4.76 (2.01 to 11.06)	7.76
Possible TIA (N=141)	1	0.71 (0.10 to 4.93)	4

For all patients seen within 24 hours of symptom onset in the rapid assessment clinic (N=552), the actual 90-day stroke rate was 1.63% (95%CI 0.85 to 3.12) vs 6.49%.²¹ **Level 3**

Scoring systems

The ABCD score was derived from the OXVASC study²⁴ where a series of clinical features in people with TIA were related to subsequent stroke risk: age (<60 years=0, ≥60=1); BP (systolic ≤140 mmHg and/or diastolic >90 mmHg=0, systolic >140 mmHg and/or diastolic >90 mmHg =1); clinical features (unilateral weakness=2, speech disturbance without weakness=1, other symptom=0); duration of symptoms (<10 mins=0, 10 to 59 mins=1, ≥60 mins=2). The ABCD score aims to identify individuals at high risk of stroke and who may require emergency intervention.

Due to the different study populations and outcomes, the results of each study are presented separately.

▷ 1.0 Rothwell et al. (2005)²⁴

One study derived a score for the 7-day risk of stroke based on a population of patients with probable or definite TIA (N=209). The score was then validated in a similar population cohort (OXVASC, N=190).^{*} The clinical usefulness of the score to 'front-line' health professionals was assessed by using it to stratify all patients with suspected TIA referred to OXVASC (N=378) and to a hospital-based weekly TIA clinic (N=210).²⁴ **Level 3**

The 7-day risk of stroke for the OXVASC cohort was 5.3% (3.0 to 7.5) and for the hospital-based cohort 5.2% (2.2 to 8.3). In the OXVASC (N=377) population-based cohort 19/377 referrals, 19 (95%) of the strokes that occurred within 7 days of presenting TIA occurred in the 101 (27%) patients with a risk score of 5 or greater. The score was still significantly predictive when the five 7-day strokes that occurred before the patient sought medical attention after the initial TIA were excluded.²⁴ **Level 3**

In the non-OXVASC hospital-referred TIA clinic (N=206) the median (IQR) time to referral to clinic and the appointment was 9 (4 to 16 days), with 42% seen within the 7 days of referral. Fourteen (7.5%) patients had a stroke before their scheduled clinical appointment. The ABCD score was a significant predictor of stroke before the clinical appointment with no events in patients with a score of less than 4.²⁴ **Level 3**

▷ 2.0 Tsivgoulis et al. (2006)²⁵

This study validated the ABCD score retrospectively by reviewing the emergency room and hospital records of patients with definite TIA (N=226). These patients were followed up prospectively for 1 month to derive a 30-day risk of stroke.²⁵

The 30-day risk of stroke was 9.7% (95%CI 5.8 to 13.6%). The ABCD score was highly predictive of both 7- and 30-day risks of stroke. The multivariate Cox regression analyses revealed that an ABCD score of 5 to 6 was an independent predictor of the 30-day stroke risk. More specifically, an ABCD score of 5 to 6 at the ED was associated with an 8-fold greater 30-day risk of stroke. Furthermore, an ABCD score of 5 to 6 was also independently significantly associated with the 7-day risk of stroke.²⁵ **Level 3**

^{*} The latter is a subgroup of people in the OXVASC diagnosed by the study neurologist with only possible TIA, made an alternative diagnosis, or could not explain the diagnosis.

Table 5.4 The 7-day risk of stroke stratified according to ABCD score at the first assessment in all referrals with suspected TIA to OXVASC and risk of stroke before the scheduled clinic appointment in all referrals with suspected TIA to the non-OXVASC hospital-referred weekly clinic.²⁴ Level 3

	Risk of stroke within 7 days		
	Patients (%)	Events (%)	Risk % (95%CI)
OXVASC			
≤1	28 (7)	0	0
2	74 (20)	0	0
3	82 (22)	0	0
4	90 (24)	1 (5)	1.1 (0 to 3.3)
5	66 (18)	8 (40)	12.1 (4.2 to 20.0)
6	35 (9)	11 (55)	31.4 (16.0 to 46.8)
Weekly clinic			
≤1	18 (9)	0	0
2	36 (18)	0	0
3	40 (20)	0	0
4	55 (26)	5 (36)	9.1 (1.5 to 16.7)
5	34 (16)	4 (29)	11.8 (0.9 to 22.6)
6	23 (11)	5 (36)	23.8 (5.6 to 42.0)

Table 5.5 The ABCD score predictive value of the risk of stroke at both 7 and 30 days

ABCD score	7 days			30 days	
	Patients (%)	Strokes (%)	Risk (%; 95%CI)	Strokes (%)	Risk (%; 95%CI)
0	5 (2)	0	0	0	0
1	12 (5)	0	0	0	0
2	22 (10)	0	0	0	0
3	58 (26)	1 (5)	1.7 (0–5.1)	2 (9)	3.5 (0–8.2)
4	66 (29)	5 (28)	7.6 (1.2–14.0)	5 (23)	7.6 (1.2–14.0)
5	47 (21)	9 (50)	19.1 (7.8–30.4)	10 (45)	21.3 (10.4–33.0)
6	16 (7)	3 (17)	18.8 (0–37.9)	5 (23)	31.3 (9.6–54.0)

▷ 3.0 Bray et al. (2007)²²

A retrospective study (N=98) evaluated the accuracy of a dichotomised ABCD to predict stroke at 7 and 90 days in patients with TIA presenting to an emergency department.²² Level 3

Table 5.6 The proportions of strokes occurring by 7 and 90 days stratified by the ABCD score on admission

ABCD score	Patients, n (%)	Stroke, n (% risk)	
		7 days	90 days
0	1 (1)	0	0
1	6 (6)	0	0
2	7 (7)	0	1 (14)
3	21 (22)	0	0
4	15 (15)	0	0
5	28 (29)	3 (11)	3 (11)
6	20 (20)	1 (5)	3 (15)
Total	98 (100)	4	7

Dichotomising the ABCD score (4 or less vs ≥ 5) categorised 48 (49%) of patients at high risk for stroke. This group included the four strokes that occurred within 7 days and six of the seven strokes that occurred at 90 days. See table 5.7 below for the accuracy of the ABCD score (high risk) at predicting the 7- and 90-day risks of stroke.²² Level 3

Table 5.7 The ABCD score (high risk) at predicting the 7- and 90-day risks of stroke

Risk (no. of strokes)	Sensitivity % (95%CI)	Specificity % (95%CI)	Positive predictive value % (95%CI)	Negative predictive value % (95%CI)
7 days (N=4)	100 (40–100)	53 (43–63)	8 (3–21)	100 (91–100)
90 days (N=7)	86 (42–99)	54 (43–64)	12.5 (5–26)	98 (88–100)

A large number of patients (79%) were aged ≥ 60 years and due to the low number of strokes for this variable, a retrospective analysis was performed when this item was removed. This decreased the number of false positives from 44 to 21 at 7 days and from 42 to 19 at 90 days, without changing the scores' ability to predict stroke.²² Level 3

▷ 4.0 Johnston et al. (2007)²³

One study validated the ABCD score in four independent groups of patients (N=2,893) diagnosed with TIA in emergency departments and clinics in the USA and UK. From this, a unified score was derived (ABCD²) optimised to predict the 2-day risk of stroke. The ABCD²

score was based on five factors (age ≥ 60 yrs (1 point); blood pressure $\geq 140/90$ mmHg (1); clinical features: unilateral weakness (2), speech impairment without weakness (1); duration ≥ 60 min (2) or 10–59 min (1); and diabetes (1)).²³ Level 3

In these four groups, 2-day risk was 0% for an ABCD² of 0 or 1, 1 to 2% for a score of 2, 0 to 3% for 3, 2 to 4% for 4, 3 to 6% for 5, 4 to 14% for 6, and 0 to 50% for 7.

Overall, when the four validation groups were combined 47/4,799 (1%) patients with complete information in the combined cohorts scored 0, 191 (4%) scored 1, 543 (11%) scored 2, 847 (18%) scored 3, 11,165 (24%) scored 4, 994 (21%) scored 5, 852 (18%) scored 6, and 160 (3%) scored 7. Table 5.8 below shows percentage range of risk of stroke at 2, 7 and 90 days for the four validation groups (the sample size of the groups ranged from N=315 to N=1,069).²³ Level 3

Table 5.8 The percentage range of risk of stroke at 2, 7 and 90 days for the four validation groups

Risk of stroke (days)	No. of strokes (%)	ABCD ² (%) (The range of % risk across the four validation groups)							
		0	1	2	3	4	5	6	7
Patients	2,889	37	138	373	560	693	545	455	88
2	2 to 5	0	0	1–2	0–3	2–4	3–6	4–14	0–50
7	3 to 7	0	0	1–2	0–3	3–11	6–7	7–25	0–50
90	6 to 10	0	0–3	2–6	1–5	5–11	10–14	11–28	18–50

Table 5.9 The data stratified as a low, moderate or high risk of stroke based on the ABCD² score

Risk (score)	2 days (N=1,628)	7 days (N=2,169)	90 days (N=1,012)
Low risk (<4)	1%	1.2%	3.1%
Moderate risk (4 or 5)	4.1%	5.9%	9.8%
High risk >5	8.1%	11.7%	17.8%

Of 4,746 patients who did not have a stroke during the emergency department evaluation for TIA, 432 (9.1%) were admitted to hospital for the initial attack; this occurred mainly in the validation group from California. Overall, 111 (85%) of 130 strokes occurring within 2 days of the TIA were in patients who were not admitted to hospital, and 45 of these 111 (41%) had an ABCD² score of greater than 5.²³ Level 3

5.2.5 Health economics evidence statement

This section contains the results of an original cost-effectiveness analysis conducted for this guideline. Detailed results are presented in Appendix C, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250

▷ All patients combined

When all patients were assessed in the same way regardless of ABCD² score, immediate specialist assessment had the least number of strokes and the most QALYs. GP care had the most strokes and least QALYs. Weekly specialist assessment was most costly and GP care least costly.

Immediate specialist assessment dominated weekly specialist assessment, that is to say it was more effective and less expensive than weekly specialist assessment. Immediate specialist assessment was cost effective compared with GP care, costing an extra £3,000 per additional QALY gained.

▷ Prioritising patients by ABCD² score

The number of strokes averted in the first 90 days after TIA varied greatly by ABCD² score group. However, immediate specialist assessment dominated weekly clinic for every group. Immediate specialist assessment was cost effective compared with GP care for all groups except 0 and 1.

▷ Limitations

Immediate specialist assessment appears to be cost effective compared to weekly clinics for all ABCD² score groups, and the results appear to be robust to changes in key parameters.

The results seem to imply that specialist assessment (immediate or weekly) is not cost effective compared with GP care for the lowest ABCD score groups but this cannot be concluded since the model does not incorporate the health gain nor the costs associated with stroke mimics. Furthermore, the model does not capture the health gain attributable to increased uptake of statins and certain other drugs, which are costed in the model.

Although the model includes costs for long-term nursing care for dependent stroke patients, informal care costs were not included since these are not within the NHS perspective. If they had been included, then immediate specialist assessment would have appeared even more cost effective.

The model is a simple representation, looking at only 90 days after the TIA for the effects of medical treatment and extrapolating from this to get long-term outcomes, and thus caution should be applied when using these results. However, the results of this analysis reinforce the conclusions of other studies.

▷ Other related studies

The Wardlaw et al. NHS HTA report indicated that the net benefit of stroke prevention clinics was dependent on the speed with which patients could be investigated or treated.²⁷ As the risk of stroke for TIA patients is high in the first month, treatment strategies which allow patients to be treated within this period appear to be cost effective.

The EXPRESS study, which was published after the development of this model, suggests that the impact of early specialist assessment on stroke risk might be greater still. This before and after cohort study found a relative reduction in stroke risk of about 80% for immediate specialist assessment compared to an appointment-based clinic.

Finally, a forthcoming report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D has constructed a similar cost-effective model comparing different assessment strategies.²⁸ Based on the provisional results, it also found that same-day clinics are cost effective compared with weekly clinics for every ABCD² score group.

▷ Conclusion

Referral of suspected TIA patients for immediate specialist assessment appears to be cost effective because it supports timely prescribing of effective drugs and selection of patients for effective surgery.

5.2.6 From evidence to recommendations

It is clear that scoring systems such as the ABCD and ABCD² are good clinical predictors and are accurate at identifying patients who are at high risk of subsequent stroke. The level of risk that might be acceptable to patients of completed stroke whilst waiting 7 days for a clinic appointment was discussed with the patient representatives on the group.

The GDG patient view is that any potential risk is a concern to patients. Informing patients of the risk they run whilst awaiting an appointment would cause unacceptable levels of anxiety and distress; they would want appropriate management without delay.

The consensus of the GDG is that high-risk patients need to be immediately identified, assessed and secondary prevention initiated. The GDG considers that high-risk patients are defined as patients with a risk of >4% over 7 days; equivalent to ABCD² score of 4 or greater. The health economic modelling evidence (please refer to Appendix C for more information, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=250) found that the cost effectiveness of immediate assessment declines with ABCD² score. However, immediate specialist assessment was cost effective compared with weekly specialist assessment even for the lowest ABCD² score group. This said, the GDG did not feel that *immediate* specialist assessment was practical for all patients, as it may result in a larger number of non-vascular events (e.g. migrainous symptoms, transient vertigo) being referred urgently to specialist services with the risk that services become overwhelmed. Providers and commissioners concerned about capacity will need to ensure that the highest risk (ABCD² >3) patients are given highest priority.

Evidence from the EXPRESS and the SOS-TIA studies emphasises the need not only for identification of patients at high risk of subsequent stroke, but also early specialist intervention, including commencement of appropriate secondary prevention treatments and early carotid endarterectomy where indicated. Secondary prevention includes antiplatelet agents, blood pressure management, anticoagulation in selected patients e.g. people with AF, exclusion of diabetes, management of dyslipidaemia including statins, and diet and lifestyle advice, particularly smoking cessation.²⁹

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

Specialist assessment includes:

- exclusion of stroke mimics
- identification of vascular territory

- identification of likely causes
- appropriate investigation and treatment.

5.2.7 RECOMMENDATIONS

- R4** People who have had a suspected TIA (that is, they have no neurological symptoms at the time of assessment (within 24 hours)), should be assessed as soon as possible for their risk of subsequent stroke using a validated scoring system,* such as ABCD².
- R5** People who have had a suspected TIA who are at high risk of stroke (that is, with an ABCD² score of 4 or above) should have:
- aspirin (300 mg daily) started immediately
 - specialist assessment and investigation within 24 hours of onset of symptoms
 - measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.
- R6** People with crescendo TIA (two or more TIAs in a week) should be treated as being at high risk of stroke (as described in recommendation 5), even though they may have an ABCD² score of 3 or below.
- R7** People who have had a suspected TIA who are at lower risk of stroke (that is, an ABCD² score of 3 or below) should have:
- aspirin (300 mg daily) started immediately
 - specialist assessment and investigation as soon as possible, but definitely within 1 week of onset of symptoms
 - measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.
- R8** People who have had a TIA but who present late (more than 1 week after their last symptom has resolved) should be treated as though they are at lower risk of stroke (see recommendation 7).

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

6 Imaging in TIA and non-disabling stroke

6.1 Suspected TIA – referral for urgent brain imaging

6.1.1 Clinical introduction

Recent evidence underlines the importance of immediate assessment and treatment of patients with TIA who are at high risk of completed stroke.³⁰ Careful history taking and examination is essential to exclude other diagnoses (e.g. migraine, seizure, syncope, tumour) and to assess vascular risk factors including hypertension, diabetes and dyslipidaemia. See section 8.2 for the use of early aspirin and other preventative measures. Early carotid scanning is essential to exclude significant carotid stenosis in patients who would fulfil criteria for carotid endarterectomy (see section 6.3). Not all patients with TIA need brain scanning. The selection of patients for urgent scanning is dependent on clinical features; it is important that brain scanning does not delay the institution of optimum secondary prevention or the detection and treatment of significant carotid stenosis. MR scanning is very much more sensitive than CT, particularly if performed early and using diffusion-weighted imaging (DWI); CT perfusion can also be used to detect small ischaemic lesions that might not be visible on standard CT.

The clinical question to be addressed is which patients with suspected TIA should undergo brain imaging.

6.1.2 Clinical methodological introduction

One meta-analysis (N=19 studies) was identified that reported on the association between clinical and demographic factors and the presence of acute ischaemic lesions on DWI in patients with TIA.³¹ The analysis included studies on patients imaged up to 14 days post event (median delay to scan: 37 hours). Level 3

6.1.3 Health economic methodological introduction

No papers were identified.

6.1.4 Clinical evidence statements

The systematic review reported a positive association between a positive DWI and motor weakness, dysphasia, dysarthria, duration of symptoms ≥ 60 mins, atrial fibrillation and ipsilateral carotid stenosis $\geq 50\%$. There were no associations between positive DWI and age ≥ 60 yrs (NS), previous hypertension (NS), current raised blood pressure (NS) and diabetes (NS).³¹ Level 3

Of the studies reporting on patients who were scanned within 24 hours or less from the index event, a positive scan was significantly associated with motor weakness and dysphasia only.³¹ Level 3

6.1.5 Health economic evidence statement

It was noted that MRI scan is considerably more expensive than CT scan – £228 per scan compared with £78 per scan.³²

6.1.6 From evidence to recommendations

There is no evidence that specifically addresses the question of which patients with TIA should be referred for urgent brain imaging. The GDG noted that good clinical assessment is essential to detect stroke mimics and to establish the vascular territory involved where possible. Brain imaging is of potential value in the detection of stroke mimics and in establishing the diagnosis where this is in doubt. In addition, brain imaging may be of value in determining the vascular territory involved where this is not clear from the clinical assessment (examples where imaging may be helpful because diagnosis is in doubt or vascular territory may need to be determined, are illustrated in the section below entitled 'Cases where brain imaging is helpful in the management of TIA'). The GDG extrapolated from the evidence presented in section 5.2 (scoring systems to identify patients with TIA at high risk) and agreed that the ABCD² score should be used to identify those patients in need of immediate assessment and management, including urgent scanning where required. These patients need MR with DWI (where there are no contraindications) within 24 hours to avoid delay in instituting secondary prevention and the detection and management of significant carotid stenosis. An expert consensus was agreed that patients with severe comorbidities may not be appropriate for scanning if the results would not change management.

6.1.7 RECOMMENDATIONS

- R9** People who have had a suspected TIA (that is, whose symptoms and signs have completely resolved within 24 hours) should be assessed by a specialist (within 1 week of onset of symptoms) before a decision on brain imaging is made.
- R10** People who have had a suspected TIA who are at high risk of stroke (for example, with an ABCD² score of 4 or above, or with crescendo TIA) in whom the vascular territory or pathology is uncertain should undergo urgent brain imaging* (preferably diffusion-weighted magnetic resonance imaging (MRI)).
- R11** People who have had a suspected TIA who are at lower risk of stroke (for example, an ABCD² score of less than 4) in whom the vascular territory or pathology is uncertain should undergo brain imaging** (preferably diffusion-weighted MRI).

▷ Cases where brain imaging is helpful in the management of TIA:

- people being considered for carotid endarterectomy (CEA) where it is uncertain whether the stroke is in the anterior or posterior circulation
- people with TIA where haemorrhage needs to be excluded, for example long duration symptoms or people on anticoagulants
- where alternative diagnosis (for example migraine, epilepsy or tumour) is being considered.

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

** The GDG felt that brain imaging is defined as 'within 1 week of onset of symptoms'. This is in line with the National Stroke Strategy.

6.2 Type of brain imaging for people with suspected TIA

6.2.1 Clinical introduction

In 2006, 78% of hospitals had neurovascular clinics, with a median time between onset and review of 12 days.³ The key purpose of the clinic is to confirm the diagnosis of TIA (and manage those patients with an alternative diagnosis) and to ensure timely and appropriate secondary prevention. There has been little clarity over the need for brain scanning, with wide variations between clinics in the proportion of patients with TIA routinely scanned. Many clinicians have used CT because of lack of access to MR but availability of MR is now improving rapidly across the UK. Brain scanning may be used to detect stroke mimic (e.g. tumour) but diagnostic yields are low, unless there are suggestive clinical features. Although CT is very sensitive to haemorrhage early after the event, bleeds may be missed if scanning is delayed. Brain imaging is of value in determining the presence of vascular lesions (which may be helpful if there is diagnostic doubt) and helping to establish vascular territory where this is not clear. MR scanning, especially with diffusion-weighted imaging/fluid-attenuated inversion recovery (DWI/FLAIR) performed early (ideally within 24 hours) has high sensitivity for the detection of small ischaemic lesions which may be missed on CT scan.³³

The clinical question to be addressed is in those patients with TIA who require brain imaging whether MR or CT provides the most information to guide treatment.

6.2.2 Clinical methodological introduction

For this question, we looked at studies that reported on the association between imaging findings and the subsequent risk of mortality or morbidity.

Five observational studies/case series were identified, all reporting on MR diffusion weight imaging (MR-DWI) findings. See table 6.1 below for a summary of the study characteristics.^{34–38}

Table 6.1 A summary of the study characteristics

Studies (no. of patients)	Patients	Time to scan (from symptoms onset)	Positive scan	Follow-up duration
Purroy et al. (2004) N=83	TIA patients attending the emergency department	Maximum 7 days	32.5%	Mean 389 days
Prabhakaran et al. (2007) N=146	TIA admissions	Within 48 hrs	25%	90 days
Boulanger et al. (2007)	Patients with motor hemiparesis or aphasic TIA lasting not longer than 5 minutes within the previous 12 hrs	Within 24 hrs	41.2%	Median 13 months
Calvert et al. (2007)	Patients admitted to a stroke unit within 48 hrs of symptom onset with a diagnosis of probable or possible TIA	Median 180 mins	32.2%	3 months
Coutts et al. (2005)	Patients with minor stroke and NIHSS score of 0 to 3 or resolved hemiparesis or aphasia lasting longer than 5 mins	Within 24 hrs	45%	90 days

6.2.3 Health economic methodological introduction

No papers were identified.

6.2.4 Clinical evidence statements

The proportion of patients with MR-DWI abnormalities ranged from 25 to 58%.

Only the results of multivariate analysis are reported here:

- At 1 year, patients without a DWI abnormality were significantly more likely to have a subsequent TIA, but significantly less likely to have a subsequent stroke, than patients with a DWI abnormality (N=85).³⁴ **Level 3**
- Patients with a DWI abnormality were significantly more likely to have an in-hospital recurrent TIA or stroke than those without a DWI abnormality (N=146).³⁵ **Level 3**
- At 3 months, DWI abnormalities were a significant independent predictor of stroke (N=203).³⁶ **Level 3**
- The presence of a DWI abnormality in patients with TIA or minor stroke was significantly associated with an increased risk of 90-day stroke (N=120).³⁷ **Level 3**
- Symptoms greater than 1 hour and DWI abnormalities were significant independent predictors of further cerebral vascular events or any vascular event (follow-up mean 389 days) (N=83).³⁸ **Level 3**

6.2.5 From evidence to recommendations

The evidence reviewed did not specifically compare CT with MR after TIA. However, it is well established that MR is more sensitive than CT in the detection of vascular lesions particularly if performed early. The consensus of the GDG was that where brain scanning was felt to be necessary following TIA, MR with DWI within 24 hours should be performed. For those patients with contraindications or unable to tolerate MR, CT scanning should be used.

6.2.6 RECOMMENDATIONS

- R12 People who have had a suspected TIA who need brain imaging (that is, those in whom vascular territory or pathology is uncertain) should undergo diffusion-weighted MRI except where contraindicated,* in which case computed tomography (CT) scanning should be used.

6.3 Early carotid imaging in people with acute non-disabling stroke or TIA

6.3.1 Clinical introduction

Carotid imaging is required to determine the presence and severity of carotid stenosis in those individuals who may be appropriate for carotid endarterectomy, i.e. those with a TIA or minor or recovered stroke involving the anterior circulation who are fit and willing for surgery. Doppler ultrasound, MR angiography and CT angiography can be used in the screening for and

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

assessment of carotid stenosis. The urgency of the carotid imaging depends on the individual's risk of stroke (defined on clinical criteria: see section 6.4). Furthermore the value of carotid surgery decreases with time from the event, surgery ceases to be of value after 12 weeks of the event in trials for men and 2 weeks for women. Imaging should therefore be done rapidly if appropriate patients are to be assessed for surgery in a timely manner.

The clinical question to be addressed is which patients with suspected stroke/TIA should be referred for urgent carotid imaging.

6.3.2 Clinical methodological introduction

Four studies reported on the association between carotid stenosis and symptoms, demographics and comorbid conditions in patients who had undergone carotid duplex scanning (N=816);³⁹ (N=5,807 scans);⁴⁰ (N=726).^{41,42} Two of the studies were retrospective;^{39,40} and two were prospective;⁴¹ (N=305).⁴² One study was excluded⁴³ as all of the data were incorporated in a more recent study.⁴⁰

In two studies the populations were relatively homogenous, one was on patients with acute stroke admitted to hospital⁴² and the other on patients admitted to hospital or seen in an outpatient clinic with acute stroke, cerebral or retinal TIA or retinal strokes.⁴¹ Two studies reported on heterogenous populations, including for example patients with TIA, dizziness and dysphasia.^{39,40}

6.3.3 Health economic methodological introduction

One study was identified that modelled the cost effectiveness of different assessment strategies for carotid stenosis.²⁷

The study was a NHS HTA report of a systematic review of the costs of less invasive tests, outpatient clinics, endarterectomy and stroke, along with a micro-costing exercise. A Markov model of the process of care following a TIA/minor stroke was developed, populated with data from stroke epidemiology studies in the UK, effects of medical and surgical interventions, outcomes, quality of life and costs. Both strokes and MIs were modelled. A survey of UK stroke prevention clinics provided typical timings of surgery. Twenty-two different carotid imaging strategies were evaluated for short- and long-term outcomes, quality adjusted life years, NHS cost and net benefit. The strategies varied according to:

- the choice and sequence of tests (which included ultrasound, computed tomographic angiography (CTA), magnetic resonance angiography (MRA), contrast enhanced MRA (CEMRA) and intra-arterial angiography (IAA)), and
- the level of stenosis at which surgery would be under-taken.

No attempt was made to assess whether carotid imaging is cost effective compared with no carotid imaging in any population.

6.3.4 Clinical evidence statements

▷ Factors associated with carotid artery disease

One retrospective study reported that patients with definite carotid symptoms (TIA, cerebrovascular accident, amaurosis fugax or dysphagia) compared with non-carotid symptoms (dizziness, syncope, confusion and vertigo) were significantly more likely to have carotid stenosis.³⁹ Level 3

One retrospective study⁴⁰ reported significant associations between:

- stenosis >70% and
 - bruit, known carotid disease, postoperative endarterectomy, smoking, high blood pressure, diabetes, peripheral vascular disease, myocardial infarct and hyperlipidaemia
- carotid occlusion and
 - bruit, known carotid disease, postoperative endarterectomy, smoking, peripheral vascular disease, myocardial infarct and a past history of stroke
- stenosis >70% & carotid occlusion and
 - bruit, known carotid disease, postoperative endarterectomy, smoking, high blood pressure, diabetes, peripheral vascular disease, myocardial infarct, past history of stroke and hyperlipidaemia.

Level 3

One prospective study reported on the association between Oxford Community Stroke Project (OCSP) subtypes (total anterior circulation stroke (TAC), lacunar stroke (LAC), partial anterior circulation stroke (PAC) and posterior anterior circulation stroke (POC)), risk factors and severe carotid stenosis (70 to 99%) in patients with acute stroke, TIA or retinal strokes. The results were used to produce a simple strategy that could be used to identify who should be referred early for duplex imaging.⁴¹ **Level 3**

Multivariate analysis identified the following factors as independent significant positive associations with severe carotid stenosis, namely ipsilateral bruit, previous TIA and a significant negative association with a lacunar event. When complete occlusion was included in the analysis, diabetes was no longer significantly associated with severe carotid stenosis. The strategy with the highest specificity was to refer patients with any three of the four factors, namely ipsilateral bruit, previous TIA or diabetes mellitus and 'not a lacunar event'. Scanning patients with three out of the four factors has the specificity of 97%, but sensitivity only 17%. Scanning any patient with one or more of these aforementioned features results in the highest sensitivity of 99%, but specificity dropped to 22%.⁴¹ **Level 3**

▷ Stroke subtype

One prospective cohort study reported on whether stroke subtype, using the OCSP clinical classification, could identify those patients with acute stroke who should preferentially be referred for carotid imaging.⁴² **Level 3**

Severe stenosis (70 to 99%) was found in 16/101 (16%; 95%CI 9 to 23%) of the partial anterior circulation infarct (PACI) group, 4/100 (4%; 0 to 8%) of the total anterior circulation infarct (TACI) group, 0/80 of patients in the LAC group and 1/24 (4%; 0 to 8%) of the posterior circulation infarct (POCI) group (χ^2 $p < 0.05$). Complete ipsilateral occlusion was found in 25 (25%) of the TAC group, 11 (11%) of the PACI group, 3 (4%) of the LAC group and none in the POC group. Severe carotid stenosis or occlusion was more frequent in the ipsilateral than the contralateral disease in the LAC and POC groups, but there was no significant difference between the ipsilateral and contralateral carotid disease in the LAC and POC groups (NS). If only patients with PAC are selected for carotid imaging (to identify severe stenosis 70 to 99%) then the sensitivity is 76%, specificity 70%, PPV 16% and the NPV is 97.5%.⁴² **Level 3**

6.3.5 Health economic evidence statements

In the cost-effectiveness model²⁷ based on contemporary UK timings, the strategies which prevented most strokes and produced greatest net benefit were those that:

- 1 allowed more patients to reach endarterectomy very quickly, and
- 2 where those patients with 50–69% stenosis would be offered surgery in addition to those with 70–99% stenosis.

This included most strategies with ultrasound as first or repeat test, and not those with intra-arterial angiography. However, the model was sensitive to less invasive test accuracy, cost and timing of endarterectomy. In patients investigated late after TIA, some tests are much less accurate and therefore contrast-enhanced magnetic resonance angiography should be used before surgery. The authors conclude that in the UK, less invasive tests could be used in place of intra-arterial angiography if radiologists trained in carotid imaging are available.

The cost effectiveness of carotid imaging compared with no carotid imaging could not be easily inferred from this study.

6.3.6 From evidence to recommendations

Carotid imaging is essential to identify those people who would benefit from carotid endarterectomy (CEA). The evidence does not identify any clinical sign that is pathognomonic for carotid stenosis although some (e.g. bruit) may be suggestive. The group therefore agreed that all people who are suitable for carotid interventions should have access to carotid imaging.

6.3.7 RECOMMENDATION

- R13 All people with suspected non-disabling stroke or TIA who after specialist assessment (see section 5) are considered as candidates for carotid endarterectomy should have carotid imaging within 1 week of onset of symptoms. People who present more than 1 week after their last symptom of TIA has resolved should be managed using the lower-risk pathway.

6.4 Urgent carotid endarterectomy and carotid stenting in people with carotid stenosis

6.4.1 Clinical introduction

While the benefits of carotid intervention for symptomatic carotid stenosis of >50% according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria⁴⁴ and >70% according to the European Carotid Surgery Trial (ECST) criteria⁴⁵ have been clearly described elsewhere.²⁹ The benefit of early surgery (within 2 weeks of symptoms) may be outweighed by the risk of adverse events in patients with recent cerebral infarction, particularly those with significant neurological disability following a stroke or who have a high anaesthetic risk. However, patients with clinically defined high-risk TIA are clearly at highest risk of stroke within 2 days of the incident, implying that for some patients, very early endarterectomy might be most beneficial. Similarly, a case-series study reported no perioperative complications associated with early carotid stenting (<14 days) in patients with symptomatic carotid artery stenosis.⁴⁶ The non-randomised EXPRESS study²⁰ suggests that patients with TIA and minor

stroke benefit considerably from a package of early medical interventions including antiplatelet agents, a statin and blood pressure treatment.

The clinical question is which patients with symptomatic carotid stenosis should be referred for early interventional procedures. It is of note that the lack of standardisation of the definition of significant carotid stenosis can be confusing. It is important that those reporting carotid imaging studies clearly state which criteria for diagnosis are being used.

6.4.2 Clinical methodological introduction

One systematic review was identified.⁴⁷ This reports that the data on CEA performed less than 1 week compared with 1 week or later (two studies, N=135 vs 1,492). The data from Rothwell et al.⁴⁸ are reported in both this systematic review and the pooled analysis.⁴⁴ However, the analysis is reported for different time periods and on different outcomes.

Two studies reported on pooled data from two large RCTs, namely the ECST and the NASCET (N=5,893).^{45,44} ECST includes a measure of the normal lumen diameter at the site of the lesion based on a visual impression of where the normal artery was before the damage caused by the stenosis. NASCET includes a measure of the diameter of the visible portion of disease-free internal carotid artery (ICA) distal to the stenosis, or the stenosis was classified as 95% if the distal ICA had collapsed (see glossary). Patients with symptomatic carotid stenosis were randomised to medical treatment or to CEA. The data are reported according to time from last symptomatic ischaemic event to randomisation or surgery. 14.5% patients in the ECST and 25.9% patients in NASCET were randomised within 2 weeks.⁴⁵ Patients were included with TIA, non-disabling ischaemic stroke, or a retinal infarction, in the territory of a stenosed carotid artery. The two trials used different techniques to measure the degree of carotid stenosis and each trial made different recommendations regarding the degree of stenosis above which surgery was effective. However, when the angiograms from the ECST were re-measured in accordance with NASCET criteria, the outcomes of the two trials were comparable. Level 1++

No RCT studies were identified on carotid stenting in acute stroke.

The prospective case series (N=238) recorded data on all patients undergoing CEA after ipsilateral acute stroke performed within 1 month of symptom onset.⁴⁹ 55% of patients were operated within 2 weeks of symptom onset. All patients had stenosis of 50% or greater. Twelve patients underwent the procedure within 24 hours of symptom onset for stroke in evolution. According to NASCET criteria, of the 72% patients with available brain imaging, 35% were cortical infarcts, 16% small border zone infarcts, 13% deep infarcts and 36% no visible infarct. The degree of stenosis, or its statistical association with outcome, was not reported in this study. Level 3

6.4.3 Health economic methodological introduction

No papers were identified.

6.4.4 Clinical evidence statements

▷ 1.0 Mortality and neurological deficits by time interval

The systematic review reported that there was no significant difference for the outcome of perioperative stroke and death when comparing neurologically stable patients undergoing CEA less than 1 week since stroke with those undergoing the procedure 1 week or more since stroke onset (NS). Patients operated early with unstable neurological symptoms (stroke in evolution,

non-specified 'urgent' cases, and crescendo TIA) did worse if they were operated in the acute phase compared to later operation.⁴⁷ **Level 1+**

From the pooled analysis, the benefit of CEA decreases as the delay to randomisation increases, for both patients with 50 to 69% stenosis and those with $\geq 70\%$ stenosis. For the former, the 5-year absolute risk reduction (ARR) in ipsilateral ischaemic stroke and operative stroke or death was significant only if the patient was randomised to CEA within 2 weeks of the last event. The number of patients who needed to undergo surgery (NNT*) to prevent one ipsilateral stroke was three. ARR was not significant for CEA performed within 2 to 4 weeks, 4 to 12 weeks or greater than 12 weeks (NS). In patients with $\geq 70\%$ stenosis, CEA gave a significant ARR for patients randomised within 2 weeks, within 2 to 4 weeks and 4 to 12 weeks but not greater than 12 weeks (NS).⁴⁴ **Level 1++**

From the prospective case-series data, there were no and two deaths in patients undergoing CEA within 1 week and within 1 to 2 weeks of symptom onset respectively. This compares with one death at 2 to 4 weeks. There was no significant difference when comparing the different time intervals (NS). Furthermore, there were no significant differences reported between the time interval from symptom onset to CEA and permanent neurological deficit (NS) or permanent or temporary neurological deficit (NS).⁴⁹ **Level 3**

▷ 1.1 Clinical and demographic indicators

Table 6.2 below gives the absolute risk reduction with surgery in 5-year actual risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery from the pooled analysis of the RCTs. This shows that the effects of surgery are modified by time since last event, gender and age such that the benefit statistically decreases as the time since last symptoms increases, and is significantly greater in males than females and in the elderly. These results are consistent across patients with 50 to 69% and 70% or more stenosis.⁴⁵ **Level 1++**

Table 6.2 The absolute risk reduction with surgery in 5-year actual risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery from the pooled analysis of the RCTs

Factor	All patients
Time since last event (weeks)	Surgical vs medical (ARR; 95%CI)
<2	85/627 vs 122/556 (9.2; 4.7 to 13.7)
2 to 4 weeks	63/602 vs 72/452 (6.4; 2.1 to 10.7)
4 to 12 weeks	147/1257 vs 148/1055 (2.9; 0.0 to 5.8)
Gender	
Male	253/2307 vs 301/1868 (6.0; 3.8 to 8.2)
Female	134/929 vs 107/789 (−0.4; −3.8 to 3.0)
Age years	
<65	186/1645 vs 163/1255 (2.2; −0.3 to 4.7)
65–74	169/1303 vs 180/1105 (4.1; 1.2 to 7.1)
≥ 75	32/288 vs 65/297 (11.9; 5.7 to 18.1)

* Number needed to treat.

Univariate analysis from the prospective case-series data showed that increasing lesion size on preoperative CT scan or MRI significantly increased the odds of permanent neurological deficit.⁴⁹ Level 3

6.4.5 From evidence to recommendations

No RCTs were identified which studied early vs late carotid interventions using the 2-week cut off for the definition of acute stroke. No evidence for early carotid stenting (within the 2-week time period of the guideline) was identified. The GDG recognised the need for further research in this area. There is a need for a randomised trial comparing the safety and efficacy of carotid stenting to CEA within 2 weeks of TIA or recovered stroke. The GDG noted the systematic review reported that there was no significant difference in outcome in perioperative stroke or death with patients undergoing CEA less than 1 week compared to greater than 1 week. The GDG also noted that only the pooled analysis reported the long-term absolute relative risk of stroke or death. The evidence for benefit of referral for early CEA was extrapolated from the two studies which reported on pooled data from two large RCTs. Differences in genders were also noted (women only benefit from surgery early while men continue to benefit from surgery for longer), the GDG therefore noted that in order for women to benefit from surgery all patients should receive surgery early. There is evidence that patients with unstable neurological symptoms (stroke in evolution, crescendo TIA) may be harmed by early surgery. In neurologically stable patients, there is no statistical difference in the incidence of postoperative neurological deficit after CEA performed at 1–4 weeks after stroke onset. There is clear evidence from pooled data which showed that the benefit of CEA decreases as the delay to randomisation increases for patients with >50% stenosis according to the NASCET criteria. It was therefore agreed by the GDG that patients should be referred for CEA within 1 week of onset. Patients who have carotid stenosis of <50% should receive best medical treatment.

6.4.6 RECOMMENDATIONS

- R14** People with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of 50–99% according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, or 70–99% according to the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria, should:
- be assessed and referred for carotid endarterectomy (CEA) within 1 week of onset of stroke or TIA symptoms
 - undergo surgery within a maximum of 2 weeks of onset of stroke or TIA symptoms
 - receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice).
- R15** People with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of less than 50% according to the NASCET criteria, or less than 70% according to the ECST criteria, should:
- not undergo surgery
 - receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice).
- R16** Carotid imaging reports should clearly state which criteria (ECST or NASCET) were used when measuring the extent of carotid stenosis.

7 Specialist care in acute stroke

7.1 Specialist stroke units

7.1.1 Clinical introduction

Patients with stroke admitted to organised stroke care (usually a stroke unit) are less likely to die and more likely to leave hospital independent than those who are cared for in general (usually medical and care of the elderly) wards. The evidence for this, documented in a systematic review initially in 1997, was the catalyst for a marked change in stroke service organisation across the NHS. The National Service Framework for the Elderly (Standard 5: stroke)⁵⁰ recommended that all stroke patients should be admitted to organised stroke units. The National Audit Office Report⁶ in 2005 noted that there had been no increase in stroke beds between 2001 and 2004 in the National Sentinel Audits; in 2004, half of eligible patients were treated in a stroke unit at some point and only 41% spent most of their hospital stay there.² However, by 2006, 91% of Trusts in the UK had a stroke unit, 62% of patients were treated in a stroke unit at some point and 54% spent most of their hospital stay on a stroke unit.³

The development of thrombolysis and other acute treatments has led to an increased emphasis on acute management of stroke in addition to rehabilitation. 52% of UK Trusts now have an acute stroke unit, characterised by access to brain imaging within 24 hours, specialist ward rounds at least 5 times a week, and acute stroke protocols and guidelines. A significant proportion also have access to CT scanning within 3 hours, continuous physiological monitoring and policies for direct admission from A&E. There is much less trial evidence available for the efficacy of acute stroke units than for rehabilitation units.

The clinical question to be addressed is whether patients who are rapidly admitted to a specialist stroke unit have better clinical outcomes than those admitted through a general ward.

7.1.2 Clinical methodological introduction

▷ Specialist stroke unit

For the purposes of this question, specialist acute care was restricted to those units which focused on assessment, diagnostic tests including brain imaging and monitoring rather than rehabilitation. Features of stroke units included continuous monitoring of physiological functions, high staff-to-patient ratio, rapid access to diagnostic tests and treatment interventions.

One Cochrane systematic review was identified comparing organised inpatient (stroke unit) care for stroke with alternative care. Here we report the subgroup analysis that compared acute (semi-intensive) stroke units (continuous monitoring, high nurse staffing levels but no life support) with 'comprehensive wards' (a cerebrovascular ward and a stroke unit) or mixed rehabilitation wards.⁵¹ **Level 2++**

One RCT (N=304) was identified that looked at differences in management processes in stroke units compared with stroke team care.⁵² **Level 1+**

Five non-randomised controlled trials or cohort studies were identified.^{53–57} Six case series/observational studies were identified.^{58–62,54} **Level 3**

The patient populations were broadly comparable with the exception of two studies. One study restricted the analysis to those patients who were living at home without community support prior to the stroke⁶³ and the remaining study involved patients with intracerebral haemorrhage.⁵⁴
Level 3

7.1.3 Health economic methodological introduction

Three economic evaluations were identified that had an acute stroke or TIA population.

Launois et al. (2004)⁶⁴ reported on a French population. Not enough description was given of what care was received for the results to be applied to a UK setting. The results were for cost per trimester spent in minor disability, which cannot be compared with other evaluations and so would be difficult to use as evidence of the cost effectiveness of a stroke unit.

Moodie et al. (2006)⁶⁵ reported on an Australian population. The units involved were all in different hospitals and so care varied even under each definition. The stroke care units and mobile services were at teaching hospitals, whereas the conventional care was in smaller suburban hospitals.

Evidence from Patel et al. (2004)⁶⁶ was based on a randomised controlled trial (Kalra et al. 2005)⁶⁷ carried out in the UK. Stroke units were compared to care by a mobile stroke team on a general ward, or domiciliary care. The mobile stroke team comprised a specialist registrar, nurse, physiotherapist and an occupational therapist. The team assessed every patient at admission and recommended a diagnostic and treatment plan based on stroke unit guidelines for implementation by the ward team. Patients were allocated to care within 72 hours of stroke. Cost effectiveness was evaluated both including the costs of informal care and excluding them. Informal care costs were calculated by two alternative methods:

- a) time was valued using the minimum wage
- b) time was valued at the average wage of a social services home help.

The evaluation had a one-year time horizon to reflect the one-year trial follow-up. Utility scores were collected at various points during the year of follow-up.

7.1.4 Clinical evidence statements

Table 7.1 below summarises the outcome data on mortality, mortality or dependency combined and measures of dependency for patients admitted to acute stroke unit care compared with alternative care. The results are reported for all patients with acute ischaemic stroke and for specific subgroups where appropriate.

▷ Mortality

When comparing all patients with acute ischaemic stroke, three studies reported significantly lower mortality rates at discharge and at follow-up associated with acute stroke units compared with alternative care.^{58, 59, 61} In the Cochrane review there was significant heterogeneity in the results and a random effects model was therefore used. There were no significant differences (NS).⁵¹ Level 3

Four studies reported significant reductions in mortality associated with stroke unit care but only for specific subgroups.^{61,63,60,55} However, the different types of care received and outcome

Table 7.1 A summary of the outcome data on mortality, mortality or dependency combined and measures of dependency for patients admitted to acute stroke unit care compared with alternative care

Study	Death	Death or dependency
Stroke unit vs alternative care		
Cochrane review (2007) ⁵¹		
Acute (semi-intensive)		
N=259	NS	NS
Mixed rehabilitation		
Overall N=274	NS	NS
Candelise et al. (2007) ⁵⁸		
N=11,572	↑SU	↑SU
Adjusted	OR 0.78 (0.64 to 0.95)	OR 0.81 (0.72 to 0.91)
Chiu et al. (2007) ⁵⁹		
N=237	↑SU	NS
	OR 0.29 (0.10 to 0.81)	
Glader et al. (2001) ⁶⁰		
N=8,194		
Adjusted		
Living at home	↑SU	↑SU
Independent ADL*	OR 0.85 (0.77 to 0.94)	OR 1.01 (0.83 to 1.23)
Dependent ADL	NS	NS
Koton et al. (2005) ⁵³		
N=616		
Adjusted	NS	↑SU
		OR 2.1 (1.3 to 3.3)
Ovary et al. (2007) ⁶¹		
N=8,743		
All	↑SU	—
	OR 1.70 (1.03 to 2.82)	
mRS** <2 & <60 yrs	↑SU	↑SU (mRs >1)
	OR 1.77 (1.11 to 3.25)	70 vs 65% p=0.004
mRS ≥3 & >60 yrs	NS	↑SU
		56.1 vs 50.6 p=0.03
Silva et al. (2005) ⁵⁵		
N=530		
All	NS	
CSS ≤4***	↑SU	NS
	OR 0.19 (0.07 to 0.54)	
CSS >4	NS	
Stavem & Ronning (2002). ^{57,54}		
N=1,128	NS	NS
Stegmayr et al. (1999) ⁶³		
N=14,308		
Independent and unimpaired consciousness	↑SU	NS
	RR 0.87 (0.79 to 0.96)	
Independent with impaired consciousness	NS	NS
NS, not significant; ↑SU, significant difference in favour of a stroke unit; *Activities of Daily Living; **modified Rankin Scale; ***Canadian Stroke Scale		

measures used across the studies preclude any conclusion regarding any differential effects of stroke units on specific patient populations. **Level 3**

The study on patients with intracerebral haemorrhage reported a significantly lower mortality rate associated with a stroke unit compared with a general medical ward.⁵⁴ **Level 2++**

▷ Death or dependency

When comparing all patients with acute ischaemic stroke, three studies reported significant differences in favour of stroke units for the outcome of combined death or dependency or measures of disability or dependency.^{58,59,53}

A further three studies reported significant differences in favour of stroke units for these outcomes but only for specific groups.^{60,61,63} **Level 3**

The study on intracerebral haemorrhage reported no significant differences for a stroke unit compared with a general medical ward with respect to number of patients discharged home or to institutionalised care (NS).⁵⁴ **Level 2++**

A further study reported there was no significant difference at 6 months on quality-of-life measures when comparing patients admitted to a stroke unit with those admitted to a general medical ward (NS).⁵⁶ **Level 2+**

▷ Length of stay

The Cochrane review reported a significantly shorter length of hospital stay in patients admitted to stroke units compared with alternative care.⁵¹ **Level 1++**

One study reported a significantly shorter duration of hospital stay associated with stroke unit care⁵⁹ and in one study patients admitted with unimpaired consciousness on admission had a significantly longer stay if they were admitted to a stroke unit compared with a general ward.⁶³ **Level 3**

Three other studies found no significant differences in the duration of hospital stay for patients on stroke units compared with general wards.^{53,58,54} **Level 3**

▷ Diagnostic procedures and treatment

One study found no processes of care (including setting, staffing, protocols, mobilisation and diagnostic exams available) were associated with a good outcome.⁵⁸ Another study reported that patients admitted to a stroke unit were monitored significantly more frequently and were significantly more likely to receive measures to reduce aspiration and to receive early nutrition compared to patients on general wards.⁵² There was limited evidence to suggest that patients admitted to stroke units underwent diagnostic tests more frequently⁵³ or more quickly⁵⁴ than those admitted to a medical ward. Pharmacological interventions were more likely to be either inappropriately stopped or delayed if patients were admitted to a general ward compared with being admitted directly to a stroke unit.^{62,53,54} **Level 3**

7.1.5 Health economic evidence statement

▷ Randomised evidence

Patel et al. (2004)⁶⁶ found that stroke units provided the most expensive care (at one year), followed by the mobile stroke team, and then domiciliary care. This did not change regardless of whether informal care was included or not.

The mobile stroke team was less effective than domiciliary care, 69% of patients avoided death or institutionalisation compared to 78% in domiciliary care. The stroke unit was most effective with 87% of patients avoiding death or institutionalisation after one year.

When the stroke unit was compared to domiciliary care, the incremental cost per additional death/institutionalisation avoided was £49,600 (excluding costs of informal care), which related to an incremental cost per QALY of £64,097 with a one-year time horizon.

▷ Observational evidence

Moodie et al. (2006)⁶⁵ found that stroke units were more expensive than conventional care in the first 28 weeks (AU\$15,000 vs \$12,000, $p=0.08$). However, severe complications were significantly reduced (5.9% vs 25%, $p<0.001$).

7.1.6 From evidence to recommendations

The relatively low overall mortality rate in the systematic review compared to most unselected hospital-based cohorts may be due to selective entry of patients into trials. It was agreed that observational studies may be more representative of the stroke population as a whole. Three studies demonstrated that patients admitted to a stroke unit received therapeutic interventions and investigations more appropriately and quickly compared to those in a general medical ward. While better processes of care are linked to better outcomes there is currently no definitive trial support that these result in a reduction in mortality and morbidity. The lack of high-quality evidence was noted.

There is a need for a randomised trial comparing direct admission to an acute stroke unit vs admission to a medical ward at least while the latter remains standard clinical practice.

In the absence of evidence on whether rapid admission to an acute unit reduces mortality, morbidity and length of hospital stay, expert consensus led to the agreement that patients should be admitted where possible directly to an acute stroke unit. Trials outside the acute setting which demonstrate that direct admission improved the processes of care were noted. In the absence of any evidence identified in acute management, the group felt that there needed to be a very good reason not to generalise overall stroke unit results to those in the acute setting.

A cost-effectiveness analysis compared stroke units to care by a mobile stroke team on a general ward, or domiciliary care. Although the cost-effectiveness ratio of over £60,000 per QALY gained compared with domiciliary care would seem to imply that stroke units are not cost effective, this result must be treated with extreme caution since the one-year time horizon is likely to have dramatically under-estimated both the QALYs gained from averting deaths and the cost savings due to averting dependence. The consensus view of the GDG is that all patients should be directly admitted to a stroke unit.

7.1.7 RECOMMENDATION

- R17 All people with suspected stroke should be admitted directly to a specialist acute stroke unit following initial assessment either from the community or accident & emergency (A&E) department.

Definition of a stroke unit:

- a discrete area in the hospital
- staffed by a specialist stroke multidisciplinary team
- access to equipment for monitoring and rehabilitating patients
- regular multidisciplinary meetings occur for goal setting.

7.2 Brain imaging for the early assessment of people with acute stroke

7.2.1 Clinical introduction

Brain imaging is essential in stroke to exclude haemorrhage and stroke mimics. The 'National clinical guidelines for stroke' (2004)²⁹ recommended scanning within 24 hours of onset of symptoms to confirm diagnosis. Only 42% of patients in the 2006 Sentinel Audit³ achieved this standard. This is unacceptably low. It is recommended that by the time of the 2008 audit, 100% of patients should be scanned within a maximum of 24 hours after admission. Access to brain scanning has been difficult in the past because of a perceived lack of urgency for scanning, problems with access to scanning, or a lack of radiology or radiography support. Even though scanner availability has increased in recent years, systems are clearly not routinely in place to allow immediate or rapid access to scanning throughout the UK. Changes in clinical practice (increased availability, changes in scan request and reporting procedures) will be required to implement the new recommendation.

The clinical question to be addressed is how quickly brain imaging should be performed following an acute stroke.

7.2.2 Clinical methodological introduction

No relevant papers were identified.

7.2.3 Health economic methodological introduction

Two economic evaluations were identified that address early brain imaging following an acute stroke.

An evaluation in the US of the health economics of early scanning assessed usual US practice with practice based on National Institute of Neurological Disorders and Stroke (NINDS) recommendations on time from arrival to hospital to scanning.⁶⁸

A UK study⁶⁹ analysed the HE issues associated with the selection and timing of CT scanning after first ever stroke, including ischaemic and haemorrhagic stroke and stroke mimics, but excluding subarachnoid haemorrhage.

7.2.4 Health economic evidence statements

Both strategies in the Stahl et al.⁶⁸ analysis involved taking stroke care through the following steps:

- symptom onset
- arrival at emergency department
- thorough evaluation by an emergency medicine physician
- CT scanning and interpretation of CT findings
- administration of tPA to eligible patients.

The current practice described was an average time of 25 minutes to emergency medicine physician evaluation and approximately 1.6 hours from onset to administration of tPA.

The NINDS strategy recommended shorter times: 10 minutes to emergency medicine physician evaluation, neurologist assessment within 10 minutes, and 25 minutes to CT scan, allowing tPA administration within an hour.

The NINDS strategy was cost-saving. The results showed an increase of 0.01 QALYs and a saving of \$434 per patient, although no time horizon was stated.

Wardlaw et al. (2004)⁶⁹ compared thirteen different scanning strategies ranging from scanning immediately to scanning within 14 days; and scanning all patients to scanning no patients. Outcomes were quantified using the modified Rankin scale (mRS) as alive and independent, dependent, or dead at 6, 12, and 24 months after stroke. Life-years were estimated up to 5 years after first-ever stroke. Scanning all patients immediately was found to be the dominant strategy (less costly and more effective).

7.2.5 From evidence to recommendations

No clinical trial was identified to answer this question. However, it is clear that there are some patients in whom urgent scanning will result in immediate changes in clinical management. In the absence of reviewing the evidence on which patients should receive urgent scanning, a consensus was reached by the group. It was agreed that patients who are on anticoagulant therapy, have a known bleeding tendency, a depressed level of consciousness, unexplained progressive or fluctuating symptoms, papilloedema, neck stiffness or fever, severe headache at onset and/or indications for thrombolysis or early anticoagulation should receive immediate (next available slot or within 1 hour; within 1 hour out of hours) brain imaging. This consensus was based on both clinical experience and a recommendation made in the Intercollegiate Stroke Working Party guideline (2004 edition).²⁹ The GDG felt that immediate imaging of this patient population would result in changes in clinical management. For the remaining acute stroke patients, the clinical consensus of the group was that scanning should be performed as soon as possible (certainly within 24 hours). The health economic evidence supports the cost effectiveness of immediate scanning, although there may be limitations to the UK study because of changes in radiology staff costings. Immediate scanning, whilst cost effective, maybe difficult to implement because of scanning availability.

7.2.6 RECOMMENDATIONS

- R18** Brain imaging should be performed immediately* for people with acute stroke if any of the following apply:
- indications for thrombolysis or early anticoagulation treatment (see sections 8.1 and 8.2)
 - on anticoagulant treatment
 - a known bleeding tendency
 - a depressed level of consciousness (Glasgow Coma Score (GCS) below 13)
 - unexplained progressive or fluctuating symptoms
 - papilloedema, neck stiffness or fever
 - severe headache at onset of stroke symptoms.
- R19** For all people with acute stroke without indications for immediate brain imaging, scanning should be performed as soon as possible.**

* The GDG felt that 'immediately' was defined as 'ideally the next slot and definitely within 1 hour, whichever is sooner' in line with the National Stroke Strategy.⁴

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

8 Pharmacological treatments for people with acute stroke

8.1 Thrombolysis in people with acute ischaemic stroke

8.1.1 Clinical introduction

Thrombolysis with alteplase in acute ischaemic stroke has been shown to significantly improve outcome in selected patients treated within 3 hours of onset of symptoms. It has been reviewed in detail in NICE Technology Appraisal (TA) 122,⁷⁰ and thus the evidence has not been reviewed again here. However, the GDG did discuss the clinical context in which alteplase should be administered, in particular the availability of appropriately trained staff in acute stroke units (see section 7.1).

Immediate access to acute stroke care, diagnosis (including brain imaging) and rapid treatment (including thrombolysis where appropriate) is a vital component of the very considerable changes in the delivery of effective acute stroke care outlined in the National Stroke Strategy.⁴ One series of 1,135 patients treated in centres across Canada showed that 37% had an excellent outcome with a symptomatic intracerebral haemorrhage rate that was lower than in the published trials (4.6%). 1.3% developed angio-oedema. Symptomatic intracerebral haemorrhage was higher in those patients where the protocol was violated, underlining the importance of treatment within guidelines.⁷¹ The NICE TA concludes that alteplase in addition to best supportive care is effective and safe in acute ischaemic stroke, provided that alteplase is only used in accordance with the marketing authorisation. In particular, it should be administered within 3 hours of onset of symptoms and only after brain haemorrhage has been definitively excluded using brain scanning. Thrombolysis in acute stroke is associated with an increased risk of haemorrhage (up to 6% of patients) and is therefore a treatment not without hazard. It was felt that staff in A&E departments, if appropriately trained and supported, can administer thrombolysis in acute stroke provided that patients can be managed within an acute stroke service with appropriate neuroradiological and stroke physician support.

8.1.2 RECOMMENDATIONS

R20 Alteplase is recommended for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke. It should only be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation. (Alteplase TA122 2007)⁷⁰

R21 Alteplase should only be administered within a well-organised stroke service with:

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

* Please see www.datadictionary.nhs.uk/data

- R22 Staff in A&E departments, if appropriately trained and supported, can administer alteplase* for the treatment of acute ischaemic stroke provided that patients can be managed within an acute stroke service with appropriate neuroradiological and stroke physician support.
- R23 Protocols should be in place for the delivery and management of thrombolysis, including post-thrombolysis complications.

8.2 Aspirin and anticoagulant treatment in people with acute ischaemic stroke

8.2.1 Clinical introduction

Acute ischaemic stroke is associated with mortality (up to 30% at 30 days) and morbidity (disability). It occurs secondary to thrombosis, usually from an atherothrombotic plaque, or to embolism, usually from the heart. Resultant blood clot or thrombus occludes an artery in the extra or intracranial cerebral vasculature to cause brain ischaemia. The size of the clot determines the diameter of the vessel occluded and thus the volume of brain affected.

Ischaemic stroke, although initially not associated with haemorrhagic change on structural imaging at presentation, may undergo a process called haemorrhagic transformation, where blood becomes visible within the infarct on scanning. This may be asymptomatic and only detected by chance on subsequent scans, or symptomatic and associated with a clinical deterioration. Symptomatic haemorrhagic transformation is more commonly associated with larger infarcts, usually within the first 2 weeks after presentation. Antiplatelet agents and anticoagulants may increase the risk of haemorrhagic transformation of cerebral infarction.

Following a stroke, patients may be immobile and thus at increased risk of venous thromboembolism (deep venous thrombosis and pulmonary embolus), the incidence of which is reduced by antiplatelet agents and anticoagulants. However, patients may also be at increased risk of bleeding complications (for example upper gastrointestinal bleeding) particularly on aspirin, and existing bleeding disorders (e.g. peptic ulceration) may be exacerbated by anticoagulants.

There is a balance between the potential therapeutic effects of antiplatelet agents and anticoagulants in the treatment of patients with acute ischaemic stroke and the reduction in thromboembolic complications, against the risk of haemorrhagic transformation of infarction and exacerbation of extracranial bleeding.

The clinical questions to be addressed are how safe and effective are antiplatelet agents and anticoagulants after an acute ischaemic stroke.

8.2.2 Clinical methodological introduction

A very small number of studies were identified that addressed the safety and efficacy of antiplatelet agents and/or anticoagulants in the treatment of patients with acute ischaemic stroke. For the purposes of this question, 'acute' was defined as studies on patients that received the first dose of trial medication 14 days or less from stroke onset.

* In accordance with its marketing authorisation.

▷ Aspirin vs other antiplatelet agents

For the comparison of aspirin versus antiplatelet agents, no systematic reviewers, meta-analysis or RCTs were identified.

▷ Antiplatelet agents vs placebo

For the comparison of antiplatelet agents versus placebo, one Cochrane systematic review was identified.⁷² One RCT was not considered further due to methodological limitations.⁷³ **Level 1++**

The Cochrane review included a total of nine studies but only the results of four studies concerning UK licensed drugs, namely aspirin (three RCTs) compared with control* (N=40,850) and aspirin plus modified release dipyridamole compared with placebo (one RCT) (N=80) are reported here (this included the two largest studies which comprised 98% of the total data in the review). The reviewers noted that the majority of patients were elderly, with a significant proportion over 70 years of age. Patients were started on treatment within 48 hours or less (aspirin therapy), or 6 days or less (aspirin plus modified release dipyridamole), of stroke onset. In the aspirin compared to control trials the dose ranged from 160 mg to 300 mg per day. In the trial comparing aspirin plus modified release dipyridamole with control the doses were 330 mg and 75 mg eight hourly, respectively. The follow-up period ranged from 4 weeks to 6 months. **Level 1++**

▷ Anticoagulants vs placebo

For the comparison of anticoagulants versus placebo, one Cochrane systematic review (N=23,547)⁷⁴ and one RCT (N=418)⁷⁵ were identified. The review included 22 RCTs testing unfractionated heparin (UFH), low molecular-weight heparins (LMWH), heparinoids, oral anticoagulants and thrombin inhibitors. All patients were started on treatment within 2 weeks of stroke onset. The follow-up period ranged from 7 days to 1 year. The RCT compared patients with acute non-lacunar hemispheric cerebral infarction treated with 5 days of unfractionated heparin (24 000 IU/day) or saline with a follow-up period of 90 days. After 5 days, both groups were prescribed aspirin 100 mg/day or oral anticoagulants. **Level 1++**

▷ Antiplatelet agents vs anticoagulants

For the comparison of antiplatelet agents versus anticoagulants, one Cochrane systematic review (N=16,558)⁷⁶ and one RCT (N=353)⁷⁷ were identified. One RCT⁷⁸ was not considered further due to methodological limitations. The Cochrane review included three trials that compared UFH and LMWH with aspirin. The results of a further trial comparing UFH plus aspirin compared with aspirin are reported separately. The follow-up period ranged from 10 days to 6 months.⁷⁶ The RCT compared LMWH with aspirin administered within 48 hours of symptom onset in Asian patients with large artery occlusive disease. The follow-up period was 6 months. Patients were prescribed nadroparin calcium 3800 anti-factor Xa IU/0.4 ml twice daily or oral aspirin 160 mg daily for 10 days, and then all received 80–300 mg once daily for 6 months.⁷⁷ **Level 1++**

* Placebo (one RCT); factorial design of aspirin, heparin, both or neither (one RCT); and no treatment (one RCT).

8.2.3 Health economic methodological introduction

Of the papers appraised, four were not considered to be of good quality. Marissal et al. (2004)⁷⁹ and Shah et al. (2000)⁸⁰ were cost-consequence analyses looking at cost per stroke avoided over a 2-year time horizon. This is unlikely to capture all the costs and effects of treatment related to prevention of stroke.

Matchar et al. (2005)⁸¹ had a lifetime time horizon which would capture all costs and effects related to stroke, but the evaluation was not reported in enough detail to fully understand what was included and how the analysis was conducted.

Six other papers were identified which were appraised. Beard et al. (2004)⁸² compared dipyridamole modified release (MR) with MR dipyridamole in combination with aspirin, low-dose aspirin, clopidogrel, and no treatment for patients who survived an initial acute stroke event. The model considered efficacy in preventing acute TIA, non-fatal vascular events, and first recurrence of acute stroke in a UK setting.

The health technology appraisal, Jones et al. (2004),⁸³ included an extended model of an industry submission. Patients with stroke, TIA, myocardial infarction, and peripheral arterial disease were treated with: aspirin, clopidogrel, aspirin plus modified release dipyridamole, or modified release dipyridamole. Results were presented for each subgroup.

The evaluation presented in Chambers et al. (1999)⁸⁴ was updated in Chambers et al. (2002).⁸⁵ In both versions the cohort was 30-day survivors of an initial ischaemic stroke in the UK. The 1999 evaluation compared no antiplatelet therapy, low-dose aspirin, MR dipyridamole, and a coformulation of low-dose aspirin plus modified-release dipyridamole. In the 2002 version, aspirin plus modified release dipyridamole was compared to aspirin alone.

Schleinitz et al. (2004)⁸⁶ and Sarasin et al. (2000)⁸⁷ were both conducted in the USA. Schleinitz et al. (2004)⁸⁶ compared aspirin with clopidogrel in patients with peripheral arterial disease, a previous non-haemorrhagic stroke, or a previous myocardial infarction. Sarasin et al. (2000)⁸⁷ compared aspirin, clopidogrel and dipyridamole in patients who have experienced stroke or TIA.

Moodie et al. (2004)⁸⁸ compared current practice in Australia to aspirin began within 48 hours of stroke or recombinant tissue-type plasminogen activator (rtPA) began within 3 hours of stroke. No details of what current practice were given.

8.2.4 Clinical evidence statements

▷ Antiplatelet agents vs placebo

The Cochrane systematic review⁷² reported that aspirin therapy compared to control was associated with a significant reduction in the number of patients who were dead or dependent or who experienced symptomatic pulmonary embolism or recurrent stroke. However, there was a small but significant increase in the number of symptomatic intracranial haemorrhages and major extracranial haemorrhages. Overall, the small RCT comparing aspirin plus modified release dipyridamole versus control reported no significant differences between the two treatments (NS). See table 8.1 below for a summary of the results.

Table 8.1 Aspirin vs control compared to aspirin plus modified release dipyridamole vs control

Antiplatelet agents versus control		
Outcome	Aspirin vs control (Sandercock et al. 2003)	Aspirin plus modified release dipyridamole vs control (Sandercock et al. 2003)
Death or dependence at final follow-up (1 month or more after randomisation)	↓ Aspirin OR 0.95; 95%CI 0.91 to 0.99; p=0.008	NE
Death from all causes during the scheduled treatment period	↓ Aspirin OR 0.92; 95%CI 0.85 to 1.00; p=0.05	NS
Death from all causes at follow-up	↓ Aspirin OR 0.92; 95%CI 0.87 to 0.98; p=0.0009	NS
Deep vein thrombosis during the treatment period	NE	↓ Aspirin plus modified release dipyridamole OR 0.35; 95%CI 0.13 to 0.95; p=0.04
Symptomatic pulmonary embolism during the treatment period	↓ Aspirin OR 0.71; 95%CI 0.53 to 0.97; p=0.03	NS
Recurrent ischaemic stroke or recurrent stroke of unknown pathological type during the treatment period	↓ Aspirin OR 0.77; 95%CI 0.69 to 0.87; p=0.00002	NS
Symptomatic intracranial haemorrhage (SIH) during the treatment period	↑ Aspirin OR 1.22; 95%CI 1.00 to 1.50; p=0.05	NS
Any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period and during long-term follow up	↓ Aspirin OR 0.87; 95%CI 0.79 to 0.97; p=0.01	NS
Major extracranial haemorrhage during the treatment period	↑ Aspirin OR 1.69; 95%CI 1.35 to 2.11; p<0.0001	NS
Complete recovery	↑ Aspirin OR 1.06; 95%CI 1.01 to 1.11; p=0.01	NE
↓ denotes a significant decrease; ↑ denotes a significant increase; NS, non-significant; NE, not evaluated		

▷ Anticoagulants vs placebo

The Cochrane review⁷⁴ reported no significant differences associated with anticoagulant therapy compared with control on the combined score of death or dependency or the number of deaths (NS). Anticoagulant therapy was associated with a significant reduction in the number of deep vein thromboses (DVTs) and pulmonary emboli (PEs) and recurrent strokes during the treatment

period. However, anticoagulant therapy was associated with significant increase in the number of symptomatic intracranial haemorrhages and major extracranial haemorrhages. See table below for a summary of the results. Level 1++

The RCT reported no significant differences associated with UFH compared saline on the number of deaths at follow-up (NS) but there was a significant increase in the number of patients in the UFH group who were 'self-sufficient' (score of 0 to 2 on the mRS) at the end of follow-up. Significantly more symptomatic intracranial haemorrhages were associated UFH.⁷⁵ See table 8.2 below for a summary of the results. Level 1++

Table 8.2 Anticoagulants versus control

Outcome	Anticoagulants vs control (Gubitz et al. 2004)	Unfractionated heparin (UH) vs saline (Camerlingo et al. 2005)
Death or dependence at final follow-up	NS	Death: NS Self-sufficiency: ↑UH 38.9% vs 28.6% (p=0.025).
Death from all causes during the scheduled treatment period	NS	NE
Death from all causes at follow-up greater than one month after randomisation	NS	NE
Deep vein thrombosis (DVTs) during the treatment period	↓ Anticoagulants OR 0.21 95%CI 0.15 to 0.29 Note: majority of DVTs detected were sub-clinical or asymptomatic	NE
Symptomatic pulmonary embolism during the treatment period	↓ Anticoagulation OR 0.60 95%CI 0.44 to 0.81	NE
Recurrent ischaemic stroke or recurrent stroke of unknown pathological type during the treatment period	↓ Anticoagulation OR 0.76 95%CI 0.65 to 0.88	NE
Symptomatic intracranial haemorrhage (SIH) during the treatment period	↑ Anticoagulation OR 2.52 95%CI 1.92 to 3.30	NE
Any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period and during long-term follow up	NS	6.2% vs 1.4% p=0.008 Asymptomatic NS
Major extracranial haemorrhage during the treatment period	↑ Anticoagulation OR 2.99 95%CI 2.24 to 3.99	NS (treatment and follow-up)

↓ denotes a significant decrease; ↑ denotes a significant increase; NS, non-significant; NE, not evaluated

▷ Antiplatelet agents vs anticoagulants

The Cochrane review reported that anticoagulant therapy compared with antiplatelet therapy was associated with a significant increase in the number of deaths, symptomatic intracranial haemorrhages and major extracranial haemorrhages and a significant decrease in the number of DVTs. UFH plus aspirin compared with aspirin alone was associated with a significant decrease in the number of recurrent strokes but an increase in the number of symptomatic intracranial haemorrhages and major extracranial haemorrhages. See table 8.3 below for a summary of the results. Level 1++

Table 8.3 Anticoagulants versus antiplatelet agents

Outcome	Anticoagulants vs antiplatelet agents (Berge et al. 2002)	UFH plus aspirin vs aspirin (Berge et al. 2002)
Death or dependence at final follow-up	NS	NS
Death from all causes during the scheduled treatment period	NS	NS
Death from all causes at follow-up	↑ Anticoagulants OR 1.10 95%CI 1.01 to 1.21	NS
Deep vein thrombosis during the treatment period	↓ Anticoagulants OR 0.19 95%CI 0.07 to 0.58 Note: only one study systematically tested for DVTs	NE
Symptomatic pulmonary embolism during the treatment period	NS	NS
Progression of symptoms during the treatment period	NS	NE
Recurrent ischaemic stroke or recurrent stroke of unknown pathological type during the treatment period	NS	↓ UFH plus aspirin 2.45% (119/4862) vs 3.21% (156/4858) OR 0.76, 95%CI 0.59 to 0.96; p=0.02 High NS ↓ Low 2.06% (50/2432) vs 3.21% (78/2429) OR 0.76; 95%CI 0.59 to 0.96; p=0.01
Symptomatic intracranial haemorrhage (SIH) during the treatment period	↑ Anticoagulants OR 2.27 95%CI 1.49 to 3.46 ↑ High dose OR 3.24 95%CI 2.09 to 5.04 ↑ Low dose OR 1.29 95%CI 0.72 to 2.32	↑ UFH and aspirin OR 2.36 95%CI 1.49 to 3.74 ↑ High dose OR 3.27 95%CI 1.76 to 6.10 Low dose NS

continued

Table 8.3 Anticoagulants versus antiplatelet agents – continued

Any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period	NS	NS
Major extracranial haemorrhage during the treatment period	↑ Anticoagulants OR 1.94 95%CI 1.20 to 3.12	↑ UFH plus aspirin OR 3.79 95%CI 2.39 to 6.01 ↑ High dose OR 5.62 95%CI 3.03 to 10.43 Low dose NS
↓ denotes a significant decrease; ↑ denotes a significant increase; NS, non-significant; NE, not evaluated		

The RCT reported no statistical differences between patients treated with LMWH and aspirin on the primary outcome of the Barthel Index (NS) measured at 6 months but a significantly greater proportion of patients had a good recovery as measured on the mRS (score 0 to 1 compared with ≥ 2 only). The rate of haemorrhagic transformation and severe adverse events were similar in both groups (NS).⁷⁷ Level 1++

8.2.5 Health economic evidence statements

Beard et al. (2004)⁸² and Chambers et al. (2002)⁸⁵ both had a 5-year time horizon. Beard et al. found the combination of aspirin plus modified release dipyridamole had a cost per QALY of \$4,207 compared to aspirin. Chambers et al. found the cost effectiveness of the same comparison was \$5,800 per QALY.

Studies by Schleinitz et al. (2004)⁸⁶ and Sarasin et al. (2000)⁸⁷ both had a lifetime time horizon. Schleinitz et al. found the comparison of clopidogrel with aspirin led to a cost of \$31,200 for each QALY gained in the clopidogrel treatment group. Sarasin et al. found that aspirin plus modified release dipyridamole was more effective than aspirin and less expensive than clopidogrel.

Jones et al. (2004)⁸³ compared the following: a) aspirin, b) clopidogrel, c) aspirin plus modified release dipyridamole, and d) modified release dipyridamole, in patients who had a previous stroke or TIA. Over a 40-year time horizon if treatment effects on non-vascular deaths were included, they found that aspirin was more effective and less expensive than the other treatment options. Over a 2-year time horizon, aspirin plus modified release dipyridamole had a cost per QALY gained of £5,500 compared with aspirin.

8.2.6 From evidence to recommendations

No RCTs, meta-analyses or systematic reviews were identified that addressed the safety and efficacy of aspirin versus other antiplatelet agents in acute ischaemic stroke. One preliminary pilot study was identified and excluded. The GDG recommended that a research study should be carried out comparing aspirin with other antiplatelet agents singly or in combination, in patients with acute ischaemic stroke and TIA.

The review of the safety and efficacy of antiplatelet agents versus placebo included some antiplatelet drugs that are not licensed in the UK. These were excluded from the analysis. The GDG agreed that from the evidence presented to it, aspirin should be recommended. It was noted that from the evidence presented, doses of 160–300 mg were reported as being equally effective.

The two largest trials recommended that aspirin should be given as soon as possible after haemorrhage had been excluded and within a maximum of 48 hours. One of these studies compared aspirin administration within 0–12 hours with administration within 12–48 hours and found no significant difference.

No specific research reviews into methods of delivery were conducted. There is little evidence comparing different methods of aspirin delivery and in most studies it has been administered by a variety of routes. The GDG agreed that aspirin should be delivered by the most clinically appropriate route (oral, rectal or by enteral tube) and that the latter two routes are appropriate for patients with dysphagia.

In the two largest RCTs, CAST and IST, aspirin therapy was continued for 2–4 weeks post stroke onset. These RCTs made up to 98% of the data within the Cochrane review and a clinical consensus was agreed by the GDG that aspirin should be continued for 2 weeks.

It was noted that there is very little evidence to guide the management of aspirin-intolerant patients. The consensus of the GDG based on clinical experience was that patients who are not truly allergic to aspirin or without contraindications should take aspirin with proton pump inhibitor cover where appropriate. The GDG used the definition of aspirin tolerance used in the NICE vascular disease TA90. Genuine aspirin intolerance was defined as people with proven hypersensitivity to aspirin-containing medicines or history of severe dyspepsia induced by low-dose aspirin. Patients who have not previously tolerated high doses of aspirin may be able to tolerate low-dose aspirin.

In patients receiving anticoagulant therapy, there was a significant reduction in the incidence of clinically significant venous thromboembolism and recurrent stroke. However, there was also a significant increase in the number of symptomatic intracranial haemorrhages and extracranial bleeds compared to placebo. Anticoagulant therapy confers no additional benefit over antiplatelet agents in acute stroke (and may be harmful) in the absence of specific indications. It was noted that there was no evidence available on long-term morbidities associated with DVT following stroke.

However, the GDG noted that some patients are at higher risk of venous thromboembolism and review at 48 hours should be undertaken. The GDG noted that there is a NICE guideline currently in development which looks at reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital.

8.2.7 RECOMMENDATIONS

- R24** All people presenting with acute stroke who have had a diagnosis of primary intracerebral haemorrhage excluded by brain imaging should, as soon as possible but certainly within 24 hours, be given:
- aspirin 300 mg orally if they are not dysphagic, or
 - aspirin 300 mg rectally or by enteral tube if they are dysphagic.
- Thereafter aspirin 300 mg should be continued until 2 weeks after the onset of stroke symptoms, at which time definitive long-term antithrombotic treatment should be initiated. People being discharged before 2 weeks can be started on long-term treatment earlier.
- R25** Any person with acute ischaemic stroke for whom previous dyspepsia associated with aspirin is reported should be given a proton pump inhibitor in addition to aspirin.

- R26 Any person with acute ischaemic stroke who is allergic to or genuinely intolerant of aspirin should be given an alternative antiplatelet agent.*
- R27 Anticoagulation treatment should not be used routinely** for the treatment of acute stroke.

8.3 Antiplatelet and anticoagulant treatment in people with acute venous stroke

8.3.1 Clinical introduction

Venous stroke (i.e. thrombosis of the intracerebral veins and venous sinuses) is a rare disorder that accounts for 0.5% of all strokes and can occur at any age. Common causes include pregnancy or puerperium, hormonal or chemotherapeutic agents, infections of the ear, face or neck, or thrombophilic disorders. The commonest clinical signs are headache, seizures, focal neurological signs, altered consciousness or papilloedema. Diagnosis is confirmed using brain imaging. Conventional brain imaging shows a variety of non-specific lesions including infarctions, haemorrhages and oedema, or may be normal in up to 25% of cases. MRI with MR venography or CT with CT venography provides more accurate diagnosis, although in some cases angiography may be necessary. D-dimer may sometimes be elevated but a normal D-dimer does not exclude the diagnosis.⁸⁹ In the past, the presence of haemorrhage has been thought to preclude treatment with anticoagulation.

The clinical question to be addressed is whether patients with acute venous stroke should receive antiplatelet or anticoagulant treatment acutely.

8.3.2 Clinical methodological introduction

One Cochrane systematic review (N=79, two RCTs) was identified that compared anticoagulant therapy with placebo for the treatment of cerebral sinus thrombosis. No other RCTs were identified.⁹⁰ Level 1++

8.3.3 Health economic methodological introduction

No papers were identified.

*Aspirin intolerance is defined in NICE technology appraisal guidance 90 as 'Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events'; see www.nice.org.uk/TA090) as either of the following:

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

** There may be a subgroup of people for whom the risk of venous thromboembolism outweighs the risk of haemorrhagic transformation. People considered to be at particularly high risk of venous thromboembolism include anyone with complete paralysis of the leg, a previous history of venous thromboembolism, dehydration or comorbidities (such as malignant disease), or who is a current or recent smoker. Such people should be kept under regular review if they are given prophylactic anticoagulation. Further details will be included in the forthcoming NICE clinical guideline 'The prevention of venous thromboembolism in all hospital patients' (publication expected in September 2009).

8.3.4 Clinical evidence statements

- ▷ Death or dependency at the end of scheduled trial follow-up

The meta-analysis showed that anticoagulant therapy was associated with a non-significant relative risk reduction in death or dependency (RR 0.46; 95%CI 0.16 to 1.31). The absolute reduction in the risk of death was –13% (95%CI –30% to +3%).⁹⁰ **Level 1++**

At the end of scheduled treatment, anticoagulation was associated a relative risk reduction of 0.33 (95%CI 0.08 to 1.21). The absolute reduction in the risk of death was –13% (95%CI –27% to +1%).⁹⁰ **Level 1++**

- ▷ Confirmed pulmonary embolism

There were no cases of confirmed pulmonary embolism.⁹⁰ **Level 1++**

- ▷ Symptomatic intracranial haemorrhage (SIH)

There were no cases of new symptomatic ICH after initiation of anticoagulant therapy.⁹⁰ **Level 1++**

- ▷ Major extracranial haemorrhage

One patient on anticoagulant therapy experienced a major non-fatal gastrointestinal haemorrhage (RR 2.9; CI 0.12 to 68.5).⁹⁰ **Level 1++**

8.3.5 From evidence to recommendations

The evidence supports early anticoagulation in confirmed venous stroke with a reduction in death and dependency. It should be noted that other complications of the stroke (seizures, oedema) should be treated appropriately. The group did not review any evidence regarding how long patients should be anticoagulated for. The GDG were unable to reach a consensus on how long patients should receive anticoagulation as this depended on the underlying cause of the stroke.

8.3.6 RECOMMENDATION

- R28** People diagnosed with cerebral venous sinus thrombosis (including those with secondary cerebral haemorrhage) should be given full-dose anticoagulation treatment (initially full-dose heparin and then warfarin (INR 2–3)) unless there are comorbidities that preclude its use.

8.4 Antiplatelet and anticoagulant treatment in people with stroke due to arterial dissection

8.4.1 Clinical introduction

Acute dissection of a cervical artery (carotid or more commonly vertebrobasilar) is not an uncommon cause of stroke.^{91,92} It is reported particularly in young people but where it is specifically looked for the incidence is similar in patients of all ages. It may occur spontaneously but has been commonly reported following neck injury (e.g. whiplash, neck hyperextension) or

manipulation, heavy lifting or sports (skiing, parachuting). Ischaemic stroke follows shearing damage to the intima of the artery with haematoma formation in the arterial wall. Thrombosis over the site of vascular injury becomes dislodged and may embolise to the brain; alternatively the vessel may be occluded by haematoma forming in the vessel wall at the site of the dissection. Symptoms usually occur within hours of injury but may follow weeks or even months later. Neck pain and Horner's syndrome may be present prior to stroke symptoms. The diagnosis is confirmed radiologically, usually by MR scan of the arteries in the neck with MR angiogram. This section addresses the evidence for antiplatelet agents and anticoagulants in stroke secondary to dissection.

The clinical question to be addressed is whether patients with acute arterial dissection should be treated with antiplatelets or anticoagulants.

8.4.2 Clinical methodological introduction

No randomised controlled trials were identified comparing antiplatelet agents with anticoagulant therapy for the treatment of acute arterial dissection. One Cochrane review was identified that reviewed antithrombotic drugs (antiplatelets or anticoagulants) for the treatment of carotid artery dissection (26 studies (no RCTs), N=327 patients for the antiplatelet agents versus anticoagulant comparison). Two further retrospective case-series studies were also identified.^{93,94} Three studies were excluded due to methodological limitations.⁹⁵⁻⁹⁷ **Level 3**

One study⁹³ (N=130) reviewed 72 patients with vertebral artery (55.4%) and 58 patients (44.6%) with carotid artery dissections. 83 (64%) patients received aspirin and 47 (36%) patients anticoagulant therapy. One study (N=60)⁹⁴ reviewed the records of patients with internal carotid artery dissection. Of these, 19 (31.7%) patients received antiplatelet agents (aspirin) and 34 (56.7%) patients received anticoagulant therapy (intravenous heparin and/or oral anticoagulants) (7 (11.6%) received no specific treatment). **Level 3**

The outcomes for the treatment of carotid artery and vertebral artery dissection are reported separately.

8.4.3 Health economic methodological introduction

No papers were identified.

8.4.4 Evidence statements

Carotid artery dissection

▷ Death and disability

There were no statistical differences between patients who received antiplatelets or anticoagulant therapy for the number of patients who died or who were dead or dependent (NS).^{98,93} **Level 3**

▷ Recanalisation

Both case series reported no statistically significant differences between the number of patients treated with antiplatelet agents or on anticoagulant therapy with complete or partial recanalisation (NS).^{93,94} **Level 3**

Vertebral artery dissection▷ **Death and dependency**

No patients died during treatment with antiplatelet agents or whilst having anticoagulant therapy.⁹³ **Level 3**

▷ **Recanalisation**

For complete recanalisation, there was a statistically significant difference in favour of anticoagulant therapy compared with antiplatelet agents but there was no statistical difference for the rates of partial recanalisation (NS).⁹³ **Level 3**

▷ **Recurrent strokes**

There was no statistical difference for the number of recurrent strokes when comparing antiplatelet agents with anticoagulant therapy (NS).⁹³ **Level 3**

8.4.5 From evidence to recommendations

From the evidence presented, the GDG noted that there was no significant difference among outcome between antiplatelet and anticoagulant treatment (assessed against death, disability, first or recurrent stroke, rate of recanalisation and partial recanalisation). One study found that for complete recanalisation, there was a significant difference in favour of anticoagulant therapy compared to antiplatelets, although this did not affect outcome. The consensus of the group was that patients should be treated with either antiplatelet or anticoagulant agents, although there is insufficient evidence to recommend one over the other. Randomisation into controlled clinical trials is recommended, but anticoagulants should be used with caution in patients with large cortical infarcts.

8.4.6 RECOMMENDATION

- R29** People with stroke secondary to acute arterial dissection should be treated with either anticoagulants or antiplatelet agents, preferably as part of a randomised controlled clinical trial to compare the effects of the two treatments.

8.5 Antiplatelet and anticoagulant treatment in people with acute stroke due to antiphospholipid syndrome**8.5.1 Clinical introduction**

Antiphospholipid syndrome is a prothrombotic syndrome that results in arterial as well as venous thrombosis and is marked by the presence of circulating antiphospholipid antibodies. Neurological involvement is common and includes migraine, memory loss and ischaemic stroke. Other manifestations include venous thromboembolism, recurrent miscarriage, thrombocytopaenia and livedo reticularis.⁹⁹

Patients are commonly anticoagulated, but the clinical question remains as to whether patients with acute stroke should be anticoagulated immediately or treated with antiplatelet agents.

8.5.2 Clinical methodological introduction

No papers were identified.

8.5.3 Health economic methodological introduction

No papers were identified.

8.5.4 From evidence to recommendation

There is insufficient evidence to support any recommendation regarding the safety and efficacy of anticoagulants versus antiplatelets for the treatment of antiphospholipid syndrome in patients with acute ischaemic stroke. People with antiphospholipid syndrome who have an acute ischaemic stroke should be managed in same way as patients without antiphospholipid syndrome.

8.5.5 RECOMMENDATION

- R30 People with antiphospholipid syndrome who have an acute ischaemic stroke should be managed in the same way as people with acute ischaemic stroke without antiphospholipid syndrome.*

8.6 Reversal of anticoagulation treatment in people with haemorrhagic stroke

8.6.1 Clinical introduction

Anticoagulation with warfarin is used in a variety of disorders where there is evidence of or risk of thromboembolism, for example with prosthetic heart valves, mural thrombus and venous thrombosis. It is most commonly prescribed in atrial fibrillation (AF), a common arrhythmia whose incidence increases with age, from 0.5% at 50–59 years to 9% at 80–89.¹⁰⁰ AF is the commonest cause of embolic stroke, and patients in AF who present with a TIA or ischaemic stroke have an overall risk of recurrent stroke of 12% in the first year and 5% per year thereafter. Treatment with warfarin reduces this risk from 12% to 4%; treatment with aspirin is less effective. However, warfarin is associated with an increased risk of bleeding complications particularly if patients are treated to a higher INR.¹⁰¹ The incidence of intracerebral haemorrhage in patients on warfarin is around 1.6%¹⁰² and increases dramatically in those patients with INR >4.¹⁰³ A high INR not only increases the risk of intracerebral haemorrhage but also worsens outcome because of subsequent expansion of haematoma. Reduction of the INR to normal values restores haemostasis and therefore haematoma expansion is less likely. There are a number of potential strategies to reduce INR, including vitamin K, fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC). Retrospective case reviews of patients with intracerebral haemorrhage and high INR have shown that all of these strategies reduce INR. PCC (7–27 IU/kg) with IV vitamin K in 11 patients reduced INR significantly from median 2.70 to median 1.13 within 10 minutes;

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

the effect was sustained 24 hours later. In two patients given PCC without IV vitamin K, INR dropped rapidly but increased 12–24 hour later. Treatment with IV vitamin K alone reduced the INR but only after 24–48 hours;¹⁰⁴ haematoma expansion occurred only in those patients with INR >2.0.¹⁰⁵ A more recent review of 18 patients undergoing neurosurgery for intracerebral haemorrhage secondary to warfarin showed rapid (within 3 minutes) reversal of anticoagulation with 20 IU/kg PCC and 5 mg IV vitamin K.¹⁰⁶ However, there have as yet been no randomised controlled trials to assess outcome.

The clinical question to be addressed is how best to reverse anticoagulation in patients with haemorrhagic stroke.

8.6.2 Clinical methodological introduction

No RCTs were identified which explored the efficacy of vitamin K, FFP, PCC or a combination of these interventions. Two short-term follow-up case series were identified, one prospective¹⁰⁷ and one retrospective.¹⁰⁸ Two long-term follow-up retrospective case series were also identified.^{109,110} **Level 3**

Two small studies compared PCC plus vitamin K with FFP plus vitamin K, one with a follow-up of 180 minutes (N=12)¹⁰⁷ and one 12 hours (N=17).¹⁰⁸ A further study with a 3-month follow-up compared FFP with vitamin K.¹⁰⁹ The remaining study compared PCC (alone or in combination with FFP or vitamin K) with FFP (alone or in combination with vitamin K) with a follow-up of 1 year. **Level 3**

It should be noted that these studies should be interpreted with caution due to a number of methodological limitations including the non-randomised design and small sample size. The different combination of interventions, dosage rates and outcome measures precluded a direct comparison between the different studies. **Level 3**

8.6.3 Health economic methodological introduction

No papers were identified.

8.6.4 Clinical evidence statements

▷ Prothrombin time

Two case series reported a greater reduction in INR values and a more rapid correction time in patients treated with PCC compared with FFP.^{107,108} **Level 3**

An additional retrospective case series compared PCC (alone or in combination with FFP) or vitamin K versus FFP (alone or in combination with vitamin K). PCC was associated with an earlier complete INR reversal (within 2 hours) compared with FFP and vitamin K alone.¹¹⁰ **Level 3**

A further case series investigated the time of administration of FFP or vitamin K related to clinical outcome. Timing of FFP was associated with a successful INR reversal. Timing of vitamin K was not associated with successful INR reversal (NS). Time to FFP was associated with both dose of and time to vitamin K. Multivariate analysis showed that every 30-minute delay in FFP administration was independently associated with a 20% decrease in the probability of a successful INR reversal within 24 hours. A similar effect was reported for vitamin K.¹⁰⁹ **Level 3**

▷ Haematoma growth

One case series reported a significantly lower incidence of haematoma growth in patients treated with PCC (alone or in combination with FFP or vitamin K) compared with those treated with FFP (alone or in combination with vitamin K) or vitamin K alone. There were no significant differences between the groups on the extent of haematoma growth (NS). **Level 3**

▷ Modified Rankin Scale (mRS)

Two case-series studies reported no association between functional outcome and treatment interventions at discharge¹⁰⁸ or at 12-month follow-up.¹¹⁰ One study compared PCC with FFP (NS)¹⁰⁸ and the other study compared PCC (alone or in combination with FFP) with FFP (alone or in combination with vitamin K) and vitamin K alone (NS).¹¹⁰ **Level 3**

8.6.5 From evidence to recommendations

It was agreed that there were little data on which to formulate an evidence-based recommendation. Case series reviewed assessed the efficacy of anticoagulation reversal rather than clinical outcome. The GDG noted that clinical practice varies considerably and that there is no randomised controlled trial evidence on which to base a recommendation. PCC and FFP can rapidly reverse anticoagulation although the volumes of FFP needed to be effective are great. IV vitamin K alone will reverse anticoagulation more slowly. The effect of PCC and FFP is not sustained unless IV vitamin K is also added.

8.6.6 RECOMMENDATION

- R31** Clotting levels in people with a primary intracerebral haemorrhage who were receiving anticoagulation treatment before their stroke (and have elevated INR) should be returned to normal as soon as possible, by reversing the effects of the anticoagulation treatment using a combination of prothrombin complex concentrate (PCC) and intravenous vitamin K.

8.7 Anticoagulation treatment for other comorbidities in people with acute stroke

8.7.1 Clinical introduction

The 2004 national clinical guidelines²⁹ recommended aspirin for the treatment of acute ischaemic stroke (up to day 14) in patients both in AF and in sinus rhythm. Early anticoagulation is known to be associated with increased risk of haemorrhagic transformation of infarction in addition to risks of extracranial bleeding particularly in patients with large cortical infarctions. Some patients may have other indications for anticoagulation, for example deep venous thrombosis (DVT), pulmonary embolus (PE), or a mechanical heart valve. Because of anxiety about the risk of haemorrhagic transformation in acute stroke, particularly in large cortical infarction, and in particular the risk of extension of haematoma after intracerebral haemorrhage, other approaches to the management of venous thromboembolism after stroke have been reported although none have been subjected to randomised controlled trial. Insertion of a inferior vena cava (IVC) filter is an option if anticoagulants are withheld.

These devices, at least in general populations without stroke, probably reduce the likelihood of PE^{111,112} but increase the risk of DVT and have not been proven to affect mortality;¹¹³ a recent review confirmed that there is no RCT evidence to clarify optimum treatment in these patients.¹¹⁴

The clinical question to be addressed is whether it is safe to give anticoagulants to patients with acute stroke who have other comorbidities and who would normally require anticoagulation.

8.7.2 Clinical methodological introduction

Atrial fibrillation

One meta-analysis on a subgroup of patients with atrial fibrillation extracted from three RCTs^{115–118} was identified.¹¹⁹ One of these three trials was conducted in a Chinese population.¹¹⁷ The studies compared aspirin, heparin/heparinoid or both. Treatment was initiated within 30 to 48 hours of stroke onset.¹¹⁹ An additional prospective case series was identified (N=386) that compared aspirin 75 to 300 mg with adjusted-dose warfarin.¹²⁰ **Level 1+**

Prosthetic heart valves

No RCTs were identified that looked at the efficacy of anticoagulation for patients with prosthetic heart valves. Two case series (one retrospective and one prospective) looked at outcomes associated with warfarin cessation and recommencement.^{121,122}

The prospective case series (N=52) reported Kaplan-Meier survival estimates for a combined group of patients with mitral (14/52), aortic (31/52) or combined mitral and aortic valves (7/52). Median time for not taking warfarin was 10 days (range 0–30 days) and follow-up was up to 30 days.¹²² **Level 3**

The retrospective case series (N=16) reported mortality and adverse events for patients (seven mitral, five aortic and one combined mitral and aortic valves) restarting oral anticoagulant therapy 3–19 days post-bleed (median 7). Follow-up was for a median of 23.5 months.¹²¹ **Level 3**

DVTs and PE

▷ Anticoagulants versus placebo

For the comparison of anticoagulants versus placebo, one Cochrane systematic review was identified.⁷⁴ The review included 22 RCTs testing UFH, LMWH, heparinoids, oral anticoagulants and thrombin inhibitors. All patients were started on treatment within 2 weeks of stroke onset. The follow-up period ranged from 7 days to 1 year. **Level 1++**

▷ Anticoagulants versus antiplatelet agents

For the comparison of anticoagulants versus antiplatelet agents, one Cochrane systematic review was identified. The review included three trials that compared UFH and LMWH with aspirin. The follow-up period of the trials ranged from 10 days to 6 months.⁷⁶ **Level 1++**

No evidence was identified on caval filters.

8.7.3 Health economic methodological introduction

Three economic evaluations were identified that related to the question. Two studies were excluded as they had reporting limitations and did not provide enough detail to enable full interpretation of the results. Desbiens et al. (2002)¹²³ included a subgroup of patients with a history of stroke or TIA but did not report the results separately. Wade (1998)¹²⁴ did not include any details of the costs, and the time horizon was only 14 days.

The third paper identified, Gage et al. (1995)¹²⁵ was methodologically sound. A history of stroke was one of a number of risk factors highlighted by the paper and the results were reported for patients with high, medium or low risk factors. However, a subgroup analysis was not carried out specifically looking at patients who had suffered a previous stroke or TIA.

8.7.4 Clinical evidence statements

Atrial fibrillation

▷ Mortality

The meta-analysis and the case-series study reported no statistical differences in the mortality rate of patients treated with antiplatelet agents compared with those on anticoagulant therapy (NS).^{119,120} **Level 3**

▷ Recurrent strokes

Two of the three trials^{117,118} in the meta-analysis reported no statistical differences in the incidence of ischaemic recurrent stroke when comparing either LMWH with aspirin or aspirin with placebo.¹¹⁹ One trial^{115,116} reported a significantly higher recurrent ischaemic stroke rate in patients on 'no heparin' compared with those on heparin (but see intracerebral haemorrhage).¹¹⁹ **Level 1+**

One long-term prospective case series reported a significantly higher incidence of recurrent stroke in patients treated with aspirin compared with warfarin. This difference was mainly due to a recurrence of cardioembolic strokes in patients presenting with cardioembolic strokes. Anticoagulation did not reduce the risk of stroke recurrence in patients presenting with lacunar strokes (NS).¹²⁰ **Level 3**

▷ 1.3 Intracerebral haemorrhage

The trial in meta-analysis reported a reduction in the incidence of recurrent ischaemic stroke associated with unfractionated heparin (UFH). An increased incidence of haemorrhagic stroke in these patients was also reported, compared with those on no heparin.^{115,116} There was no statistical difference in the incidence of haemorrhagic stroke for aspirin in comparison with either placebo or control (NS).¹¹⁹ **Level 1+**

The prospective case series reported no statistical difference in the rate of intracerebral haemorrhage when patients on warfarin were compared with those on aspirin (NS).¹²⁰ **Level 3**

▷ Disability/functional outcome

One trial^{115,116} in the meta-analysis evaluated this outcome and there were no statistically significant differences found between anticoagulants and antiplatelet agents in the number of patients who were 'alive and independent' (NS).¹¹⁹ **Level 1+**

Prosthetic heart valves

▷ Mortality and adverse events

The prospective case-series study reported the Kaplan-Meier survival estimate for the probability of having ischaemic events at 7 days following warfarin treatment cessation at 2.9% (95%CI 0% to 7.6%). This remained unchanged at 14 and 30 days after ictus. Mortality rates at day seven and 14 were 18/52 (35%) and 20/52 (38%) respectively. Anticoagulation treatment (intravenous heparin or oral warfarin) was restarted in 7/52 (13%) and 26/52 (50%) of patients at day 7 and 14 respectively. There were no cases of recurrent intracerebral haemorrhage during hospitalisation.¹²² **Level 3**

The retrospective case series reported that 2/16 (13%) patients had died but neither had evidence of valve thrombosis (time frame not specified). At follow-up 11/13 (85%) patients were alive. 3/13 (23%) suffered neurological symptoms attributable to cerebral emboli at a rate of 12% per patient-year.¹²¹ **Level 3**

Deep vein thrombosis (DVT) and pulmonary embolism (PE)

▷ 1.0 Anticoagulants versus placebo

The Cochrane systematic review reported the following results:⁷⁴

▷ 1.1 Deep vein thrombosis during the treatment period (10 trials)

Anticoagulants were associated with a highly significant reduction in the odds of DVT although the majority of DVTs detected were sub-clinical or asymptomatic (note that there was significant heterogeneity between the trials).⁷⁴ **Level 1++**

▷ 1.2 Symptomatic pulmonary embolism (PE) (14 trials)

No trial systematically sought asymptomatic PE by performing ventilation – perfusion scans in all patients at the end of the treatment period. Anticoagulation was associated with a significant reduction in the odds of PE. The frequency of PE during the treatment period was low but variable ranging from 1%¹¹⁶ to 7%.^{126,127,74} **Level 1++**

▷ 2.0 Anticoagulants vs antiplatelet agents

The Cochrane systematic review reported the following results:⁷⁶

▷ 2.1 Deep vein thrombosis

The Cochrane review reported (two trials) significantly fewer symptomatic DVTs during the treatment period in patients taking anticoagulants than antiplatelets. One very small trial reported no significant difference (NS).⁷⁶ **Level 1++**

▷ 2.2 Pulmonary embolisms

The incidence of symptomatic pulmonary embolism during the treatment period was not significantly different when comparing anticoagulants with antiplatelets (NS).⁷⁶ Level 1++

8.7.5 Health economic evidence statements

Gage et al. (1995)¹²⁵ found that for patients with a high risk of secondary stroke warfarin was preferred to both no treatment and aspirin. For patients with a medium risk of stroke, warfarin was preferred to no treatment, and had a cost per QALY of \$8,000.

8.7.6 From evidence to recommendations

▷ Atrial fibrillation

In a meta-analysis of two large RCTs, there was no statistically significant difference in the number of aspirin-treated compared with no aspirin/control treated patients who died. An RCT comparing a low molecular weight heparin (LMWH) with aspirin also reported no significant difference in mortality rates at 14 days and 3 months. The GDG noted that the National Stroke guidelines (2004)²⁹ recommended the avoidance of anticoagulants in AF for 2 weeks following acute stroke because of evidence from anticoagulation/antiplatelet studies in acute stroke (including patients in AF) of increased rates of haemorrhagic transformation in patients treated with anticoagulants in the first 14 days of referral. The GDG consensus was that the decision to administer anticoagulation should be reconsidered at 2 weeks. This is consistent with the recommendation made in the National Stroke guidelines (2004).

A single health economic evaluation was found. It is noteworthy that the case series reviewed by the GDG reported somewhat different results from the RCTs, with a significant reduction in mortality in favour of anticoagulation compared to antiplatelet agents. This may be explained by the fact that these series looked at a much longer follow-up period which is outside the remit of this guideline. The GDG agreed that the recommendation should be based on the results of the RCTs which are of high quality and cover the appropriate time period. The GDG recommended that patients with uncomplicated AF and acute ischaemic stroke should be treated with antiplatelet agents for 2 weeks following stroke before starting or restarting anticoagulation.

One evaluation found warfarin to be cost effective compared with aspirin. However, the study did not take account of the increase in haemorrhagic stroke highlighted in the clinical evidence statement. Had this consequence been incorporated into the analysis, it is likely that anticoagulation would no longer appear to be cost effective compared with aspirin.

▷ Heart valves

Patients with prosthetic heart valves in situ may require long-term anticoagulation¹²⁸ to reduce the risk of systemic embolism. Mechanical heart valves require long term anticoagulation to a target INR of 3–4 with first generation valves and 2.5–3.5 with newer generation prosthetic valves. In a patient with a prosthetic heart valve already established on anticoagulation who suffers an ischaemic stroke, there are clearly potential risks associated with continuing anticoagulation which need to be balanced against the risk of further systemic embolism in the absence of anticoagulation. No RCTs were identified that looked at the efficacy of anticoagulation for patients with prosthetic heart valves after stroke. One prospective case series

identified a probability of ischaemic events following warfarin cessation at 2.9% at 7 days, and in a series of 52 patients no cases of recurrent intracerebral haemorrhage were identified after restarting anticoagulation at day 7 or 14. The risk of haemorrhagic transformation of infarction is difficult to calculate and the GDG agreed that in the absence of a risk algorithm the decision on whether to continue anticoagulation treatment would depend on the severity of the stroke along with the risk of thromboembolism for an individual. In patients with a major stroke and significant risk of haemorrhagic transformation anticoagulation should be stopped for the first 14 days and aspirin treatment substituted. The subsequent addition of aspirin or modified release dipyridamole to anticoagulation should be considered in patients who suffer systemic embolism despite adequate intensity of anticoagulation.

▷ Deep vein thrombosis (DVT) and Pulmonary Emboli (PE)

No evidence was found on the safety and efficacy of anticoagulant agents versus placebo for patients with acute stroke who may require anticoagulation for comorbidities such as deep vein thrombosis or pulmonary emboli. Evidence was identified on the prevention of deep vein thrombosis or pulmonary emboli after stroke. One Cochrane review, including 22 RCTs comparing anticoagulation (started within 2 weeks of stroke onset) with placebo, found that anticoagulants were associated with a highly significant reduction in the odds of DVT, although most were asymptomatic or sub-clinical. There was a significant reduction in the odds of PE with anticoagulation although the frequency was low. No trial systematically sought PE by ventilation/perfusion scanning and the trials were noted to be heterogenous. One systematic review compared anticoagulants with antiplatelet agents and found significantly fewer symptomatic DVTs in the anticoagulant treated group. There was no significant difference in the incidence of symptomatic pulmonary embolism during the treatment period. A historical cohort study compared therapeutic anticoagulation with heparin prophylaxis and antiplatelets and found that only therapeutic anticoagulation achieved a statistically significant reduction in venous thromboembolic events. It was noted that the risk of symptomatic haemorrhage on anticoagulants is very low (approximately 1%). These studies do not address the question of the safety of anticoagulants in the treatment of DVT and PE after stroke.

The GDG agreed a consensus recommendation in the absence of RCT evidence to guide treatment of venous thromboembolism in acute stroke. Patients with ischaemic stroke should be anticoagulated and patients with haemorrhagic stroke either anticoagulated or treated with caval filter to prevent further PE.

8.7.7 RECOMMENDATIONS

- R32 People with disabling ischaemic stroke who are in atrial fibrillation (AF) should be treated with aspirin 300 mg for the first 2 weeks before considering anticoagulation treatment.
- R33 In people with prosthetic valves who have disabling cerebral infarction and who are at significant risk of haemorrhagic transformation, anticoagulation treatment should be stopped for 1 week and aspirin 300 mg substituted.
- R34 People with ischaemic stroke and symptomatic proximal deep vein thrombosis or pulmonary embolism should receive anticoagulation treatment in preference to treatment with aspirin unless there are other contraindications to anticoagulation.

- R35 People with haemorrhagic stroke and symptomatic deep vein thrombosis or pulmonary embolism should have treatment to prevent the development of further pulmonary emboli using either anticoagulation or caval filter.

8.8 Statin treatment in people with acute stroke

8.8.1 Clinical Introduction

There is a concern that statin treatment, although clearly of benefit in reducing the risk of ischaemic stroke in terms of secondary prevention, may increase the risk of early haemorrhagic expansion or haemorrhage transformation in the acute phase.¹²⁹ Observational studies have not shown an association between blood cholesterol concentrations and risk of stroke of all types, but this could mask a positive association with ischaemic stroke and an inverse association with haemorrhagic stroke.¹³⁰ For each 1 mmol/l reduction in concentration of LDL cholesterol achieved with statins over a 5-year period, there was an associated relative risk reduction of any vascular event of 20% in a prospective meta-analysis of 14 statin trials in 90,056 individuals¹³¹ including any stroke and ischaemic stroke, with no excess of haemorrhagic stroke. However, in those patients with a prior history of stroke or TIA there was a non-significant excess of haemorrhagic stroke.¹³² The recent Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial¹³³ addressed the issue of the safety and efficacy of statin treatment with more recent TIA or non-cardioembolic stroke. Patients were randomised between 1 and 6 months after non-disabling TIA or stroke to atorvastatin 80 mg vs placebo and treated for a median of 4.9 years. A reduction in LDL of 1.4 mmol/l and a significant reduction in stroke was observed in the treatment group compared to placebo. However, the reduction was in ischaemic stroke with a significant excess of haemorrhagic stroke in the treated group. It is unclear whether this is a chance finding, whether it was confined to those with small vessel disease (which might be less susceptible to the effects of statins than large artery thromboembolism and more predisposed to cerebral microbleeds) or whether there are other factors that underlie the association between low cholesterol and haemorrhagic stroke, for example alcohol consumption.¹³⁴ Statins may have a neuroprotective effect;¹³⁵ they are anti-inflammatory¹³⁶ and have beneficial effects on endothelial function and haemostasis. A retrospective analysis of a consecutive case series of 155 patients who received intravenous tPA for middle cerebral artery ischaemic stroke¹³⁷ identified baseline NIHSS score, age and prior treatment with statins as independent predictors for good outcome. Early treatment with statins reduces recurrence of ischaemic events in coronary syndromes¹³⁸ with a reduction in inflammatory markers.¹³⁹ A pilot study of acute treatment with statins (MISTICS)* following stroke has reported interim results.¹⁴⁰ The FASTER** study planned to assess the efficacy of early antiplatelets and statins, was halted because of increased statin use pre-stroke.¹⁴¹ The developers noted that NICE has recently published a NICE lipid modification clinical guideline. This is not relevant for the acute stroke and TIA population addressed within this guideline. However the lipid modification guideline does include secondary prevention guidance for people with stroke.

The clinical question to be addressed is whether patients with acute stroke should be given early treatment with statins.

* Markers of inflammation after Simvastatin in ischaemic cortical stroke.

** Fast assessment of stroke and transient ischaemic attack to prevent early recurrence.

8.8.2 Clinical methodological introduction

▷ Statin withdrawal

One RCT (N=89) was identified and reported on the influence of statin pre-treatment and its withdrawal on the outcome of acute ischaemic stroke patients.¹⁴² **Level 1+**

Patients were admitted within 24 hours of symptom onset. Patients on statins prior to the stroke were randomised to 'statin withdrawal' for the first 3 days after admission or to immediately receive atorvastatin 20 mg/day (non-statin withdrawal).¹⁴² **Level 1+**

▷ Pre-morbid statin treatment

A small number of studies were identified that explored whether patients already on statins, and who subsequently have a stroke, have reduced mortality and morbidity.^{143–145} None of the three studies identified were RCTs. One cross-sectional/cohort study compared patients with ischaemic stroke or TIA who were on statins prior to the index event (N=152) with those that were not on statins (N=1539).¹⁴³ One retrospective case-referent study compared patients with ischaemic or haemorrhagic stroke who were on statins (N=125) and those that were not on statins (N=250).¹⁴⁴ A third study prospectively evaluated ischaemic stroke patients (of less than 24 hours in duration) on statins prior to the event (N=30) with those that were not (N=137).¹⁴⁵ **Level 2+**

8.8.3 Health economic methodological introduction

No papers were identified.

8.8.4 Clinical evidence statements

Statin withdrawal

At 3-month follow-up, patients who withdrew from statins showed a significantly higher incidence of death or dependency (mRS >2) and early neurologic deterioration compared with the non-statin withdrawal patients. Statin withdrawal is associated with a 4.7-fold increase in the risk of death or dependency at 3 months. In a secondary analysis (N=215) patients in the statin-withdrawal group were compared with a reference group of patients who had not previously been treated with statins. There were no statistical differences between the groups on the outcome of death or dependency (NS). The proportion of patients with early neurologic deterioration was significantly greater in the statin-withdrawal group compared with the reference group of no previous statin treatment.¹⁴² **Level 1+**

Pre-morbid statin treatment

▷ Mortality

One study reported on this outcome.¹⁴⁴ After adjusting for the uneven distribution of comorbidity between the two groups, a conditional logistic regression model showed that previous statin use was not a significant predictor of an early discharge home (versus late discharge home or death) (NS).¹⁴⁴ **Level 2+**

▷ Disability

One study reported that at 1-week follow-up, statin treatment was significantly associated with stroke severity only if the event was severe (mRS 5 to 6). There was a significant interaction between the diabetes and pre-treatment with statins. No patient with diabetes and pre-treated with statins had a mRS of 5 or 6, compared with 16% not on statins. When patients with diabetes and on statin treatment were excluded from the analysis, there was no longer a statistical effect (NS).¹⁴³ **Level 2+**

A further study reported that at 3-month follow-up, the proportion of patients who were living without notable disability was significantly higher in the group pre-treated with statins. There was no statistical difference on the mRS (NS). In a univariate analysis, statin use was an independent predictor of Barthel Index 95 to 100 but not mRS.¹⁴⁵ **Level 2+**

▷ Stroke type

One study reported that lacunar strokes were statistically more frequent in the statin group than the no statin group.¹⁴⁵ **Level 2+**

8.8.5 From evidence to recommendations

Statin withdrawal is associated with worse clinical outcome after ischaemic stroke than when pre-morbid statin treatment is continued. However, the GDG noted that no evidence is presently available on the safety and efficacy of initiating lipid lowering statin therapy for patients with an acute stroke. The consensus of the GDG was that as yet there is no evidence for initiating statins in acute stroke, but there is evidence to support continuing statin treatment in those who were taking statins prior to stroke. The consensus of the GDG is that it would be safe to start statins after 48 hours. There is clearly benefit from initiation of statins after the acute phase of stroke in vascular risk reduction. Secondary prevention is outside the remit of the acute period of this guideline. However, the GDG noted that secondary prevention is covered within the Intercollegiate Stroke Working Party guideline due to be published in July 2008.

8.8.6 RECOMMENDATIONS

- R36 Immediate initiation of statin treatment is not recommended in people with acute stroke.*
- R37 People with acute stroke who are already receiving statins should continue their statin treatment.

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

9 Maintenance or restoration of homeostasis

9.1 Supplemental oxygen therapy

9.1.1 Clinical introduction

Oxygen supplementation by mask has been usual practice in emergency pre-hospital and hospital care in acutely ill patients after appropriate assessment.¹⁴⁶ There have been suggestions that hyperbaric and standard oxygen therapy might theoretically be of value after acute stroke, but might equally be harmful. Oxygen retention is hazardous in patients with CO₂ retention. It is well established that following cerebral ischaemia, there is a reduction in cerebral oxygen metabolism in both the ischaemic and penumbral areas, associated with changes in blood flow. There remains clinical uncertainty as to whether supplemental oxygen in patients without hypoxia improves outcome. Patients who are hypoxic should be managed according to appropriate guidelines.

The clinical question to be addressed is whether patients who are not hypoxic should be treated with oxygen supplementation.

9.1.2 Clinical methodological introduction

Two studies were identified that reported on the effect of supplemental oxygen in patients with acute stroke (time from symptom onset to presentation: 14 days or less).^{147,148} One of these studies was excluded due to methodological limitations.¹⁴⁸ **Level 1+**

The remaining study was a quasi-randomised controlled trial (N=550) comparing acute stroke patients who received 100% oxygen (3 l/min) (N=292) for the first 24 hours compared with a control group (N=292) which did not receive additional oxygen.* The patient population had a mean age of 75 years and 12.7% were diagnosed with haemorrhagic stroke.¹⁴⁷ **Level 1+**

9.1.3 Health economic methodological introduction

No papers were identified.

9.1.4 Clinical evidence statements

▷ Mortality, neurological impairment and disability

At 1-year follow-up, there were no statistical differences between patients given oxygen therapy compared with control patients in terms of mortality or neurological impairment (Scandinavian Stroke Score, SSS) or disability (Barthel Index) (NS).¹⁴⁷ **Level 1+**

▷ Stroke severity

The 1-year survival rate for patients with moderate or mild strokes (SSS score ≥ 40 on admission) was higher in the control group than patients who received supplemental oxygen. There were no

* 33 patients in the treatment group did not receive supplemented oxygen as described (not given such treatment or were treated for less than 24 hours) and 66 patients in the control group were given oxygen but for a lot less than 24 hours.

statistical differences between patients with severe stroke (SSS score <40 on admission) and controls (NS). There were no other statistical differences between the levels of stroke severity on measures of mortality or dependency when compared with controls (NS).¹⁴⁷ **Level 1+**

9.1.5 From evidence to recommendations

Conventional practice is to give supplemental oxygen to patients with oxygen saturations of less than 95%. The study discussed showed no benefit of supplemental oxygen on mortality or morbidity. It was noted that baseline oxygen saturations had not been recorded in the study discussed, and that any study of oxygen saturation would need to control for other physiological variables such as glucose. No recommendation can be made on the benefit of supplemental oxygen after acute stroke, although a consensus recommendation that saturations of <95% should be treated was agreed.

9.1.6 RECOMMENDATION

- R38 People who have had a stroke should receive supplemental oxygen only if their oxygen saturation drops below 95%. The routine use of supplemental oxygen is not recommended in people with acute stroke who are not hypoxic.

9.2 Blood sugar control

9.2.1 Clinical introduction

Hyperglycaemia in acute ischaemic stroke has been shown in a number of studies to be a risk factor for death and more severe disability. Post-stroke hyperglycaemia is common, and occurs across the spectrum of stroke severities. Hyperglycaemia is also a common finding after myocardial infarction and in patients with major acute medical and surgical illness, and there is evidence that intensive management of hyperglycaemia in these cases improves outcome.¹⁴⁹ An integral part of acute stroke care is the monitoring and management of physiological variables, including plasma glucose concentration. It is not known whether intensive management of blood glucose, analogous to the management of high blood glucose in myocardial infarction, might improve outcome. It is of note that in stroke, the relationship between hyperglycaemia and outcome is partly dependent upon the type of stroke; outcome after non-lacunar stroke appears to be particularly susceptible to mild hyperglycaemia.^{150,151}

The clinical question to be addressed is whether patients with acute stroke who have mildly elevated blood glucose levels should have treatment with insulin.

9.2.2 Clinical methodological introduction

One RCT (N=933) was identified that compared clinical outcomes in patients treated with glucose-potassium insulin (GKI) (N=469) with those receiving saline (N=464). The trial was terminated early due to slow enrolment (planned N=2,355).¹⁵² **Level 1++**

The study included patients with acute stroke (haemorrhagic stroke 2.4% and 2.8% for GKI and saline respectively) presenting 24 hours from symptom onset and with mild to moderate hyperglycaemia (admission glucose range 6.0 to 17 mmol). GKI was administered for a minimum of 24 hours to maintain capillary blood glucose concentration at 4–7 mmol/l. Trial

hyperglycaemia was defined as a capillary glucose of less than 4 mmol/l that persisted for more than 30 min, after which rescue dextrose (10 ml, 50%) was administered.¹⁵² **Level 1++**

The majority of patients had only mild to moderate increases in admission plasma glucose (median on admission 7.6 mmol/l (IQR 6.7 to 9.0)). 54.9% patients had a normal HbA_{1c} (<6.2%), 191 (31.4%) had an acceptable percentage (HbA_{1c} 6.2 to 7.5%) and 83 (13.7%) had a high percentage (HbA_{1c} >7.5%).¹⁵² **Level 1++**

9.2.3 Health economic methodological introduction

No papers were identified.

9.2.4 Clinical evidence statements

▷ Mortality and disability

At 90 days, there were no statistical differences in mortality rates between those patients given GKI and placebo patients (NS).¹⁵² **Level 1++**

At 90 days, there were no statistical differences on the mRS, Barthel Index or the European Stroke Scale (ESS) between the GKI- and placebo-treated patients (NS).¹⁵² **Level 1++**

Overall, 73 (15%) GKI-treated patients required rescue intravenous glucose treatment for hypoglycaemia (capillary glucose \leq 4 mmol/l persisting more than 30 minutes after temporary discontinuation of the GKI infusion). There were no statistical differences in the mortality rates among patients receiving rescue dextrose and the other GKI patients (NS).¹⁵² **Level 1++**

▷ Time from symptom onset

At 90 days, there was no statistical difference in mortality for those patients treated within 6 hours of stroke onset compared with patients in the placebo group (NS).¹⁵² **Level 1++**

▷ Complications

At 72 hours, there were no statistical differences between the two groups with respect to the number of complications at 72 hours (NS).¹⁵² **Level 1++**

9.2.5 From evidence to recommendations

The United Kingdom Glucose Insulin in Stroke Trial (GIST-UK) was the only study identified that compared a glucose-lowering regimen with control. The study randomised patients within 24 hours of symptom onset and the intervention lasted for 24 hours. The GDG noted that hyperglycaemia after stroke tends to last longer than 24 hours, and that the intervention may have been too brief to have a lasting effect. There was no evidence to support the tight control of blood glucose in patients with mild to moderate elevated blood glucose levels (median 7–9 mmol/l). Patients with pre-existing diabetes should be treated according to current guidelines. The group consensus was that glucose levels above 11 mmol/l following stroke should be treated. The Type 2 diabetes guideline¹⁵³ recommends that patients with diabetes are treated to achieve or maintain their target HbA_{1c} level. The consensus of the group was that where possible patients with acute stroke should be treated to maintain blood glucose concentrations between 4–11 mmol/l. The group agreed to include the Type 1 diabetes recommendation on optimal insulin therapy.

9.2.6 RECOMMENDATIONS

- R39** People with acute stroke should be treated to maintain a blood glucose concentration between 4 and 11 mmol/l.
- R40** Optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, should be provided to all adults with diabetes who have threatened or actual myocardial infarction or stroke. Critical care and emergency departments should have a protocol for such management. (NICE Type 1 diabetes guideline, recommendation 165).¹⁵⁴

9.3 Blood pressure control

9.3.1 Clinical introduction

Blood pressure abnormalities are common after acute stroke. Many patients have pre-existing hypertension that may or may not have been treated before the stroke. There is uncertainty as to whether usual antihypertensive treatments should be continued following acute stroke; patients with swallowing difficulties may be unable to take oral medication even if it is prescribed. Blood pressure changes may occur as a result of disturbed cardiovascular autonomic regulation, with changes in absolute blood pressure levels and blood pressure variability. Elevated blood pressure is common; 54% of patients in the International Stroke Trial had systolic blood pressure >160 mmHg. High blood pressure after stroke may be associated with poor short-term and long-term prognosis, and may be associated with the development of oedema or haemorrhage. However, in most patients the blood pressure spontaneously reduces over the first 4–10 days after the stroke. There are potential concerns that a reduction in blood pressure early after stroke may reduce cerebral blood flow and impair penumbral viability, thus affecting outcome. The effects of blood pressure lowering or elevation may differ in different stroke subtypes. There is some evidence that pressor treatment may be of benefit in stroke.* There may be differential effects of different classes of antihypertensive agents, with some evidence that angiotensin-converting enzyme inhibitors and angiotensin 2 receptor blockers may be more effective than diuretics or calcium channel blockers. Both hypertension and marked hypotension are associated with poor outcome after stroke, and there is considerable clinical uncertainty as to the optimal management of blood pressure acutely after stroke.

The clinical question to be addressed is whether manipulation of blood pressure is safe or improves outcome in acute stroke.

9.3.2 Clinical methodological introduction

Two Cochrane systematic reviews and four RCTs were identified that addressed the question of whether manipulating blood pressure in patients with acute stroke affects mortality or morbidity. Studies with a sample size of 100 or less were excluded. Of the two Cochrane systematic reviews, one compared calcium agonists with control/placebo (N=7,521, 28 trials)¹⁵⁵ and one glyceryl trinitrate (GTN) (N=227, two trials).¹⁵⁶ Four additional RCTs were identified: (N=265);¹⁵⁷ (N=454);¹⁵⁸ (N=302);¹⁵⁹ (N=339).¹⁶⁰ **Level 1+**

* Mistri AK, Robinson TG, Potter JF. Pressor therapy in acute ischaemic stroke – systematic review. *Stroke* 2006;37(6):1565–1571.

The studies on calcium antagonists initiated therapy from between 6 hours or less to 72 hours from stroke onset.^{155,157,158} **Level 1+**

The remaining Cochrane review reported on GTN compared with control/placebo.¹⁵⁶ In the studies included, therapy was initiated between 4 to 5 days from stroke onset. **Level 1++**

One phase II RCT compared an angiotensin II antagonist with placebo in patients who had a ≥ 200 mmHg systolic and/or ≥ 110 mmHg diastolic 6 to 24 hours after admission or ≥ 180 mmHg systolic and/or ≥ 105 mmHg diastolic 24 to 36 hours after admission.¹⁶⁰ **Level 1+**

An RCT conducted in patients with hemispheric stroke (conscious and able to swallow) sustained within 48 hours, compared beta-blockers with placebo initiated 4 to 5 days from stroke onset.¹⁵⁹ **Level 1+**

9.3.3 Health economic methodological introduction

No papers were identified.

9.3.4 Clinical evidence statements

Calcium antagonists

The Cochrane review included patients with acute ischaemic stroke randomised within 14 days after stroke onset. The calcium antagonists included in the review were intravenous isradipine (one trial), oral nimodipine (18 trials), oral and intravenous nimodipine (six trials), flunarizine (three trials), nicardipine (one trial) and oral PY108-608 (one trial).¹⁵⁵ **Level 1++**

One additional RCT reported on a combination of intravenous and oral nimodipine (1 mg/hr (low dose), 2 mg/hr (high dose) both for 5 days plus oral nimodipine 120 mg for 16 days). All of the patients had ischaemic stroke and were randomised within 24 hours of stroke onset.¹⁵⁷ **Level 1+**

The remaining study, based in primary care (Netherlands), included patients with ischaemic and haemorrhagic stroke. Patients received 120 mg/daily of nimodipine or placebo. The patients were randomised within 6 hours of stroke onset and the duration of treatment was 10 days.¹⁵⁸ **Level 1+**

▷ Mortality (at end of treatment and follow-up)

The Cochrane review found no statistical differences in the mortality rate of patients given a calcium antagonist compared with those patients in the control/placebo group (NS).¹⁵⁵ One of the separate RCTs reported a similar finding for nimodipine compared with placebo (NS).¹⁵⁸ **Level 1++**

The remaining study reported that at 21 days follow-up, patients on nimodipine with a reduction of diastolic blood pressure $\geq 20\%$ (high dose) had a significantly increased risk of death compared with placebo patients.¹⁵⁷ **Level 1+**

▷ Dependency (at end of treatment and follow-up)

The Cochrane review found no statistical differences on measures of dependency in patients given a calcium antagonist compared with those patients in the control/placebo group (NS).¹⁵⁵ One RCT also reported no statistical differences (NS).¹⁵⁸ **Level 1++**

One study reported a statistically higher level dependency and mortality combined in patients treated with nimodipine compared with placebo. In a multivariate analysis, patients with a reduction of diastolic blood pressure $\geq 20\%$ in (high dose) in the nimodipine group had a significantly increased risk of death or dependency (Barthel Index < 60) compared with placebo patients.¹⁵⁷ **Level 1+**

▷ Recurrent stroke

The Cochrane review found no statistical differences when patients on calcium antagonists were compared with control/placebo (NS).¹⁵⁵ **Level 1++**

▷ Time to treatment

The Cochrane review reported no statistical difference in outcomes between early treatment (≤ 12 hours after stroke onset) with calcium antagonists compared to placebo (NS). There was no statistical difference on mortality when early treatment was compared with treatment started later than 24 hours (NS).¹⁵⁵ **Level 1++**

▷ Route of administration (intravenous versus oral)

The Cochrane review reported no statistical difference in outcomes when comparing intravenous and oral nimodipine (NS).¹⁵⁵ **Level 1++**

▷ Adverse events

In the Cochrane review, for the largest flunarizine trial there was a significant increase of adverse events in the active intervention group. There were no statistical differences in adverse events in the remaining studies included either in the review or the two additional RCTs (NS).^{157,158} **Level 1+**

Transdermal glyceryl trinitrate (GTN)

A Cochrane review on two RCTs compared GTN 5 to 10 mg daily with no patch or placebo in patients with acute stroke (N=117 ischaemic and N=10 haemorrhagic stroke).¹⁵⁶ **Level 1+**

▷ Blood pressure

GTN significantly lowered 24-hour ambulatory systolic blood pressure. There was no statistical difference for diastolic blood pressure (NS).¹⁵⁶ **Level 1++**

▷ Mortality and deterioration

At 3-month follow-up, patients treated with GTN showed no statistical differences in mortality rate (NS), mortality and deterioration combined (NS) or death or dependency combined (NS).¹⁵⁶ **Level 1++**

Angiotensin II antagonist

One RCT reported on patients who were treated with candesartan cilextil 4 mg on day 1 increasing to 8 or 16 mg on day 2 if blood pressure exceeded 160 mmHg systolic or 100 mmHg diastolic. The treatment was targeted to a blood pressure reduction of 10 to 15% within 24 hours.¹⁶⁰ **Level 1+**

▷ Blood pressure

During the placebo-controlled phase in the first 7 days, there were no statistical differences in blood pressure between the groups (NS). There were no differences at 12 months (NS). In 164/166 patients in the placebo group, candesartan cilexetil was started on day 7 due to a hypertensive 24-hour blood pressure profile.¹⁶⁰ **Level 1+**

▷ Mortality and vascular events

There was no statistical difference in the cumulative 12-month mortality for candesartan cilexetil versus placebo (NS).¹⁶⁰ **Level 1+**

There was a statistical difference in favour of candesartan cilexetil compared with placebo on the number of vascular events and on the combined outcome of cumulative 12-month mortality and the number of vascular events.¹⁶⁰ **Level 1+**

▷ Functional outcome

There were no statistical differences between candesartan cilexetil and placebo on the Barthel Index at 3 months (NS).¹⁶⁰ **Level 1+**

▷ Concomitant medication, drug tolerance, adverse events

There were no statistical differences between candesartan cilexetil and placebo regarding the use of concomitant medication, drug tolerance or adverse events during follow-up.¹⁶⁰ **Level 1+**

Beta-blockers

An RCT compared two beta-blockers, namely atenolol 50 mg daily, propranolol slow release 80 mg daily, with placebo.¹⁵⁹ **Level 1+**

▷ Neurological changes (based on neurological assessment)

When patients given propranolol or atenolol were combined and compared with placebo, there was a statistical higher number of mean neurological changes (signs and symptoms on neurological assessment) associated with placebo compared to beta-blockers at 1 day to 1 week and 1 day to 1 month.¹⁵⁹ **Level 1+**

▷ Functional outcome (activities of daily living)

At 1 month, there was a statistical difference in activities of daily living in favour of placebo, compared with atenolol and propranolol. There was no statistical difference at 1 week or 6 months (NS).¹⁵⁹ **Level 1+**

▷ Rate of discharge

There was no statistical difference in the rate of hospital discharge (NS).¹⁵⁹ **Level 1+**

▷ Adverse events

Eight patients experienced definite side effects from beta-blockers.¹⁵⁹ **Level 1+**

9.3.5 From evidence to recommendations

There was a lack of evidence in the studies assessed to suggest that manipulating blood pressure in acute stroke (within the first 72 hours) using beta-blockers or calcium channel antagonists compared to control/placebo had any beneficial effect on mortality, dependency or stroke recurrence. There is clinical concern that lowering blood pressure acutely may have a deleterious effect. There was discussion of the possible benefits of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers after acute stroke; it was agreed that no specific recommendations could be made until the publication of the current trials.

The issue of severe hypertension was discussed. There are clearly circumstances such as hypertensive encephalopathy or co-existing cardiac or vascular emergency (e.g. aortic dissection) when active management of severe hypertension (consensus: systolic blood pressure >200 mmHg) may be indicated. The effects of this on acute stroke are unknown.

The GDG acknowledged that current trial results will not be available until at least 2009.

9.3.6 RECOMMENDATIONS

- R41** Antihypertensive treatment in people with acute stroke is recommended only if there is a hypertensive emergency with one or more of the following serious concomitant medical issues:
- hypertensive encephalopathy
 - hypertensive nephropathy
 - hypertensive cardiac failure/myocardial infarction
 - aortic dissection
 - pre-eclampsia/eclampsia
 - intracerebral haemorrhage with systolic blood pressure over 200 mmHg.
- R42** Blood pressure reduction to 185/110 mmHg or lower should be considered in people who are candidates for thrombolysis.

10 Nutrition and hydration

10.1 Assessment of swallowing function

10.1.1 Clinical introduction

Dysphagia (swallowing difficulty) is common after acute stroke with reported incidence varying in different studies depending on definition but commonly quoted at around 40%.¹⁶¹ Patients who have dysphagia are likely to have poorer outcomes, specifically a higher incidence of death, disability, chest infection and longer length of stay. The majority of patients will recover, however, a proportion will have persistent abnormal swallowing physiology and aspiration at 6 months despite resuming oral intake.¹⁶² Food and fluids may be withdrawn if the patient is felt to be at risk of aspiration of oropharyngeal contents into the trachea. Withdrawal of food or fluid necessitates immediate replacement of fluids to avoid dehydration which can be given intravenously or subcutaneously. However, the concurrent need for oral medications and nutrition often necessitates early placement of a nasogastric (NG) feeding tube for patients with abnormal swallow. Tube feeding may be supplemented or replaced by modified fluids (thickened) or diet (puree or soft diet) as swallowing recovers. Non-oral feeding is not entirely without hazard and it does not prevent the aspiration of saliva. Being placed nil by mouth also has psychological impact. Screening for swallowing difficulty after stroke is a key part of the clinical assessment of an acute stroke patient, and is one of the important process indicators for stroke.³ Swallow safety can be evaluated using an agreed swallow screening tool which can be administered as soon as possible after admission by an appropriately trained healthcare professional. Usually, small volumes of water are administered and a judgment is made about whether the patient coughs, has a change in voice quality, respiratory patterns, pooling of fluid within the oral cavity or leakage from the mouth. This technique does not pick up 'silent' aspiration. Careful clinical observation and monitoring are essential even after a patient has 'passed' a swallow screen. A more detailed swallow assessment will usually include a detailed assessment of behaviour, function and cognition as it relates to swallowing and assessment with a broader range of food and fluids of varying texture and consistency. It may also include instrumental assessment such as fiberoptic endoscopic evaluation of swallowing (FEES). Videofluoroscopy (VF) is the 'gold' standard assessment for the detection of aspiration and its underlying pathophysiology. It is the only technique that can evaluate the efficacy of therapeutic interventions such as postural techniques and dietary modifications. However, it has some limitations for stroke in that patients need to be able to sit up and follow detailed instructions and that specially-trained staff are required. This may not be practical particularly early after stroke. FEES is more accessible in that it can be performed at the bedside, however, it too requires the patient to be compliant and able to follow instructions. It has limitations in its ability to detect aspiration during the swallow and aspiration has to be assumed from post-swallow residue patterns in the pharynx and larynx. It is difficult to determine the efficacy of therapeutic interventions with FEES alone. However it is not associated with radiation exposure and can be repeated whenever necessary.

The clinical question to be addressed is how best to assess the presence and severity of swallowing difficulties after stroke.

10.1.2 Clinical methodological introduction

- ▷ Accuracy of bedside swallowing assessment vs videofluoroscopy vs fibreoptic endoscopic evaluation of swallowing

Five studies were identified that reported the diagnostic accuracy of bedside swallowing assessment (BSA), videofluoroscopy (VF) and fibreoptic endoscopic evaluation of swallowing (FEES).^{163–167} One additional study was on a newly developed screening tool, the Gugging Swallowing Screen (GUSS).¹⁶⁸ Only studies which compared two or more of these investigations were included. However, two of these studies reported on the accuracy of clinical signs and historical information elicited from BSA and medical assessment, rather than comparing the accuracy of BSA directly with VF.^{165,166} Three studies investigated the reliability of BSA.^{164–166} One study was excluded due to methodological limitations.¹⁶⁹ The GUSS was compared with FEES.¹⁶⁸

One study (N=60) looked at the sensitivity and specificity of BSA for predicting aspiration on VF of swallowing.¹⁶⁵ A follow-up of this study reported on a larger sample (N=165) to determine whether individual or a combination of measures on a BSA are associated with aspiration on VF.¹⁶⁶ **Level 1b++**

One study (N=128) looked at the diagnostic accuracy of BSA compared with VF, and interobserver agreement for the clinical and videofluoroscopic diagnosis of swallowing disorders and aspiration admitted to an acute stroke unit.¹⁶³ **Level 1b++**

A small study (N=49) compared BSA with FEES¹⁶⁷ and a further study (N=20) reported the inter- and intra-judge reliability of a BSA.¹⁶⁴
Level 1b++

The GUSS (N=19 and N=30) is a simple stepwise bedside screen that assesses non-fluid and fluid nutrition with the aim of reducing the risk of aspiration during the test to a minimum. The GUSS yielded four categories of severity (0 to 9 severe, 10 to 14 moderate, 15 to 19 mild, and 20 points as no dysphagia). The validity of the GUSS was established by FEES.¹⁶⁸ **Level 1b++**

All of the studies were prospective. The patient populations were broadly comparable, except one study reported on stroke patients who were younger in comparison to the other studies (mean 60 years).¹⁶³ **Level 2+**

One study included patients within 24 hours of stroke onset¹⁶⁷ and one 7 days or less.¹⁶³ The remaining three studies included patients up to 6 weeks post stroke, but the significant majority were examined within 2 weeks.^{164–166} **Level 1b++**

- ▷ Effect on clinical outcomes

Overall, five studies were identified.^{170,171,162,172,173}

Three studies compared patients with and without swallowing impairment using a BSA,^{173,172,170} and two BSA and VF.^{174,162} Follow-up periods ranged from discharge to 5 years. **Level 3+**

10.1.3 Health economic methodological introduction

No papers were identified.

10.1.4 Clinical evidence statements

Accuracy of bedside swallowing assessment vs videofluoroscopy vs fiberoptic endoscopic evaluation of swallowing

▷ Bedside swallowing assessment (BSA) and videofluoroscopy (VF)

One study on patients with acute stroke reported that BSA underestimated the frequency of dysphagia and overestimated the frequency of aspiration when compared with VF. The table below reports the data for any clinical evidence of dysphagia or aspiration.¹⁶³ **Level 1b++**

Two studies reported on the accuracy of a BSA at predicting aspiration on VF;^{165,166} one of these was a follow-up study.¹⁶⁶ Only the results of a global judgement of aspiration from the 3-oz swallow test are reported here (see table 10.1 below), but a regression analysis revealed that the most important predictors of aspiration in addition to this measure were the presence of dysphonia and jaw weakness.¹⁶⁶ **Level 1b++**

Table 10.1 The results of a global judgement of aspiration from the 3-oz swallow test

	Incidence on VF	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Mann et al. Dysphagia	82/128 (64%)	73% (62 to 82%)	89% (76 to 96%)	92% (83 to 97%)	65% (52 to 77%)
Mann et al. Aspiration	28/128 (22%)	93% (76 to 99%)	63% (53 to 72%)	41% (29 to 54%)	97% (89 to 100%)
McCullough et al. (2001) Aspiration	22/60 (37%)	68%* 77%**	82% 63%	NR NR	NR NR
McCullough et al. (2005) Aspiration	43/165 (26%)	54%***	89%	62%	86%

NR, not reported; *Spontaneous cough on trial swallow; **Overall estimate of aspiration. No other signs of measures met the criteria for sensitivity or specificity (60% or more);¹⁶⁵ ***Global measure of aspiration¹⁶⁶

▷ BSA compared with FEES

A study reported on whether BSA could predict aspiration compared with FEES.

The accuracy of BSA was sensitivity 86%, specificity 30%, PPV 73% and NPV 73%. These results indicate that BSA underestimated aspiration risk when compared with FEES and overestimated aspiration risk in patients who did not exhibit aspiration risk.¹⁶⁷ **Level 1b++**

▷ GUSS compared with FEES

Table 10.2 below shows the sensitivity, specificity, PPVs and NPVs for the GUSS; these were compared with the FEES results in the first sample. The content validity of GUSS indicated that there was a significantly higher aspiration risk with liquids compared with semisolid textures, supporting the subtest sequence used for the test. **Level 1b++**

Table 10.2 The sensitivity, specificity, PPVs and NPVs for the GUSS, these were compared with the FEES results in the first sample

GUSS	FEES, highest score		Accuracy
	Aspiration risk, PAS (5 to 8)	No Aspiration Risk, PAS (1 to 4)	
First sample (N=19)			
Aspiration risk (0 to 14)	13		3 PPV 81%
No aspiration risk (15 to 20)	0	3	NPV 100%
	Sensitivity 100%	Specificity 50%	Prevalence 68%
Second sample (N=30)			
Aspiration risk (0 to 14)	14	5	PPV 74%
No aspiration risk (15 to 20)	0	11	NPV 100%
	Sensitivity 100%	Specificity 69%	Prevalence 10%

PAS, Penetration-Aspiration Scale; PPV, positive predictive value; NPV, negative predictive value

▷ Inter- and intra-judge reliability

Four studies study reported on the reliability of a BSA.^{163–166} **Level 1b++**

The interobserver agreement in the clinical diagnosis of any evidence of a swallowing disorder and aspiration between two speech pathologists on initial clinical assessment was good. Similar results were reported on VF for any evidence of a swallowing disorder aspiration.¹⁶³ **Level 1b++**

The inter- and intra-judge reliability for a 3-oz swallow test and an overall measure of the presence or absence of aspiration was good.^{165,166} Inter- and intra-judge reliability for relating the presence or absence of aspiration from VF was good.¹⁶⁵ An additional study reported relatively low intra-judge reliability between two speech–language pathologists on the 3-oz swallow and an overall rating of dysphagia but good inter-judge reliability.¹⁶⁴ **Level 1b++**

The interrater reliability of the GUSS performed by two ‘therapists’ with a maximum of 2 hours between the two assessments (first sample N=19) was excellent.¹⁶⁸ **Level 1b++**

▷ Effect on clinical outcomes

Overall, swallowing impairments were associated with increased mortality.^{171,173,170} Two studies reported a significantly higher proportion of patients with aspiration compared to those without an episode of pneumonia or a chest infection.^{171,174} One study reported that risk of developing pneumonia was almost four times higher for young aspirating patients compared with young non-aspirating patients. This reduced to 1.75 times for old aspirating patients compared with old non-aspirating patients. Three studies reported an association with measures of disability and dysphagia.^{171,173,170} **Level 2+**

One study reported that dysphagia was statistically associated with a longer stay in hospital.¹⁷¹ Two studies reported that patients with dysphagia were statistically more likely to be discharged to institutional care¹⁷¹ or were living in a nursing home at a follow-up.¹⁷³ **Level 2++**

In four studies, multivariate analysis reported that dysphagia or swallowing impairment at baseline was an independent predictor of outcome, namely mortality,^{172,170,171} disability,¹⁷⁰ chest infection.¹⁶² **Level 2++**

10.1.5 From evidence to recommendations

Swallow screening is useful in determining early management of feeding after stroke, however, it is not very accurate in isolation. The sensitivity and specificity of screening is such that some patients will be judged unsafe to swallow when there is no evidence on instrumental assessment that they are aspirating, and a smaller number will be assessed as safe to swallow when in fact they are not. The GUSS bedside screen appears to be a better predictor than other clinical assessments of aspiration as detected by FEES, but the numbers in this study are small.

There is good evidence for a link between dysphagia and poor clinical outcome (chest infection, death, disability, discharge destination, length of stay) reinforcing the need for early detection and management.

Although aspiration is clearly associated with worse outcome, there is no evidence that the withdrawal or modification of oral intake prevents chest infection or other adverse outcomes. Research evidence is lacking and would be difficult to obtain, as it would be unethical to give oral food or most fluids to patients who are aspirating although a trial of water in this situation might be possible.

No evidence that directly compared FEES vs VF was reviewed. Each instrumental assessment has its advantages and disadvantages. VF is most widely available but is limited by practical considerations (the need to sit up and to be able to follow instructions) as well as radiation dosage. FEES is more appropriate for patients who are immobile and for whom VF might be impractical. One limitation of FEES is that the moment of swallowing is not visualised, and therefore provides less neurophysiological information than VF. Both techniques may be difficult to interpret especially by inexperienced practitioners and specialist training is necessary. All assessments only reveal the swallow at one moment in time so all patients need careful monitoring and observation and reassessment when necessary. The group were concerned that patients with persistent dysphagia were at risk of malnutrition and that those patients who remained dysphagic after 3 days should have access to detailed instrumental examination.

The patient representatives on the GDG felt that the assessment used should be that which provides the most accurate diagnosis. They also felt that it is important to distinguish whether or not tube feeding is required, and that if tube feeding is required then it is commenced as soon as possible. There was concern from the group that the recommendation was based on relatively little evidence.

10.1.6 RECOMMENDATIONS

- R43 On admission, people with acute stroke should have their swallowing screened by an appropriately trained healthcare professional before being given any oral food, fluid or medication.
- R44 If the admission screen indicates problems with swallowing, the person should have a specialist assessment of swallowing, preferably within 24 hours of admission and not more than 72 hours afterwards.
- R45 People with suspected aspiration on specialist assessment or who require tube feeding or dietary modification for 3 days should be:
 - reassessed and be considered for instrumental examination
 - referred for dietary advice.

10.2 Timing of enteral feeding

10.2.1 Clinical introduction

Many patients cannot swallow safely after an acute stroke, either because their conscious level is too low to swallow safely or because they have a specific oropharyngeal swallowing deficit. These patients normally have initial intravenous fluids to maintain hydration. Non-oral feeding with either NG, percutaneous endoscopic gastrostomy/jejunostomy (PEG/PEJ) or radiologically inserted gastrostomy (RIG) tubes may be subsequently instituted but there is little evidence to guide when tube feeding should start. Feeding tubes are not without hazard. NG tubes are normally inserted on the ward by nursing staff. They may rarely be mis-inserted in the trachea, or not inserted far enough into the oesophagus with the risk in both cases that feed may be introduced into the trachea. Some patients find it difficult to tolerate an NG tube at all and it may be uncomfortable if left in for a long period of time. PEG/PEJ requires an endoscopy, which carries a small risk especially in patients with chest problems. There are rare risks of perforation particularly in patients who have difficulty cooperating with the procedure. RIG requires a radiologist but may have some advantages over PEG/PEJ for elderly patients or those with chest problems. These risks are in general outweighed by the benefit of adequate feeding but there is little evidence to suggest the optimum time for tube insertion. Occasionally, perhaps in a severely ill patient with a poor prognosis, a decision will be made to withdraw active treatment and insertion of a feeding tube may not be appropriate. Non-commencement or withdrawal of feeding is a difficult decision which should be made in full consultation with the patient (where possible) and family, as well as the multidisciplinary team, taking into account the patient's best interest, any advance directives and the Mental Capacity Act 2005.

The clinical question to be addressed is when is the most appropriate time to initiate tube feeding in patients with acute stroke who cannot swallow safely.

10.2.2 Clinical methodological introduction

▷ Early versus late initiation of tube feeding

For this question, only one RCT (N=859) addressed the question of whether early versus late tube feeding (NG or PEG) reduced mortality and morbidity. The study compared early with delayed feeding, but that in reality people could be randomised up to 3 days post event and then took 1–2 days to start feeding, so this may lead to underestimation of the possible benefit/harm of very early feeding. The follow-up period was a median 6.5 months for the avoid tube feeding and 6.8 months in the early tube feeding.¹⁷⁵ **Level 1++**

No evidence was identified on nasal bridles or RIG tubes.

▷ Nasogastric (NG) vs percutaneous endoscopically-guided gastrostomy (PEG)

Two studies were identified which addressed the question of whether NG compared with PEG is associated with reduced mortality and morbidity.^{175,176} One of these was excluded due to methodological limitations.¹⁷⁶ **Level 1++**

The included study was an open label RCT (N=321) on patients admitted to hospital with a first or recurrent within 7 days of stroke onset. The RCT compared feeding by NG with PEG. Patients could be randomised up to 30 days of hospital admission. Patients were followed up at 6 months by a person blinded to the intervention they had received.¹⁷⁵ **Level 1++**

10.2.3 Health economic methodological introduction

No papers were identified.

10.2.4 Clinical evidence statements

Early versus late initiation of tube feeding

▷ Mortality and disability

There were no significant differences between the two groups in terms of mortality or death or poor outcome combined (mRS 3 to 5) (NS).¹⁷⁵ There was no statistical difference between the two groups on the Kaplan-Meier survival curves (NS).¹⁷⁵ **Level 1++**

▷ In-hospital complications

There was a statistically higher proportion of gastrointestinal haemorrhages in the early tube group compared with the avoid tube group.¹⁷⁵ **Level 1++**

▷ Discharge destinations

There was no statistical difference between the groups on discharge destinations (NS) or residence at final follow-up (NS).¹⁷⁵ **Level 1++**

▷ Quality of life (EuroQol)

There was no statistical difference between the two groups on a measure of quality of life (NS).¹⁷⁵ **Level 1++**

▷ Adverse events

There were no apparent differences in the number of recorded adverse events between the two groups, but statistical analyses were not performed.¹⁷⁵ **Level 1++**

Nasogastric (NG) vs percutaneous endoscopically-guided gastrostomy (PEG)

▷ Mortality and disability

There was no statistical difference between groups with respect to the absolute risk of death (NS). There was no statistical difference between the Kaplan-Meier survival curves for each group (NS). There was a statistical increase in the absolute risk of death or poor outcome combined in the PEG group compared with the NG group.¹⁷⁵ **Level 1++**

▷ In-hospital complications

There was a significantly higher incidence in the number of gastrointestinal haemorrhages in the NG group compared with the PEG group.¹⁷⁵ **Level 1++**

▷ Discharge destinations

There was no statistical difference between the groups on discharge destinations (NS) or residence at final follow-up (NS).¹⁷⁵ **Level 1++**

▷ Quality of life

There was no statistical difference between the two groups on a measure of quality of life (NS).¹⁷⁵ **Level 1++**

▷ Adverse events

There were no apparent differences between the two groups in terms of the number of adverse events reported, but no statistical analyses were performed.¹⁷⁵ **Level 1++**

10.2.5 From evidence to recommendations

The Feed or Ordinary Diet (FOOD) trial showed no statistically significant difference between early versus late tube feeding with respect to mortality, morbidity, adverse events, disability, quality of life or discharge destination.

Although the confidence intervals for the effect of early feeding are wide, meaning that the data are consistent with significant benefit or harm, it was felt by the group to be more biologically plausible to have a small benefit from early tube feeding rather than a negative effect.

Better functional outcomes were associated with feeding via NG tube than PEG tube. The increase in GI haemorrhages in the NG group were not reflected in increases in mortality or outcome. The group agreed that NG tube feeding should be the intervention of choice for acute stroke (excluding those receiving palliative care) if it is practical to do so and that nasal bridle tubes or gastrostomy should be the intervention of choice if it is impractical to use a NG tube.

10.2.6 RECOMMENDATION

R46 People with acute stroke who are unable to take adequate nutrition and fluids orally should:

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

10.3 Oral nutritional supplementation

10.3.1 Clinical introduction

Adequate hydration and nutrition is a major concern after stroke, where swallowing difficulty, reduced awareness, motor and sensory or visual deficit, loss of appetite, depression or cognitive impairment may make it difficult for a patient to maintain normal nutrition and hydration. Poor nutritional status is linked to poorer outcome after stroke.¹⁷⁷ The FOOD study included a trial of oral supplementation vs no supplements in a group of patients with normal swallow after stroke who were felt to be adequately nourished. No improvement in outcome was observed.

The clinical question to be addressed is whether patients who are not identified as being malnourished should receive nutritional supplementation after stroke.

10.3.2 Clinical methodological introduction

Two studies were identified that reported on whether, for those patients who can take adequate oral fluids, routine oral nutritional supplementation increases the proportion of patients with stroke surviving without disability. One study was an open label RCT (N=4,023) on patients with first or recurrent stroke, and who were admitted to hospital within 7 days of stroke onset. All patients were adequately nourished on admission. Patients were randomised to receive either a normal hospital diet (NHD) or a NHD and nutritional supplementation consisting of three 120-ml doses (1.5 kcal/ml) (equivalent to 20g of protein). The majority of patients had relatively minor strokes due to the exclusion criteria of not having a swallowing impairment. The mean age was 71 years. The majority of patients (77%) were considered to be of normal weight. The mean duration of stay from enrolment was 34 days. The follow-up period was 6 months.¹⁷⁵ **Level 1++**

An additional single blind RCT (N=42) was excluded from the evidence review due to methodological limitations.¹⁷⁸ **Level 1+**

No studies were identified on fluids.

10.3.3 Health economic methodological introduction

No papers were identified.

10.3.4 Clinical evidence statements

▷ Mortality and disability

There were no statistical differences in the mortality rate as measured by Kaplan-Meier survival curves or disability on the mRS between the patients who received a NHD plus supplementation compared with those on a NHD (NS).¹⁷⁵ **Level 1++**

▷ In-hospital complications

There were no hospital complications thought to be related to intervention.¹⁷⁵ **Level 1++**

▷ Discharge destination and length of hospital stay

There were no reported significant differences in the discharge destination (NS) or the length of hospital stay.¹⁷⁵ **Level 1+**

10.3.5 From evidence to recommendations

In the FOOD trial only adequately nourished patients were included in the trial. Although routine nutritional supplementation is not associated with improved outcomes there is no evidence in the trial to support withholding of focused supplementation from those who are assessed as malnourished. There is evidence from systematic review¹⁷⁹ of benefits of nutritional supplementation in malnourished elderly people. A significant proportion of patients with stroke are malnourished on admission and the GDG consensus is that all patients should be weighed and have their nutritional state assessed and treated where appropriate. For those at risk of malnutrition, nutrition support should be initiated, which may include oral nutritional supplements, referral for dietary advice and/or tube feeding.

10.3.6 RECOMMENDATIONS

- R47 All hospital inpatients on admission should be screened for malnutrition and the risk of malnutrition. Screening should be repeated weekly for inpatients (wording extracted from the NICE Nutrition Support recommendation).¹⁸⁰
- R48 Screening should assess body mass index (BMI) and percentage unintentional weight loss and should also consider the time over which nutrient intake has been unintentionally reduced and/or the likelihood of future impaired nutrient intake. The Malnutrition Universal Screening Tool (MUST), for example, may be used to do this. (NICE Nutrition Support recommendation).¹⁸⁰
- R49 When screening for malnutrition and the risk of malnutrition, healthcare professionals should be aware that dysphagia, poor oral health and reduced ability to self-feed will affect nutrition in people with stroke.
- R50 Screening for malnutrition and the risk of malnutrition should be carried out by healthcare professionals with appropriate skills and training. (NICE Nutrition Support recommendation).¹⁸⁰
- R51 Routine nutritional supplementation is not recommended for people with acute stroke who are adequately nourished on admission.
- R52 Nutrition support should be initiated for people with stroke who are at risk of malnutrition. This may include oral nutritional supplements, specialist dietary advice and/or tube feeding.
- R53 All people with acute stroke should have their hydration assessed on admission, reviewed regularly and managed so that normal hydration is maintained.

11 Early mobilisation and optimum positioning of people with acute stroke

11.1.1 Clinical introduction

Mobilisation of patients is a cornerstone of modern acute stroke care. Although most therapy interventions have not been subjected to randomised controlled trial, they have been derived from extensive experience. Therapists and nurses use mobilisation programmes that aim to reduce secondary complications of immobility such as infection, venous thromboembolism, orthostatic hypotension and infection. In addition, therapy interventions are used to position patients in order to reduce the likelihood of contractures and shoulder subluxation, and to avoid hypoxia. There are potential adverse effects of early mobilisation, for example blood pressure changes and falls. There is indirect evidence that reduction of complications through early mobilisation contributes to the reduction of deaths and better outcomes in stroke unit care compared to general ward care,¹⁸¹ but evidence is lacking. There is, however, evidence to show that patients on stroke units currently spend a small proportion of their time (13% of the working day) engaged in activities with the potential to reduce the complications of immobility.¹⁸² The details of the interventions most likely to improve outcome are not known, and the time at which early mobilisation should start is unclear.

The clinical questions to be addressed are whether patients with acute stroke should be mobilised early and whether there is any benefit in placing them in specific positions.

11.1.2 Clinical methodological introduction

▷ Early mobilisation

Two single-blind RCTs were identified that looked at the association between early mobilisation and morbidity or mortality.^{183,184}

No studies were identified on very early mobilisation (within 48 hours).

One study (N=156) from China evaluated physiotherapy initiated within 1 week of stroke onset. The intervention consisted of one 45-minute session a day, 5 days a week for a total of 4 weeks. This was compared with patients who received no professional or regular physiotherapy for the entire time they were admitted in hospital. The use of a non-active treatment comparison represents a considerable methodological limitation of this study. In addition, 28/78 (35.9%) of patients were lost to follow-up in the physiotherapy arm.¹⁸³ Level 1+

▷ Positioning patients

Two studies were identified that looked at the association between positioning and mortality and morbidity in patients with stroke.^{185,186} Of these, one was a systematic review (four studies)¹⁸⁵ and one a cross-sectional study.¹⁸⁶ The systematic review looked at the effect of body positioning on oxygen saturation¹⁸⁵ and the cross-sectional study on body positioning and upper airway construction.¹⁸⁶ The systematic review was unable to pool the data due to a high degree of heterogeneity.¹⁸⁵ Level 3

One study (N=27) focused on gait relearning through locomotor activities and included the use of a tilt table, a limb-load monitor, rested exercises with a Kinetron isokinetic device and a treadmill. This intervention was started 'early' (mean 8.3 days after stroke) and compared with early (mean 8.8 after stroke) and intense 'traditional' therapy and 'later' (mean 13 days after stroke) and less intensive traditional therapy. For the experimental group therapy was given for mean 1.74 hr/day in two sessions compared with 1.79 hr/day in two sessions and 0.72 hr/day in the early intense and later less-intensive traditional therapy respectively.¹⁸⁴ **Level 3**

It should be noted that these studies have limited applicability with respect to the interventions used i.e. a control arm of no regular physiotherapy and gait training. Furthermore, the studies were highly variable with respect to design, interventions and outcomes.

11.1.3 Health economic methodological introduction

No papers were identified.

11.1.4 Clinical evidence statements

Early mobilisation

▷ Activities of daily living

At 30-day follow-up, the study comparing early physiotherapy with no routine therapy reported a statistical difference on the modified Barthel Index in favour of early therapy. At 6 months, this difference was no longer significant (NS). This may be due to the number of drop-outs and low statistical power.¹⁸³ **Level 1+**

▷ Gait velocity

The study on gait training reported at 6 weeks, total time dedicated to gait training was correlated with gait velocity but total therapy time was not correlated with gait velocity (NS). This effect disappeared at 3 and 6 months post stroke.¹⁸⁴ **Level 1+**

▷ Functional scores

Both studies reported no statistical differences between the interventions on 'functional' outcomes e.g. the Fugl-Meyer Score (NS).^{183,184} **Level 1+**

Positioning patients

▷ Oxygen desaturation

Only one RCT out of the four studies included in the systematic review reported a statistical effect of an intervention compared with control. The study reported a significant association between higher oxygen saturation when sitting in a chair than any other position for those that could sit out. Lying on the left side was significantly associated with decreased oxygen saturation.¹⁸⁵ **Level 3**

▷ Upper airway obstruction

In a study on prevalence of upper airway obstruction in the first 24 hours of stroke, one of the potential associated risk factors recorded was the position in which the person was nursed.

Patients had a significantly higher respiratory disturbance index (RDI) when nursed in a supine, supine left or supine right position than in any other position (prone, prone left and prone right).¹⁸⁶ Level 3

11.1.5 From evidence to recommendations

There are insufficient data to comment on the safety of very early mobilisation in patients with acute stroke, but there is no evidence that it is harmful. In one study in which no physiotherapy was compared with early mobilisation, patients who received no physiotherapy had worse outcomes but this gives no data on what form of early mobilisation is most effective. Early mobilisation has many potential advantages including reducing the risk of chest infection, preventing DVTs, early access to water and fluids (thus improving hydration) and access to nutrition. The consensus was that these potential advantages outweighed any disadvantages. This was also supported by the patient representatives who felt that early mobilisation was more likely to have a positive psychological effect on the patient and prolonged bed rest was likely to be detrimental to patients with acute stroke.

One study examined the effect of nursing patients in specific positions on oxygen saturation. Sitting up resulted in improved oxygen saturations, again supporting the group consensus that early positioning including sitting is of benefit, helping to maintain oxygen saturation above 95% (see section 9.1) and reducing the likelihood of hypostatic pneumonia.

11.1.6 RECOMMENDATIONS

- R54 People with acute stroke should be mobilised as soon as possible (when their clinical condition permits) as part of an active management programme on a specialist stroke unit.
- R55 People with acute stroke should be helped to sit up as soon as possible (when their clinical condition permits).

12 Avoidance of aspiration pneumonia

12.1.1 Clinical introduction

Aspiration pneumonia may be a devastating complication of stroke and is associated with increased mortality and poor outcomes. 40% of patients with stroke acutely have swallowing difficulties, some of which may not be detectable clinically. Those assessed as having dysphagia are recommended a variety of options for oral intake, from no oral intake, through modification of fluid (small volumes, thickened fluids) and food (puree or soft consistency) to normal intake. It is common sense that patients who aspirate oral contents should not be fed orally, but little is known about the safety of water by mouth. Normal saliva production is 1–2 litres per day, so even patients denied access to oral fluids are aspirating large fluid volumes. Patients are often much more distressed by withdrawal of fluids than of food, and despite adequate fluid replacement by other means (intravenous or subcutaneous infusions or tube feeding) feel thirsty and have a dry mouth. Oral hygiene is very much more difficult to maintain in patients denied oral fluids, and aspiration of infected saliva may contribute to the development of pneumonia.

The clinical question to be addressed is how best to reduce the likelihood of patients with acute stroke developing aspiration pneumonia.

12.1.2 Clinical methodological introduction

One RCT was identified that compared acute stroke patients within 3 weeks of stroke onset with previously identified thin liquid aspiration (verified by videofluoroscopy) (N=20). Groups were randomised between those who were given thickened liquids plus additional water compared with those given thickened liquids only.¹⁸⁷ Level 1+

The patient population had a mean age of 77 years. In the group given thickened liquids with additional water, five of the patients had consistent aspiration of thin liquids (>50% of swallows), four had inconsistent aspiration of thin liquids (10 to 15% of swallows) and one had infrequent aspiration of thin liquids (<10% of swallows). Seven of the patients had an absent protective cough reflex at the level of the vocal folds. Level 1+

In the control group (thickened liquids only), two patients had inconsistent aspiration and six infrequent aspiration. Five of the patients did not have a protective cough reflex at the level of the vocal folds. Level 1+

12.1.3 Health economic methodological introduction

No papers were identified.

12.1.4 Clinical evidence statements

- ▷ End point of no thin aspiration

There was no statistical difference between patients given thickened liquids and access to water compared with those on thickened liquids only with respect to the time taken to reach the end point of no thin liquid aspiration (NS).¹⁸⁷ Level 1+

▷ Daily intake of liquids

Patients on thickened liquids only had a statistical higher intake of thickened liquids compared to those on thickened liquids with additional water.¹⁸⁷ **Level 1+**

▷ Follow-up videofluoroscopic evaluations

There was no statistical difference between patients with thickened liquids and access to water compared with those on thickened liquids only (NS) with respect to the number of follow-up videofluoroscopic evaluations (NS).¹⁸⁷ **Level 1+**

▷ Complications

No patients developed pneumonia, dehydration, or complications during the course of the study or at 30-day follow-up.¹⁸⁷ **Level 1+**

12.1.5 From evidence to recommendations

There is insufficient evidence addressing the withdrawal or modification of oral intake in the prevention of aspiration pneumonia after stroke. One study showed that the modification of oral intake through thickened fluids was not as unsafe as the group had expected. No studies were identified which addressed the issue of giving water to patients who are assessed as having dysphagia for fluids. The withdrawal or modification of oral intake when trying to prevent aspiration pneumonia is a contentious issue amongst healthcare professionals and the insufficient evidence highlights the need by the group for a research recommendation in these areas. There was a consensus that an important reason for giving patients water would be to enable them to maintain adequate oral hygiene and to reduce patient distress. The consensus of the group was that there was insufficient evidence on which a recommendation could be made.

12.1.6 RECOMMENDATION

- R56 In people with dysphagia, food and fluids should be given in a form that can be swallowed without aspiration following specialist assessment of swallowing.

13 Surgery for people with acute stroke

13.1 Surgical referral for acute intracerebral haemorrhage

13.1.1 Clinical introduction

Primary intracerebral haemorrhage occurs in about 10% of strokes. It is severely disabling and associated with high mortality. Although the incidence of intracerebral haemorrhage has fallen overall in the last 20 years, largely due to improved identification and treatment of hypertension, there has not been an equivalent fall in incidence in elderly patients.¹⁸⁸ This is likely to be due to anticoagulant associated haemorrhage and amyloid angiopathy in the elderly. As the population ages, the absolute number of haemorrhages in the elderly might increase in future. The commonest cause of intracerebral haemorrhage is hypertension, but other causes should be considered including underlying structural abnormalities (e.g. tumour, arterio-venous malformation) and recreational drug use. The 30-day mortality is higher in deep haemorrhages than lobar, and increases with increasing volume of bleed.¹⁸⁹ Complications of intracerebral haemorrhage include expansion of haematoma, hydrocephalus, intraventricular haemorrhage and oedema. Patients with cerebellar haematoma are at particular risk of deterioration, specifically direct compression of the brain stem and cerebellum, and hydrocephalus. Apart from reversal of anticoagulation medical treatment remains supportive; although Factor VIIa showed promise with a reduction in the volume of haematoma expansion, a recent RCT showed no evidence of significant patient benefit. The risk of haematoma expansion, coning and hydrocephalus underlies the importance of careful neurological monitoring in specialist units, and 24-hour access to CT scanning in cases of deterioration. The surgical evacuation of haematoma has been used in selected patients and recently subjected to randomised controlled trial.

The clinical question is which patients with primary intracerebral haemorrhage should be referred for surgical evacuation.

13.1.2 Clinical methodological introduction

This question addresses the issue of whether there are any clinical or demographic factors on presentation that can be used to identify which patients should be referred urgently to surgery for primary intracerebral haemorrhage (PICH). As the question does not address the safety or efficacy of surgery, only RCTs which included statistical analysis of clinical or demographic factors associated with or predictors of, outcome are reported.*

Two RCTs were identified that compared surgery with medical treatment for PICH.^{190,191} One multicentre RCT, the International Surgical Trial in Intracerebral Haemorrhage (STICH) (N=1,033), compared early surgery (N=503) (within 24 hours of randomisation) plus medical treatment with initial conservative therapy (N=530) (medical treatment) although some patients went on to surgery later.¹⁹⁰ Eligibility criteria included CT evidence of a spontaneous PICH that had arisen in the past 72 hours. Patients were admitted to the trial if the neurosurgeon felt there was equipoise regarding the benefits of either treatment. **Level 1++**

* Outcomes associated with surgery are reported for completeness.

One RCT (N=100) compared surgery using endoscopy (N=50) with medical treatment (N=50) for spontaneous PICH. Patients were eligible if the haematoma was greater than 10 cu cm and the interval between stroke and start of treatment was less than 48 hours. Only univariate analyses were reported and this combined with the small sample size limits the generalisability of these results.¹⁹¹ **Level 1+**

13.1.3 Health economic methodological introduction

No papers were identified.

13.1.4 Clinical evidence statements

▷ Mortality and function outcome

The STICH showed that the mortality rate at 6 months was not statistically different for the early surgery and conservative treatment (NS). On prognosis-based indices of the extended Glasgow Coma Scale, there was no statistical difference between the early surgery and conservative treatment group (NS). With the prognosis-based mRS, there was no statistical difference at 6 months when comparing the early surgery group with conservative treatment (NS).¹⁹⁰ **Level 1++**

In the trial comparing endoscopic intervention with medical treatment, during the first week significantly fewer patients treated surgically died compared with those treated medically (14 vs 28%; $p < 0.01$). None of the endoscopically treated patients were reported to have died from a surgically related complication. 2/50 (4%) surgical patients suffered a rebleed in the early postoperative phase and deteriorated clinically. 15/50 (30%) medically treated patients experienced an early rebleed. At 6 months, the mortality rate was significantly lower in the surgically treated patients compared with those treated medically (42 vs 70%; $p < 0.01$).¹⁹¹ **Level 1++**

▷ Clinical and demographic factors

The STICH showed that if the haematoma was 1 cm or less from cortical surface, a significantly less favourable outcome was associated with early surgery compared with conservative management (66 vs 74%; 95%CI 0.47 to 1.01; $p = 0.02$). There were no statistical associations between a favourable outcome for early surgery compared with conservative management for the prognostic variables of age, GCS, side of haematoma, site of haematoma, haematoma volume, intended method of evacuation, deficit of affected arm/leg, deficit of speech, any thrombolytic or anticoagulant treatment (NS).¹⁹⁰ **Level 1++**

For the study on endoscopic intervention, surgery was associated with significantly lower mortality rate and significantly higher incidence of good outcome with no or minimal deficit compared with medical treatment for the following factors: age <60 years, haematoma >50 cu cm; preoperative status of somnolent or alert and a subcortical haematoma.¹⁹¹ **Level 1+**

13.1.5 From evidence to recommendations

There is little consensus between the published studies as to which patients should or should not be considered for surgical intervention. The largest published RCT, the STICH study, relied on the clinical uncertainty of the treating neurosurgeon as to whether an individual patient would benefit from surgical intervention in its inclusion criteria. In this study, 25% of the patients who were randomised for conservative therapy later went on to have surgery. This may be as a result of deterioration. There were no papers identified in the evidence review which specifically addressed hydrocephalus in association with intracerebral haemorrhage. There was no strong evidence on which to set an age threshold above which surgery should not be considered. The consensus of the group was that previously fit patients with a lobar haemorrhage with hydrocephalus, or those who are deteriorating neurologically where draining of the haematoma might improve outcome should be referred for surgery. In addition, patients with small deep haemorrhages, straightforward lobar haemorrhages, large haemorrhages and significant prior comorbidities, and patients with a GCS score of lower than 8 were unlikely to benefit from surgery. There were no RCTs identified that specifically addressed cerebellar haemorrhages. However, the consensus was that patients with cerebellar haematoma should be carefully and regularly monitored for changes in neurological status that might indicate the development of coning or hydrocephalus by specialists in neurosurgical or stroke care.

The group were aware of the ongoing STICH II trial which is addressing the issue of the surgical management of lobar haemorrhages.

Please refer to chapter 8, section 8.7 for recommendations on the reversal of anticoagulation in patients with haemorrhagic stroke.

13.1.6 RECOMMENDATIONS

- R57 Stroke services should agree protocols for the monitoring, referral and transfer of people to regional neurosurgical centres for the management of symptomatic hydrocephalus.
- R58 People with intracranial haemorrhage should be monitored by specialists in neurosurgical or stroke care for deterioration in function and referred immediately for brain imaging when necessary.
- R59 Previously fit people should be considered for surgical intervention following primary intracranial haemorrhage if they have hydrocephalus.
- R60 People with any of the following rarely require surgical intervention and should receive medical treatment initially:
 - small deep haemorrhages
 - lobar haemorrhage without either hydrocephalus or rapid neurological deterioration
 - a large haemorrhage and significant prior comorbidities before the stroke
 - a score on the Glasgow Coma Scale (GCS) of below 8 unless this is because of hydrocephalus
 - posterior fossa haemorrhage.

13.2 Surgical referral for decompressive hemicraniectomy

13.2.1 Clinical introduction

A rare complication of large middle cerebral artery infarction is life threatening, space occupying brain oedema termed malignant middle cerebral artery infarction. It has a mortality rate of 80%¹⁹² and usually presents within 2–5 days of stroke onset. It occurs in younger patients without brain atrophy. There have been a number of reports of benefit from decompressive hemicraniectomy, but concerns remain as to the benefits in terms of both survival and good clinical outcome. Neurosurgeons in many centres have been reluctant to operate partly because of their experiences of hemicraniectomy in other conditions. However, ongoing trials such as Rescue-ICP for brain injury are beginning to change practice. Poor outcomes may be related to late referral of patients when surgery is performed after brain damage has become irreversible. Timely referral is vital to ensure that intervention takes place before damage is irreversible.

The clinical question is which patients with malignant middle cerebral artery infarction should be referred for surgery.

13.2.2 Clinical methodological introduction

Two studies were identified that addressed the question of which patients should be referred urgently for decompressive surgery.^{193,194}

One study (N=93), pooled individual patient data from three RCTs, namely DECIMAL, DESTINY and HAMLET*, in order to estimate the effects of decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (MCA).¹⁹⁴ All of the RCTs randomised patients to either surgery (N=51) or conservative management (N=42). Data were included only for patients aged 18 to 60 years treated within 48 hours of randomisation. In addition, on CT the infarct had to be 50% of the MCA territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume >145 cm² on MRI. Exclusion criteria for the pooled analysis included a prestroke score on the mRS of ≤ 2 and a life expectancy of less than 3 years. Level 1++

One systematic review (12 retrospective and prospective case series) (N=138 (129 plus nine patients added from the authors' own institution) reported a pooled analysis of the outcomes associated with decompressive surgery.¹⁹³ Patients were included if the infarct involved the MCA plus another vascular territory. A dichotomised outcome score was used with a good outcome defined as functional independence or mild to moderate disability and a poor outcome as severe disability or death. Level 3

13.2.3 Health economic methodological introduction

No papers were identified.

* DECIMAL, decompressive craniectomy in malignant middle cerebral artery infarcts; DESTINY, decompressive surgery for treatment of malignant infarction of the middle cerebral artery trial; HAMLET, hemicraniectomy after MCA infarction with life-threatening edema trial.

13.2.4 Clinical evidence statements

▷ Mortality and functional outcome

In the pooled analysis, at 12 months, surgery compared with conservative management was associated with a lower mortality rate. See table 13.1 below.¹⁹⁴ **Level 1++**

Table 13.1 The results of surgery compared to conservative management (taken from the pooled analysis)

Outcome	Outcome/patients		
	Conservative %	Surgery %	OR (95%CI)
Mortality	71	22	0.10 (0.04 to 0.27)
mRS >4	76	26	0.10 (0.04 to 0.27)
Age <50 yrs	71	23	0.10 (0.03 to 0.35)
Age ≥50 yrs	91	31	0.13 (0.02 to 0.76)
Time to randomisation <24 hrs	81	31	0.12 (0.04 to 0.43)
Time to randomisation ≥24 hrs	69	18	0.13 (0.03 to 0.54)
No aphasia	82	22	0.06 (0.01 to 0.31)
Aphasia	74	29	0.14 (0.04 to 0.50)

The systematic review reported that 42% of patients had a good outcome (functionally independent or mild to moderate disability), 80 (58%) poor outcomes (severe disability or death) and the mortality rate was 24%.¹⁹³ **Level 3**

▷ Prognostic indicators

For the pooled analysis of the RCT data, surgery was beneficial (mRS score of 4 or less) for the predefined subgroups of age (above or below 50 years), aphasia (duration above or below 24 hours) and time to randomisation (above and below 24 hours). See table above.¹⁹⁴ **Level 1++**

For the pooled analysis of the case-series data, a significantly higher proportion of patients older than 50 years compared with those 50 years or less were severely disabled or dead after surgery. The mortality rate was also significantly higher after surgery in patients older than 50 years compared with those 50 years or less.¹⁹³ There was no statistical difference in the proportion of patients severely disabled or dead or those with a poor outcome between those patients who underwent surgery within 24 hours compared with those who underwent surgery after 24 hours (NS). There was no statistical difference on the outcome of disability when patients with herniation prior to surgery were compared with those without signs of herniation (NS). This may be due to low statistical power.¹⁹³ **Level 3**

13.2.5 From evidence to recommendations

The need for early intervention in malignant middle cerebral artery infarction is increasingly recognised. The consensus of the group was that those patients identified in the pooled analysis

study¹⁹⁴ should be referred for decompressive hemicraniectomy. The evidence base supports the use of decompressive hemicraniectomy up to the age of 60. The meta-analysis showed that there is a significant increase in morbidity in patients over 50 years old, which suggests added caution is needed in selecting patients over 50 years for hemicraniectomy. It should be noted that the evidence relates only to patients under the age of 60 years; this condition is not seen in older people probably because with the inevitable loss of brain volume with age, there is additional intracranial space to accommodate oedema with cerebral infarction. This accounts for the age limits stated in this guideline.

The data from a large non-randomised series suggested that outcome is substantially improved if treatment is initiated within 24 hours of stroke onset as compared to longer time windows for treatment. The pooled analysis took into account patients referred up to 45 hours, but the consensus of the group was that the prospective studies suggest that earlier referral is associated with better outcome. It is vital that patients at risk of malignant middle cerebral artery infarction are identified early, undergo careful, regular neurological monitoring by specialists in stroke or neurosurgical care, and deteriorating patients are referred immediately to a neurosurgical centre.

13.2.6 RECOMMENDATIONS

- R61** People with middle cerebral artery (MCA) infarction who meet all of the criteria below should be considered for decompressive hemicraniectomy. They should be referred within 24 hours of onset of symptoms and treated within a maximum of 48 hours:
- aged 60 years or under
 - clinical deficits suggestive of infarction in the territory of the MCA with a score on the National Institute of Health Stroke Scale (NIHSS) of above 15
 - decrease in the level of consciousness to give a score of 1 or more on item 1a of the NIHSS
 - signs on CT of an infarct of at least 50% of the MCA territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume greater than 145 cm³ as shown on diffusion-weighted MRI.
- R62** People who are referred for decompressive hemicraniectomy should be monitored by appropriately trained professionals, skilled in neurological assessment.

14 Research recommendations

The following questions were prioritised as key research recommendations by the GDG:

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

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

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

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

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

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

▷ Additional research recommendations identified by the group:

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

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