STROKE: DIAGNOSIS AND INITIAL MANAGEMENT OF ACUTE STROKE AND TRANSIENT ISCHAEMIC ATTACK (TIA)

National clinical guideline for chronic conditions

Published by the Royal College of Physicians
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# Guideline Development Group members

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<th>Name</th>
<th>Job Title</th>
<th>Employing organisation</th>
<th>Representing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pippa Tyrrell</td>
<td>Clinical Advisor</td>
<td>Salford Royal NHS Foundation Trust/University of Manchester</td>
<td>NCC-CC</td>
</tr>
<tr>
<td>Anthony Rudd</td>
<td>GDG Chair</td>
<td>Guy’s and St Thomas’ NHS Foundation Trust</td>
<td>NCC-CC</td>
</tr>
<tr>
<td>Katherine Cullen</td>
<td>Health Economist</td>
<td>NCC-CC</td>
<td>NCC-CC</td>
</tr>
<tr>
<td>Alison Richards</td>
<td>Information Scientist</td>
<td>NCC-CC</td>
<td>NCC-CC</td>
</tr>
<tr>
<td>Sharon Swain</td>
<td>Research Fellow</td>
<td>NCC-CC</td>
<td>NCC-CC</td>
</tr>
<tr>
<td>Claire Turner</td>
<td>Senior Project Manager</td>
<td>NCC-CC</td>
<td>NCC-CC</td>
</tr>
<tr>
<td>David Wonderling</td>
<td>Senior Health Economist</td>
<td>NCC-CC</td>
<td>NCC-CC</td>
</tr>
<tr>
<td>Alan Bowmaster</td>
<td>Patient/Carer representative</td>
<td></td>
<td>Patient/Carer representative</td>
</tr>
<tr>
<td>Diana Day</td>
<td>Stroke Specialist Research Nurse,</td>
<td>Addenbrookes Hospital NHS Trust</td>
<td>Stroke Nurses Forum</td>
</tr>
<tr>
<td>Gary Ford</td>
<td>Professor of Pharmacology of Old Age</td>
<td>The Newcastle Upon Tyne Hospitals NHS Foundation Trust</td>
<td>British Association of Stroke Physicians/Royal College of Physicians</td>
</tr>
<tr>
<td>Steve Hatton</td>
<td>Paramedic/Emergency Care Practitioner</td>
<td>Yorkshire Ambulance Service NHS Trust</td>
<td>British Paramedic Association</td>
</tr>
<tr>
<td>Joe Korner</td>
<td>Patient/Carer representative</td>
<td>The Stroke Association</td>
<td>Patient/Carer representative</td>
</tr>
<tr>
<td>Richard McManus</td>
<td>Clinical Senior Lecturer in Primary Care and General Practitioner</td>
<td>University of Birmingham</td>
<td>Royal College of General Practitioners</td>
</tr>
<tr>
<td>Andy Molyneux</td>
<td>Consultant Neuroradiologist</td>
<td>Oxford Radcliffe Hospitals NHS Trust</td>
<td>Royal College of Radiologists</td>
</tr>
<tr>
<td>John Potter</td>
<td>Professor in Geriatrics and Stroke medicine</td>
<td>University of East Anglia</td>
<td>British Geriatrics Society</td>
</tr>
<tr>
<td>Rhoda Allison (invited expert)</td>
<td>Consultant Therapist in Stroke</td>
<td>Teignbridge PCT</td>
<td>Chartered Society of Physiotherapists (GDG1, 2 and 9)</td>
</tr>
<tr>
<td>Name</td>
<td>Position</td>
<td>Organization</td>
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</tr>
<tr>
<td><strong>Julie Barker</strong></td>
<td>Senior Dietitian</td>
<td>United Bristol Healthcare Trust</td>
<td>British Association Dietetics (GDG1, 7 and 9)</td>
</tr>
<tr>
<td><strong>Peter Kirkpatrick</strong></td>
<td>Consultant Neurosurgeon</td>
<td>Addenbrookes NHS Trust</td>
<td>Society of British Neurological Surgeons (GDG10)</td>
</tr>
<tr>
<td><strong>Peter Lamont</strong></td>
<td>Consultant Vascular Surgeon</td>
<td>United Bristol Healthcare Trust</td>
<td>Vascular Society (GDG1, 2, 5, 6 and 10)</td>
</tr>
<tr>
<td><strong>Mariane Morse</strong></td>
<td>Principal Speech and Language Therapist</td>
<td>Newcastle PCT</td>
<td>Royal College of Speech and Language Therapists (GDG7 and 9)</td>
</tr>
<tr>
<td><strong>Peter Rothwell</strong></td>
<td>Consultant Neurologist</td>
<td>Oxford Radcliffe Hospitals NHS Trust</td>
<td>Association of British Neurologists (GDG 4, 5 and 12)</td>
</tr>
<tr>
<td><strong>Neil Baldwin</strong></td>
<td>Consultant in Stroke Medicine</td>
<td>North Bristol Healthcare Trust</td>
<td>British Geriatrics Society (GDG12)</td>
</tr>
<tr>
<td><strong>Saw Willis</strong></td>
<td>Paramedic Lecturer Practitioner</td>
<td>London Ambulance Service and Greenwich University</td>
<td>British Paramedic Association (GDG2)</td>
</tr>
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Preface

Insert text from NCC director
DEVELOPMENT OF THE GUIDELINE
1. Introduction

1.1. Background

1.1.1 Stroke is a treatable disease. 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 in need of most active intervention, effective acute interventions, and an understanding of the processes of care that contribute to 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 have documented changes in secondary care provision over the last 10 years, with increasing numbers of patients 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 processes of care and clinical outcome.

1.1.1.2 This guideline covers the evidence for interventions in the acute stage of a stroke or transient ischaemic attack (TIA). Most of the evidence considered relates to interventions in the first 48 hours after onset of symptoms, although in some cases this period can be up to 2 weeks. This guideline is a stand-alone document, but is designed to be read alongside the Intercollegiate Working Party (ICWP) guideline on stroke rehabilitation, which considers evidence for interventions from the acute stage into rehabilitation and life after stroke.

Definition

1.1.1.3 Stroke is defined by the World Health Organisation 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.

Incidence:

1.1.1.4 Stroke is a major health problem in the UK. It accounted for over 56,000 deaths in England and Wales in 1999, which represents 11% of all deaths. The majority of people survive a
first stroke, often with significant morbidity. Approximately 110,000 people suffer a first or recurrent stroke and a further 20,000 people suffer a TIA each year in England. 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.4

Health and Resource Burden:

1.1.1.5 Stroke is estimated to cost around the economy in England around £7 billion per year, comprising direct costs to the NHS of £2.8 billion, informal care costs of £2.4 billion and costs to the economy of lost productivity and disability of £1.8 billion.4

1.1.1.6 Until recently, stroke has not been 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 (2007)5 which outlines an ambition for stroke including all aspects of care from emergency response to life after stroke.

2. Methodology

2.1. Aim

2.1.1.1 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 transient ischaemic attacks (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 acute management of stroke and TIAs.

- Details areas of uncertainty or controversy requiring further research.

- Provides a choice of guideline versions for differing audiences.

2.2. Scope

2.2.1.1 The guideline was developed in accordance with a scope, which detailed the remit of the guideline originating from the Department of Health and specified those aspects of diagnosis
and acute management of stroke and transient ischaemic attacks care to be included and excluded.

2.2.1.2 Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by NICE.¹ The full scope is shown in Appendix B.

2.3. Audience

2.3.1.1 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 Acute Stroke and TIA

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

- Having two people with experience of acute 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

2.5.1.1 These include:

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- 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, although NICE expect their guidelines to be read alongside the Summaries of Product Characteristics.

• Overall, the evidence review identified very few RCTs or high quality case-control or cohort studies. Many of the studies had a small sample size and were consequently statistically under-powered. Many studies relied 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

2.6.1.1 Related NICE guidance:


2.7. Background

2.7.1.1 The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual\(^1\) and the methodology pack\(^6\) specifically developed by the NCC-CC for each chronic condition guideline (see http://www.rcplondon.ac.uk/college/ceeu/ncccc_index.htm). The developers’ role and remit is summarised in Figure 1 below.
Figure 1: Role and remit of the developers

| National Collaborating Centre for Chronic Conditions (NCC-CC) | 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 the National Institute for Health and Clinical Excellence (NICE). A multiprofessional partners’ board inclusive of patient groups and NHS management governs the NCC-CC. |
| NCC-CC Technical Team | The technical team met approximately two weeks before each Guideline Development Group (GDG) meeting and comprised the following members: GDG chair, GDG clinical advisor, Information scientist, Research fellow, Health economist, Project manager. |
| Guideline Development Group | The GDG met monthly (November 2006 to November 2007) and comprised a multi-disciplinary team of professionals and people with experience of acute stroke or TIA who were supported by the technical team. The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline. |
| Guideline Project Executive (PE) | 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. The PE comprised of: NCC-CC Director, NCC-CC Assistant Director, NCC-CC Manager, NICE Commissioning Manager, Technical Team. |
| Formal consensus | At the end of the guideline development process the GDG met to review and agree the guideline recommendations. Members of the GDG declared any interests in accordance with the NICE technical manual. A register is given in Appendix E. |

Stroke: Full guideline DRAFT 1 (January 2008)
2.8. The process of guideline development

2.8.1.1 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

2.8.1.2 The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refine and approve these questions, which are shown in Appendix A.

2. Searching for the evidence

2.8.1.3 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.

2.8.1.4 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 were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See Appendix A for literature search details.

3. Appraising the evidence

2.8.1.5 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.

2.8.1.6 All procedures are fully compliant with the:

- NCC-CC Quality assurance document and systematic review chart available at: http://www.rcplondon.ac.uk/college/NCC-CC

4. Health economic evidence

2.8.1.7 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.

2.8.1.8 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

2.8.1.9 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 2.1.

2.8.1.10 Evidence tables are available on-line at (to be completed upon publication)

6. Grading the evidence statements

Table 1 Grading the evidence statements NICE 2007

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>+</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
</tbody>
</table>
1\(^{-}\) Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias\(^{a}\)

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\(^{a}\)

3 Non-analytic studies (for example, case reports, case series)

4 Expert opinion, formal consensus

\(^{a}\) Studies with a level of evidence ‘–’ should not be used as a basis for making a recommendation.

**7. Agreeing the recommendations**

2.8.1.11 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.

2.8.1.12 The GDG also reached agreement on the following:
- five recommendations as key priorities for implementation
- five key research recommendations
- algorithms.

2.8.1.13 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.

2.8.1.14 Audit criteria for this guideline will be produced for NICE by CASPE Research 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

2.8.1.15 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

- 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 evidence-base, or any economic modelling

- From evidence to recommendations
  This section sets out the Guideline Development Group (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

2.8.1.16 The evidence tables are not published as part of the full guideline but are available on-line at (to be completed upon publication). These describe comprehensive details of the primary evidence that was considered during the writing of each section.

9. Writing the guideline

2.8.1.17 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.

2.8.1.18 The following versions of the guideline are available:

Full version: Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCC-CC. Available at (to be completed upon publication)

NICE version: Documents the recommendations without any supporting evidence. Available at (to be completed upon publication)

"Quick reference guide": An abridged version. Available online upon publication

"Understanding NICE guidance": A lay version of the guideline recommendations Available online upon publication

10. Updating the guideline
2.8.1.19 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 31st October 2007 to be considered. Future guideline updates will consider evidence published after this cut-off date.

2.8.1.20 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

2.9.1.1 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.

2.9.1.2 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

2.10.1.1 The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.
3. Key messages of the guideline

3.1. Key priorities for implementation

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

3.1.1.2 People with a suspected TIA who are at high risk of stroke (e.g. an ABCD² score of 4 or above) should receive:
   - immediate initiation of aspirin
   - specialist assessment within 24 hours of onset of symptoms
   - commencement of secondary prevention as soon as the diagnosis is confirmed.

3.1.1.3 All people with suspected stroke should be admitted directly to a specialist acute stroke unit.

3.1.1.4 Brain imaging should be performed immediately (ideally the next slot and definitely within 1 hour, whichever is sooner) for people with acute stroke who have:
   - indications for thrombolysis or early anticoagulation, or
   - been taking anticoagulant treatment, or
   - a known bleeding tendency, or
   - a depressed level of consciousness, or
   - unexplained progressive or fluctuating symptoms, or
   - papilloedema, neck stiffness or fever, or
   - severe headache at onset of onset of stroke.

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

3.2.1.1 These algorithms are provided as separate files: algorithm 1 is the TIA algorithm and algorithm 2 is the stroke algorithm.
### 4. Glossary and definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase</td>
<td>A drug used for thrombolysis</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>A group of drugs used to reduce the risk of clots forming by thinning the blood.</td>
</tr>
<tr>
<td>Anti phospholipid syndrome</td>
<td>Sometimes called sticky blood syndrome because the blood clots too quickly due to antibodies that form against the body’s phospholipids.</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>A group of drugs used to prevent the formation of clots by stopping platelets in the blood sticking together.</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>Is caused as a result of a small tear forming in the tunica intima lining of the arterial wall.</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index – a index of body weight corrected for height.</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>2 carotid arteries supply the front half of the brain with blood.</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>A surgical procedure used to clear the inside of the carotid artery of atheroma.</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>The narrowing of the carotid arteries in the neck.</td>
</tr>
<tr>
<td>Cohort study</td>
<td>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.</td>
</tr>
<tr>
<td>Confidence interval (CI)</td>
<td>A range of values which contains the true value for the population with a stated “confidence” (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.</td>
</tr>
<tr>
<td>Cochrane review</td>
<td>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).</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography an X-ray technique used to examine the brain.</td>
</tr>
<tr>
<td>Cost-effectiveness analysis</td>
<td>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</td>
</tr>
</tbody>
</table>
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).

DVT  Deep vein thrombosis.

Dysphagic  A difficulty in swallowing.

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.

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.

Infarct  An area of cell death due to the result of a deprived blood supply.

INR  International normalised ratio.

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.

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.

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.

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.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHS</td>
<td>National Health Service. This guideline is written for the NHS in England and Wales.</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence – a special health authority set up within the NHS to develop appropriate and consistent advice on health care technologies, and to commission evidence-based guidelines.</td>
</tr>
<tr>
<td>NSF</td>
<td>National Service Framework – a nationwide initiative designed to improve delivery of care for a related group of conditions.</td>
</tr>
<tr>
<td>Observational study</td>
<td>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.</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolism: a blood clot in the lungs.</td>
</tr>
<tr>
<td>PEG/PEJ</td>
<td>Percutaneous endoscopic gastrostomy/jejunostomy used for feeding. A gastroscope is used to insert a tube through the wall of the abdomen into the stomach.</td>
</tr>
<tr>
<td>PCC</td>
<td>Prothrombin complex conjugate.</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Refers to the level of comfort, enjoyment, and ability to pursue daily activities.</td>
</tr>
<tr>
<td>Quality-of-life adjusted year (QALY)</td>
<td>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.</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised clinical 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 minimize experimental bias.</td>
</tr>
<tr>
<td>ROSIER</td>
<td>Recognition of stroke in the emergency room used to establish the diagnosis of stroke or TIA.</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk.</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>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.</td>
</tr>
<tr>
<td>Specialist</td>
<td>A clinician whose practice is limited to a particular...</td>
</tr>
<tr>
<td><strong>branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Stakeholder</strong></td>
<td>Any national organisation, including patient and carers’ groups, healthcare professionals and commercial companies with an interest in the guideline under development.</td>
</tr>
<tr>
<td><strong>Statistical significance</strong></td>
<td>A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 (p&lt;0.05).</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>The damaging or killing of brains 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.</td>
</tr>
<tr>
<td><strong>Systematic review</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Technology Appraisal</strong></td>
<td>Formal ascertainent and review of the evidence surrounding a health technology, restricted in the current document to appraisals undertaken by NICE.</td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td>Transient ischaemic attack a stroke which recovers within 24hrs of onset of symptoms.</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>A formation of a blood clot</td>
</tr>
<tr>
<td><strong>Thrombolysis</strong></td>
<td>The use of drugs to break up a blood clot. Two examples of thrombolysis drugs are tPA and Alteplase.</td>
</tr>
<tr>
<td><strong>tPA</strong></td>
<td>Tissue plasminogen activator a drug used for thrombolysis</td>
</tr>
<tr>
<td><strong>Venous stroke</strong></td>
<td>The formation of a blood clot in the intracerebral veins and venous sinuses</td>
</tr>
<tr>
<td><strong>Video Fluoroscopy</strong></td>
<td>Videofluoroscopy is a test for assessing the integrity of the oral and pharyngeal stages of the swallowing process. Involves videotaping fluoroscopic images as the patient swallows a bolus of barium.</td>
</tr>
<tr>
<td><strong>WHO</strong></td>
<td>World Health Organization.</td>
</tr>
</tbody>
</table>
THE GUIDELINE
5. The rapid recognition of symptoms and diagnosis

5.1. Pre-hospital health professional checklists for the prompt recognition of symptoms of TIA and stroke

5.1.1. Clinical introduction

5.1.1.1 People who present with acute stroke or TIA need urgent 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. A number of tools have been designed to help paramedics and other health care professionals recognise symptoms in the community. Other tools have been developed to improve the speed of diagnosis on arrival in the Accident and Emergency department to avoid delay in the delivery of specialist assessment and management.

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

5.1.2. Clinical methodological introduction

5.1.2.1 A number of different pre-hospital ‘assessment tools’ were identified for use by paramedics, namely the Face, Arm, Speech Test (FAST)\(^7;8\), Los Angeles Pre-hospital Stroke Screen (LAPSS)\(^9\), The Cincinnati Prehospital Stroke Scale (CPSS)\(^10\) and Melbourne Ambulance Stroke Screen (MASS)\(^11;12\). In addition one assessment tool, The Recognition of Stroke in the Emergency Room (ROSIER)\(^13\) has been developed for use by emergency room hospital personnel.

Level II+

5.1.2.2 Studies varied considerable with respect to patient selection, setting (e.g., hospital versus field study) and outcomes. The table below outlines the different pre-admission and emergency assessment tools.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>ASSESSMENT TOOL</th>
<th>ADMINISTERED BY</th>
<th>NUMBER OF PATIENTS/ASSESSMENTS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidwell et al. (2000)</td>
<td>Los Angeles pre-hospital stroke screen (LAPSS)</td>
<td>Paramedics</td>
<td>N=171</td>
<td>History items: age &gt;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.</td>
</tr>
<tr>
<td>Bray et al. (2005a, 2005b)</td>
<td>Melbourne Ambulance Stroke Screen (MASS)</td>
<td>Paramedics</td>
<td>N=100 (a) N=210 (b)</td>
<td>History items: age &gt;45 yrs, seizure history, at baseline wheelchair bound or bedridden and blood glucose. Physical assessment: facial droop, hand grip, arm drift and speech abnormalities.</td>
</tr>
<tr>
<td>Room (ROSIER)</td>
<td>Physical assessment: facial weakness, arm weakness, leg weakness, speech disturbance and visual field defects</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.1.3. Health economic methodological introduction

5.1.3.1 No studies were identified.

5.1.4. Clinical evidence statements

1.0 Face Arm and Speech Test (FAST)

5.1.4.1 Two studies evaluated the diagnostic accuracy of the FAST by paramedics.\(^7\);\(^8\)

Level 1b+

5.1.4.2 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 emergency room (ER) doctors.\(^7\)

Level 1b+

5.1.4.3 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 estimated of sensitivity of 79%.\(^7\) There were no statistical differences between the ambulance paramedics, primary care doctors and emergency room 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 primary care or ER doctors, although the strokes they admitted tended to be more severe and may have therefore been easier to diagnose.\(^7\)

Level 1b+

5.1.4.4 A further ‘in the field’ study reported acceptable interobserver agreement between neurological signs recorded in the FAST by paramedics and stroke physicians after admission.\(^8\)

Level 1b+

1.1 The Cincinnati Prehospital Stroke Scale (CPSS)

5.1.4.5 This study prospectively validated the CPSS used by prehospital care providers (paramedics and emergency medical technicians (EMTs)).\(^14\)

Level II+

\(^*\) 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
5.1.4.6 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 a physician and 59% and 89%, respectively when scored by a pre-hospital provider.14

Level II+

1.2 Los Angeles pre-hospital stroke screen (LAPSS)

5.1.4.7 The diagnostic accuracy of paramedics using LAPSS in the field was compared with that of emergency department and final hospital discharge diagnoses.9]

Level II+

5.1.4.8 In patients with completed LAPSS forms (corrected for documentation error) the sensitivity was 91% (95%CI 76 to 98%); specificity 97% (93 to 99%); positive predictive value 97% (84 to 99%); and negative predictive value 98% (95 to 99%).9]

Level II+

1.3 Melbourne Ambulance Stroke Screen (MASS)

5.1.4.9 Two studies were identified for this assessment scale 11,12.

Level II+

5.1.4.10 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%).11

Level II+

5.1.4.11 Another study performed an in-field validation of the MASS (100 assessments). The MASS showed equivalent levels of sensitivity compared to the CPSS (90 (81 to 96) vs. 95% (86 to 98); NS) but was significantly superior to that of the LAPSS (90 vs. 78% (67 to 87)). The specificity of the MASS was equivalent to that of the LAPSS (74 (53 to 88) vs. 85% (65 to 95); NS) but was significantly superior to that of the CPSS (74 vs. 56% (36 to 74)) 12. The positive predictive values of MASS, LAPSS and CPSS were 90 (81 to 96), 93 (83 to 98) and 85 (75 to 92) %, respectively, the negative predictive values for the MASS,
LAPSS and CPSS were 74 (53 to 88), 59 (42 to 74) and 79 (54 to 93) %, respectively.

Level II+

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

5.1.4.12 One study prospectively validated the ROSIER in stroke/TIA patients used by emergency room physicians.\textsuperscript{13}

Level Ib+

5.1.4.13 A cut-off of 1+ or above for stroke, 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 are presented in the table 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\%).\textsuperscript{13}

5.1.4.14 Level Ib+

<table>
<thead>
<tr>
<th></th>
<th>ROSIER % (95%CI)</th>
<th>CPSS % (95%CI)</th>
<th>FAST % (95%CI)</th>
<th>LAPSS % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>93 (89-97)</td>
<td>85 (80-90)</td>
<td>82 (76-88)</td>
<td>59 (52-66)</td>
</tr>
<tr>
<td>Specificity</td>
<td>83 (77-89)</td>
<td>79 (73-85)</td>
<td>83 (77-89)</td>
<td>85 (80-90)</td>
</tr>
<tr>
<td>Positive</td>
<td>90 (85-95)</td>
<td>88 (83-93)</td>
<td>89 (84-94)</td>
<td>87 (82-92)</td>
</tr>
<tr>
<td>Predictive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Value</td>
<td>88 (83-93)</td>
<td>75 (68-82)</td>
<td>73 (66-80)</td>
<td>55 (48-62)</td>
</tr>
</tbody>
</table>

5.1.5. From evidence to recommendations

5.1.5.1 The use of a validated tool to identify the symptoms and signs of suspected stroke and TIA increases diagnostic accuracy. A study of ambulance paramedics, A&E and primary care doctors using the FAST (Face Arm and Speech Test) assessment demonstrated a high positive predictive value for accurate diagnosis of stroke and TIA. Immediate diagnosis improves the speed of access to specialist care.

5.1.5.2 One study using the MASS validated tool compared the diagnostic accuracy of untrained vs. trained paramedics and found that training improved the accuracy of diagnosis.

5.1.5.3 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 LAPS, but would not be practicable to do outside
hospital. The GDG reviewed the evidence and concurred that
while a pre-hospital assessment 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

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

5.1.6.2 In people with sudden onset of neurological symptoms,
hypoglycaemia should be excluded.

5.1.6.3 People who are admitted to A&E with a suspected stroke or TIA
should have the diagnosis established rapidly using a validated
tool, such as ROSIER.

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

5.2.1. Clinical introduction

5.2.1.1 Patients with transient neurological symptoms may
underestimate their significance. They delay seeking specialist
care or may wait days to see a General Practitioner. The Inter-
Collegiate Working Party Guidelines in 2001\textsuperscript{15} 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 one week. The National
Sentinel Audit in 2006\textsuperscript{16} 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 OXVASC study demonstrates that some patients
are at high risk from completed stroke long before this time.

5.2.1.2 A systematic review of the risk of stroke within seven days of
TIA identified 18 independent cohorts (N=10 126 patients)
(search 2007).

5.2.1.3 15 reported at two days after TIA and 17 at seven days. The
pooled risk of stroke at two days was 3.1% (95%CI 2.0 to 4.1)
and at seven 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.\textsuperscript{17}
5.2.1.4 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 (Early Use of EXisting PREventative Strategies for Stroke (EXPRESS) study) \(^{18}\), a before and after observational study of patients with TIA attending a dedicated clinic, found that in the initial stage patients waited 20 days from clinic appointment with a letter to the GP to first administration of medication. In the second phase of the study medication was directly dispensed and administered in the clinic. Stroke rates were much lower in the second phase. In this study, the therapeutic intervention was a tailored “basket” of interventions rather than any specific study medication. Another observational study showed lower than expected rates of stroke in patients managed in a “24 hour” TIA clinic. \(^{19}\)

5.2.1.5 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**

5.2.2.1 One prospective cohort study (EXPRESS) \(^{18}\) and one observational study SOS-TIA \(^{19}\) were identified that looked at outcomes in patients with TIA who had undergone urgent assessment and treatment.

5.2.2.2 One study was a prospective population-based sequential comparison study (Early Use of EXisting PREventative Strategies for Stroke (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 four-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.\textsuperscript{18}

Level 2++

5.2.2.3 A prospective observational study (N=1085) evaluated the impact of a 24 hour rapid assessment clinic for patients with suspected TIA. Clinical assessment occurred within four hrs of admission. Patients with minor stroke, definite or possible TIA were prescribed antithrombotic medication immediately. The study reported on the risk of recurrent in stroke in patients treated in a rapid access clinic compared with that predicted on the basis of signs and symptoms of admission (ABCD\textsuperscript{2}) SOS-TIA.\textsuperscript{19}

Level 3

Scoring systems

5.2.2.4 Five studies were identified, all evaluated the accuracy of the one scoring system, namely the ABCD or a derivation of this (ABCD\textsuperscript{2} score), to predict early stroke risk after transient ischaemic attack (TIA).\textsuperscript{20, 21, 22, 23} One study was excluded due to methodological limitations.\textsuperscript{24}

5.2.3. Health economic methodological introduction

5.2.3.1 No papers were identified

5.2.4. Clinical evidence statements

\textit{Early vs. late assessment}

5.2.4.1 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.\textsuperscript{18}

Level 2++

5.2.4.2 At one month a statistically 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 or were referred to carotid surgery within seven days or less or 30 days or less.\textsuperscript{18}

Level 2++

5.2.4.3 There was no statistical 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 three days) compared with phase two (median less than one day). A significantly higher proportion of patients were seen within six hrs or less from first call to medical attention to assessment in the study clinic in phase two than in phase one. Consequently, they 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).\textsuperscript{18}

Level 2++

5.2.4.4 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).\textsuperscript{18}

Level 2++

5.2.4.5 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).\textsuperscript{18}

Level 2++

5.2.4.6 The prospective observational study evaluating the impact of a 24 hour rapid assessment clinic for patients with suspected TIA reported\textsuperscript{19}:

- 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 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
5.2.4.7 The table 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.¹⁹

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Number of strokes, n</th>
<th>Reported (95%CI)</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N=1052)</td>
<td>13</td>
<td>1.24 (0.72 to 2.12)</td>
<td>5.96</td>
</tr>
<tr>
<td>Definite TIA + no brain lesion (N=524)</td>
<td>7</td>
<td>1.34 (0.64 to 2.78)</td>
<td>6.13</td>
</tr>
<tr>
<td>Definite TIA + new brain lesion (N=105)</td>
<td>7</td>
<td>4.76 (2.01 to 11.06)</td>
<td>7.76</td>
</tr>
<tr>
<td>Possible TIA (N=141)</td>
<td>1</td>
<td>0.71 (0.10 to 4.93)</td>
<td>4</td>
</tr>
</tbody>
</table>

5.2.4.8 For all patients seen within 24 hrs 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%.¹⁹

Level 3

Scoring systems

5.2.4.9 The ABCD score was derived from the OXVASC study where a series of clinical features in people with TIA were related to subsequent stroke risk: age [< 60 years=0, ≥ 60=1]; BP [systolic ≤140mm Hg and/or diastolic >90 mm Hg=0, systolic >140 mm HG and/or diastolic >90mm Hg =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.

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

1.0 Rothwell et al. (2005)

5.2.4.11 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 (Oxford Vascular Study OXVASC, N=190)†. The clinical usefulness of the score to ‘front-line’ heath 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).²²

Level 3

†The latter is a sub-group of people in the OXVASC diagnosed by the study neurologist with only possible TIA, made an alternative diagnosis, or could not explain the diagnosis
5.2.4.12 The 7-days 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 the presenting TIA occurred in the 101 (27%) patients with a risk score of 5 or greater. The 7-day risks were 0.4% (0 to 1.1) in 274 (73%) patients with a score less than 5, 12.1% (4.2 to 20.0) in 66 (18%) patients with a score of 5, and 31.4% (16.0 to 46.8) in 35 (9%) patients with a score of 6. 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.\textsuperscript{22}

Level 3

5.2.4.13 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. 14 (7.5%) patients had a stroke before their scheduled clinical appointment. The ABCD score was a statistically significant predictor of stroke before the clinical appointment with no events in patients with a score of less than 4.\textsuperscript{22}

Level 3

5.2.4.14 The table below shows the 7-day risk of stroke stratified according 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.\textsuperscript{22}

Level 3

<table>
<thead>
<tr>
<th></th>
<th>Risk of stroke within 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (%)</td>
</tr>
<tr>
<td>OXVASC</td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>28 (7)</td>
</tr>
<tr>
<td>2</td>
<td>74 (20)</td>
</tr>
<tr>
<td>3</td>
<td>82 (22)</td>
</tr>
<tr>
<td>4</td>
<td>90 (24)</td>
</tr>
<tr>
<td>5</td>
<td>66 (18)</td>
</tr>
<tr>
<td>6</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Weekly clinic</td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>18 (9)</td>
</tr>
<tr>
<td>2</td>
<td>36 (18)</td>
</tr>
<tr>
<td>3</td>
<td>40 (20)</td>
</tr>
<tr>
<td>4</td>
<td>55 (26)</td>
</tr>
<tr>
<td>5</td>
<td>34 (16)</td>
</tr>
</tbody>
</table>
5.2.4.15 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 one month to derive a 30-day risk of stroke.23

5.2.4.16 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-day and 30-day risk of stroke. The multivariate Cox regression analyses revealed that a ABCD score of 5 to 6 was an independent predictors 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.23

Level 3

<table>
<thead>
<tr>
<th>ABCD score</th>
<th>Patients (%)</th>
<th>Strokes (%)</th>
<th>Risk (%), 95% CI</th>
<th>Strokes (%)</th>
<th>Risk (%), 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>12 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>22 (10)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>58 (26)</td>
<td>1 (5)</td>
<td>1.7 (0.5-5.1)</td>
<td>2 (9)</td>
<td>3.5 (0.8-2.1)</td>
</tr>
<tr>
<td>4</td>
<td>66 (29)</td>
<td>5 (28)</td>
<td>7.6 (1.2-14.0)</td>
<td>5 (23)</td>
<td>7.6 (1.2-14.0)</td>
</tr>
<tr>
<td>5</td>
<td>47 (21)</td>
<td>9 (50)</td>
<td>19.1 (7.8-30.4)</td>
<td>10 (45)</td>
<td>21.3 (10.4-33.0)</td>
</tr>
<tr>
<td>6</td>
<td>16 (7)</td>
<td>3 (17)</td>
<td>18.8 (0.37.9)</td>
<td>5 (23)</td>
<td>31.3 (9.6-54.0)</td>
</tr>
</tbody>
</table>

3.0 Bray et al. (2007)

5.2.4.17 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.20

Level 3

5.2.4.18 The table below reports the proportions of strokes occurring by 7 and 90 days stratified by the ABCD score on admission.

<table>
<thead>
<tr>
<th>ABCD score</th>
<th>Patients, n (%)</th>
<th>7 days</th>
<th>Stroke, n (% risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>90 days</td>
</tr>
<tr>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>6 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>7 (7)</td>
<td>0</td>
<td>1 (14)</td>
</tr>
<tr>
<td>3</td>
<td>21 (22)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>15 (15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>28 (29)</td>
<td>3 (11)</td>
<td>3 (11)</td>
</tr>
</tbody>
</table>
5.2.4.19 Dichotomising the ABCD score (4 or less versus ≥ 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 below for the accuracy of the ABCD score (high risk) at predicting the 7 and 90–day risk of stroke.20

<table>
<thead>
<tr>
<th>Risk (No. strokes)</th>
<th>Sensitivity % (95%CI)</th>
<th>Specificity % (95%CI)</th>
<th>Positive Predictive Value % (95%CI)</th>
<th>Negative Predictive Value % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 days (N=4)</td>
<td>100 (40-100)</td>
<td>53 (43-63)</td>
<td>8 (3-21)</td>
<td>100 (91-100)</td>
</tr>
<tr>
<td>90 days (N=7)</td>
<td>86 (42-99)</td>
<td>54 (43-64)</td>
<td>12.5 (5-26)</td>
<td>98 (88-100)</td>
</tr>
</tbody>
</table>

5.2.4.20 A large number of patients (79%) were aged ≥60 yrs 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.20

5.2.4.21 One study validated the California score and the ABCD score in four independent groups of patients (N=2893) 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 ≥140/90 mm Hg [1]; clinical features: unilateral weakness [2], speech impairment without weakness [1]; duration ≥60 min [2] or 10-59 min [1]; and diabetes [1] 21.

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

5.2.4.23 Overall, when the four validation groups were combined 47/4799 (1%) patients with complete information in the combined cohorts scored 0, 191 (4%) scored 1, 543 (11%) scored 2, 847 (18%) scored 3, 11165 (24%) scored 4, 994
(21%) scored 5, 852 (18%) scored 6, and 160 (3%) scored 7. The table below shows percentage range of risk of stroke at 2, 7 and 90 –days for the four validation groups.²¹

<table>
<thead>
<tr>
<th>Level 3</th>
</tr>
</thead>
</table>

| ABCD² (%) | 
| (The range of % risk across the four validation groups) |

<table>
<thead>
<tr>
<th>Risk of stroke (days)</th>
<th>No. of strokes (%)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients 2889</td>
<td></td>
<td>37</td>
<td>138</td>
<td>373</td>
<td>560</td>
<td>693</td>
<td>545</td>
<td>455</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1-2</td>
<td>0-3</td>
<td>2-4</td>
<td>3-6</td>
<td>4-14</td>
<td>0-50</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1-2</td>
<td>0-3</td>
<td>3-11</td>
<td>6-7</td>
<td>7-25</td>
<td>0-50</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
<td>0</td>
<td>0-3</td>
<td>2-6</td>
<td>1-5</td>
<td>5-11</td>
<td>10 -14</td>
<td>11 -28</td>
<td>18 -50</td>
</tr>
</tbody>
</table>

5.2.4.24 The table below shows the data stratified as a low, moderate or high risk of stroke based of the ABCD² score.

<table>
<thead>
<tr>
<th>Risk (Score)</th>
<th>2 day (N=1628)</th>
<th>7 day (N=2169)</th>
<th>90 days (N=1012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (&lt;4)</td>
<td>1%</td>
<td>1.2%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Moderate risk (4 or 5)</td>
<td>4.1%</td>
<td>5.9%</td>
<td>9.8%</td>
</tr>
<tr>
<td>High risk &gt;5</td>
<td>8.1%</td>
<td>11.7%</td>
<td>17.8%</td>
</tr>
</tbody>
</table>

5.2.4.25 Of 4746 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, mainly in the Californian groups. 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 5.²¹

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5.2.5. From evidence to recommendations

5.2.5.1 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.
5.2.5.2 Their 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.

5.2.5.3 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) suggests that the most cost effective service design overall is immediate (within 24 hour) assessment of patients with TIA. Cost-effectiveness of immediate assessment declines with ABCD² score. Specialist assessment was not cost-effective for scores of 0 or 1. However, the sample sizes for the stroke rates used in the model for these lower risk groups are small and there are additional benefits of specialist assessment not included in the model such that the QALYs gained from specialist assessment may have been under-estimated. 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.

5.2.5.4 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.

5.2.5.5 These scoring systems exclude certain populations such as those with recurrent events and those on anticoagulation who also need urgent evaluation.

5.2.6. Recommendations

5.2.6.1 People with a suspected TIA should be assessed for their risk of subsequent stroke using a validated scoring system, such as ABCD².

5.2.6.2 People with a suspected TIA who are at high risk of stroke (e.g. an ABCD² score of 4 or above) should receive:
- immediate initiation of aspirin
- specialist assessment within 24 hours of onset of symptoms
• commencement of secondary prevention as soon as the diagnosis is confirmed.

5.2.6.3 People with a suspected TIA who are at low risk of stroke (e.g. an ABCD² score of less than 4) should receive:
• immediate initiation of aspirin
• specialist assessment as soon as possible, but definitely within 1 week of onset of symptoms
• commencement of secondary prevention as soon as the diagnosis is confirmed.
6. Imaging in TIA and non-disabling stroke

6.1. What type of brain imaging should be used in people with a suspected TIA?

6.1.1. Clinical Introduction

6.1.1.1 In 2006, 78% of hospitals had neurovascular clinics, with a median time between onset and review of 12 days. 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 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.

6.1.1.2 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.

6.1.2. Clinical methodological introduction

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

6.1.2.2 Five observation studies/case series were identified, all reporting on MR diffusion weight imaging (MR-DWI) findings.

6.1.3. Health economic methodological introduction

6.1.3.1 No papers were identified.

6.1.4. Clinical evidence statements

6.1.4.1 The proportion of patients with MR-DWI abnormalities ranged from 25 to 58%.
6.1.4.2 Only the results of multivariate analysis are reported here:

- At one 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).\textsuperscript{26} 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).\textsuperscript{27} Level 3

- At three months, DWI abnormalities were a significant independent predictor of stroke (N=203).\textsuperscript{28} 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 risk (N=120).\textsuperscript{29} Level 3

- Symptoms greater than one hour and DWI abnormalities were significant independent predictors of further cerebral vascular events or any vascular event (follow-up mean 389 days) (N=83).\textsuperscript{30} Level 3

6.1.5. From evidence to recommendations

6.1.5.1 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.

6.1.6. Recommendations

6.1.6.1 People with a suspected TIA who require brain imaging (i.e. those in whom vascular territory or pathology is uncertain) should undergo MR with DWI (magnetic resonance with diffusion-weighted imaging) except where contraindicated\textsuperscript{‡}, in which case CT (computed tomography) should be used.

\textsuperscript{‡} Contraindications to MR scanning include people who have any of the following: a pacemaker, shrapnel, some brain aneurysm clips and heart valves, metal fragments in eyes, severe claustrophobia.
6.2. Which people with a suspected TIA should be referred for urgent brain imaging?

6.2.1. Clinical introduction

6.2.1.1 Recent evidence underlines the importance of immediate assessment and treatment of patients with TIA who are at high risk of completed stroke. 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. Early aspirin and other preventative measures (see section 8.1). 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.

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

6.2.2. Clinical methodological introduction

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

Level 3

6.2.3. Health economic methodological introduction

6.2.3.1 No papers were identified

6.2.4. Clinical evidence statements

6.2.4.1 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 ≥ 50%. There were no associations between positive DWI and age ≥ 60 yrs (NS), previous hypertension (NS), current raised blood pressure (NS) and diabetes (NS).

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6.2.4.2 Of the studies reporting on patients who were scanned within 24 hrs or less from the index event, a positive scan was
significantly associated with motor weakness and dysphasia only.\textsuperscript{31}

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6.2.5. From evidence to recommendations

6.2.5.1 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 potentially of 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. 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 ABCD\textsuperscript{2} 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.

6.2.6. Recommendations

6.2.6.1 People with a suspected TIA whose symptoms and signs have completely resolved should be assessed by a specialist before a decision on brain imaging is made.

6.2.6.2 People with a suspected TIA at high risk of stroke (e.g. an ABCD\textsuperscript{2} score of 4 or greater) in whom vascular territory or pathology is uncertain should undergo urgent brain imaging (preferably MR with DWI) within 24 hours of onset of symptoms.

6.2.6.3 People with a suspected TIA at low risk of stroke (e.g. an ABCD\textsuperscript{2} score of less than 4) in whom vascular territory or pathology is uncertain should undergo brain imaging (preferably MR with DWI) within 1 week of onset of symptoms.
6.3. Early carotid imaging in people with acute non-disabling stroke or TIA

6.3.1. Clinical introduction

6.3.1.1 Carotid imaging is required to determine the presence and severity of carotid stenosis in those individuals that 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 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.

6.3.1.2 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

6.3.2.1 Four studies reported on the association between carotid stenosis and symptoms, demographics and co-morbid conditions in patients who had undergone carotid duplex scanning (N=816)\(^{32}\), (N=5807 scans)\(^{33}\), (N=726)\(^{34, 35}\). Two of the studies were retrospective\(^{32, 33}\) and two were prospective\(^{34, 35}\) (N=305).\(^{35}\) One study was excluded\(^{36}\) as all of the data was incorporated in a more recent study.\(^{33}\)

6.3.2.2 In two studies the populations were relatively homogenous, one was on patients with acute stroke admitted to hospital\(^{35}\) and the other on patients admitted to hospital or seen in an outpatient clinic with acute stroke, cerebral or retinal transient ischemic

**Examples where brain imaging may be helpful in the management of TIA**

- People being considered for CEA where it is uncertain whether the stroke is in the anterior or posterior circulation.
- People where it is uncertain whether the TIA is due to hemorrhage or infarction.
- Where alternative diagnosis e.g. migraine, epilepsy or tumour is being considered.
attack (TIA) or retinal strokes.\textsuperscript{34} Two studies reported on heterogenous populations, including for example patients with TIA, dizziness and dysphasia.\textsuperscript{32, 33}

6.3.3. Health economic methodological introduction

6.3.3.1 One study was identified that modelled the cost-effectiveness of different assessment strategies for carotid stenosis.\textsuperscript{37}

6.3.4. Clinical evidence statements

\textit{Factors associated with carotid artery disease}

6.3.4.1 One retrospective study reported that patients with definite carotid symptoms (TIA, cerebrovascular accident, amarousis fugax or dysphagia) compared with non-carotid symptoms (dizziness, syncope, confusion and vertigo) were statistically more likely to have carotid stenosis.\textsuperscript{32}

Level 3

6.3.4.2 One retrospective study\textsuperscript{33} reported significant statistical associations between:

Level 3

6.3.4.3 Stenosis >70% and

- Bruit, known carotid disease, postoperative endarterectomy, smoking, high blood pressure, diabetes, peripheral vascular disease, myocardial infarct and hyperlipidaemia

6.3.4.4 Carotid occlusion and

- Bruit, known carotid disease, post operative endarterectomy, smoking, peripheral vascular disease, myocardial infarct and a past history of stroke

6.3.4.5 Stenosis >70% & carotid occlusion and

- Bruit, known carotid disease, post operative endarterectomy, smoking, high blood pressure, diabetes, peripheral vascular disease, myocardial infarct, past history of stroke and hyperlipidaemia

Level 3

6.3.4.6 One prospective study reported on the association between Oxford Community Stroke Project (OCSP) subtypes, 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.\textsuperscript{34}

Level 3
6.3.4.7 Multivariate analysis identified the following factors as independent significant positive associations with severe carotid stenosis, namely ipsilateral bruit, diabetes, previous TIA and a significant negative association with a lacunar event. When complete occlusion was included in the analysis, diabetes was no longer statistically associated with severe carotid stenosis (NS). 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 afore mentioned features results in the highest sensitivity of 99%, but specificity dropped to 22%.34

Level 3

**Stroke sub-type**

6.3.4.8 One prospective cohort study reported on whether stroke sub-type, using the OCSP clinical classification, could identify those patients with acute stroke who should preferentially be referred for carotid imaging.35

Level 3

6.3.4.9 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 lacunar infarct (LACI) group and 1/24 (4%; 0 to 8%) of the posterior circulation infarct (POCI) group ($\chi^2 p<0.05$). Complete ipsilateral occlusion was found in 25 (25%) of the TACI group, 11 (11%) of the PACI group, 3 (4%) of the LACI group and none in the POCI group. Severe carotid stenosis or occlusion was more frequent in the ipsilateral than the contralateral disease in the LACI and POCI groups, but there was no significant difference between the ipsilateral and contralateral carotid disease in the LACI and POCI groups (NS). If only patients with PACI are selected for carotid imaging (to identify severe stenosis 70 to 99%) then the sensitivity is 76%, specificity 70%, positive predictive value 16% and the negative predictive value is 97.5%.35

Level 3

6.3.5. Health economic evidence statements

6.3.5.1 Using a threshold of £30,000 per QALY gained, the most cost-effective strategy was to conduct an ultrasound scan and then offer endarterectomy to all patients with a 50-99% stenosis. As well as offering cost savings by avoiding confirmatory tests after ultrasound scanning, this strategy minimised the average time to endarterectomy, thus maximising the health gain.
6.3.6. From evidence to recommendations

6.3.6.1 Carotid imaging is essential to identify those people who would benefit from 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

6.3.7.1 All people with suspected non-disabling stroke or TIA and who are candidates for carotid intervention should have carotid imaging within 1 week of onset of symptoms.

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

6.4.1. Clinical introduction

6.4.1.1 While the benefits of carotid intervention for symptomatic carotid stenosis of >50% according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria and >70% according to the European Carotid Surgery Trial (ECST) criteria has been clearly described elsewhere 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 event, implying that for some patients, very early endarterectomy might be most beneficial. The non randomised EXPRESS study 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.

6.4.2. Clinical methodological introduction

6.4.2.1 Two studies reported on pooled data from two large RCTs, namely the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (N=5893). Patients with symptomatic carotid stenosis were randomised to medical treatment or to CEA. No studies were identified on carotid stenting in acute stroke. The data are reported according to time from last symptomatic ischemic event to randomisation or surgery.
patients in the ECST and 25.9% patients in NASCET were randomised within two weeks. Patients were included with TIA, non-disabling ischemic 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 affective. 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++

6.4.2.2 The prospective case series (N=238) recorded data on all patients undergoing CEA after ipsilateral acute stroke performed within one month of symptom onset. 55% of patients were operated on within two weeks of symptom onset. All patients had stenosis of 50% or greater. Twelve patients underwent the procedure within 24 hrs 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

6.4.3.1 No papers were identified

6.4.4. Clinical evidence statements

1.0 Mortality and neurologic deficits by time interval

6.4.4.1 The systematic review reported that there was no statistical difference for the outcome of perioperative stroke and death when comparing patients undergoing CEA less than one week since stroke with those undergoing the procedure one week or more since stroke onset (NS).42

Level 1+

6.4.4.2 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 ≥ 70% stenosis. For the former, the 5-year absolute risk reduction (ARR) in ipsilateral ischemic stroke and operative stroke or death was significant only if the patient was randomised to CEA within two weeks of the last event. The number of patients who need to undergo surgery (NNT) to prevent one ipsilateral stroke was three. ARR was not significant for CEA performed within two to four weeks, four to twelve weeks or greater than twelve weeks (NS). In patients with ≥ 70% stenosis, CEA gave a significant ARR for patients
randomised within two weeks, within two to four weeks and four to twelve weeks but not greater than twelve weeks (NS).\textsuperscript{38}

\textbf{Level 1++}

6.4.4.3 From the prospective case series data, there were no and two deaths in patients undergoing CEA within one week and within one to two weeks of symptom onset respectively. This compares with one death at two to four weeks. There was no statistical difference when comparing the different time intervals (NS). Furthermore, there were no statistical differences reported between the time interval from symptom onset to CEA and permanent neurological deficit (NS) or permanent or temporary neurologic deficit (NS).\textsuperscript{41}

\textbf{Level 3}

\textit{1.1 Clinical and demographic indicators}

6.4.4.4 The table below gives the absolute risk reduction with surgery in 5-year actuarial risk of ipsilateral carotid ischemic 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, is statistically greater in males than females and in the elderly. These results are consistent across patients with 50 to 69% and 70% or more stenosis.\textsuperscript{39}

\textbf{Level 1++}

6.4.4.5 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 neurologic deficit.\textsuperscript{41}

\textbf{Level 3}

\textit{6.4.5. From evidence to recommendations}

6.4.5.1 No RCT’s were identified which studied early vs. late carotid interventions using the two week cut off for the definition of acute stroke. No evidence for early carotid stenting (within the two week time period of the guideline)was identified. The evidence for benefit of referral for early carotid intervention is extrapolated from the two studies which reported on pooled data from two large RCTs. There are sex differences (women only benefit from surgery early while men continue to benefit from surgery for longer). There is less benefit from early surgery for patients who are medically unfit. In neurologically stable patients there is no statistical difference in the incidence of post operative 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 carotid endarterectomy within one week of onset. Patients who have carotid stenosis of <50% should receive best medical treatment.

6.4.6. Recommendations

6.4.6.1 People with acute non-disabling stroke or TIA who have symptomatic carotid stenosis of 50–99% according to the NASCET criteria, or 70–99% according to the ECST criteria, should:

- be assessed and referred for carotid endarterectomy within 1 week of onset of symptoms
- receive treatment within a maximum of 2 weeks of onset of symptoms.

6.4.6.2 People with 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 (e.g. control of blood pressure, antiplatelet drugs [aspirin and dipyridamole] and cholesterol lowering through diet and drugs).
7. Specialist care in acute stroke

7.1. Specialist stroke units

7.1.1. Clinical introduction

7.1.1.1 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) recommended that all stroke patients should be admitted to organised stroke units. The National Audit Office Report 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. 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.

7.1.1.2 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.

7.1.1.3 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

7.1.2.1 For the purposes of this question, specialist acute care was restricted to those units which focused on assessment, diagnostic tests 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.

7.1.2.2 One Cochrane systematic review was identified comparing organised inpatient (stroke unit) care for stroke with alternative
Here we report the sub-group 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 (one study).\textsuperscript{45}

**Level 2++**

7.1.2.3 One RCT (N=304) was identified that looked at differences in management processes in stroke units compared with stroke team care.\textsuperscript{46}

**Level 1+**

7.1.2.4 Five non-randomised control trials or cohort studies were identified.\textsuperscript{47, 48, 49, 50, 51} Six case series/observational studies were identified.\textsuperscript{52, 53, 54, 55, 56, 48}

**Level 3**

7.1.2.5 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 stroke\textsuperscript{57} and the remaining study was on patients with intracerebral haemorrhage.\textsuperscript{48}

**Level 3**

### 7.1.3. Health economic methodological introduction

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

7.1.3.2 Launois et al. (2004)\textsuperscript{58} reported on a French population. Not enough description was given of what care was received to be able to apply the results 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.

7.1.3.3 Moodie et al. (2006)\textsuperscript{59} 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.

7.1.3.4 Evidence from Patel et al. (2004)\textsuperscript{60} (also Kalra et al. 2005)\textsuperscript{61} was based on a randomised controlled trial carried out in the UK. Stroke units were compared to care by a mobile stroke team on a general ward, or domiciliary care. Patients were allocated to care within 72 hours of stroke. Cost-effectiveness was evaluated both including the costs of informal care and excluding them.\textsuperscript{,} Informal care costs were calculated by two
alternative methods: a) time was valued using the minimum wage; and 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

7.1.4.1 The table 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 ischemic stroke and for specific sub-groups where appropriate.

<table>
<thead>
<tr>
<th>Study</th>
<th>Death</th>
<th>Death or dependency</th>
<th>Outcome (if not death or dependency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane review (2007)⁴⁵ Acute (semi-intensive) N=322</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mixed rehabilitation N=211</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Overall N=533</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Candelise et al. (2007)⁵² N=11 572</td>
<td>SU</td>
<td>SU</td>
<td></td>
</tr>
<tr>
<td>Chiu et al. (2007)⁵³ N=237</td>
<td>SU</td>
<td>NS</td>
<td>FIM⁸ score Discharged home</td>
</tr>
<tr>
<td>Glader et al. (2001)⁵⁴ N=8194</td>
<td>SU</td>
<td>SU</td>
<td>Independent ADL</td>
</tr>
<tr>
<td>Independent ADL⁶</td>
<td>NS</td>
<td>SU</td>
<td></td>
</tr>
<tr>
<td>Dependent ADL</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Koton et al. (2005)⁴⁷ N=616</td>
<td>NS</td>
<td>SU</td>
<td>FIM and death mRS⁶ ≥ 3 or death</td>
</tr>
<tr>
<td>Ovary et al. (2007)⁵⁵ N=8743</td>
<td>SU</td>
<td>-</td>
<td>Living at home</td>
</tr>
<tr>
<td>All &lt; 60 yrs</td>
<td>SU</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>mRS &lt; 2</td>
<td>SU</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 yrs</td>
<td>NS</td>
<td>SU</td>
<td></td>
</tr>
<tr>
<td>mRS ≥ 3</td>
<td>NS</td>
<td>SU</td>
<td></td>
</tr>
<tr>
<td>Silva et al. (2005)⁴⁹ N=530</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>All CSS ≤ 4⁴</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CSS &gt; 4</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Stavem &amp; Ronning (2002)⁵¹, ⁴⁸ N=1128</td>
<td>NS</td>
<td>NS</td>
<td>Discharged home</td>
</tr>
<tr>
<td>Stegmayr et al. (1999)⁵⁷</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=14 308</td>
<td>Independent and unimpaired consciousness</td>
<td>SU</td>
<td>SU</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td>Independent with impaired consciousness</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS not statistically significant; SU significant difference in favour of a stroke unit; a Functional Independence Measures; b Activities of Daily Living; c modified Rankin Scale; d Canadian Stroke Scale

**Mortality**

7.1.4.2 When comparing all patients with acute ischemic stroke, three studies reported statistically lower mortality rates at discharge and at follow-up associated with acute stroke units compared with alternative care. 52, 53, 55

Level 3

7.1.4.3 Four studies reported statistically significant reductions in mortality associated with stroke unit care but only for specific sub-groups. 55, 57, 54, 49 However, the different types of care received and outcome measures used across the studies preclude any conclusion regarding any differential effects of stroke units on specific patient populations.

Level 3

7.1.4.4 The study on patients with intracerebral haemorrhage reported a significantly lower mortality rate associated with a stroke unit compared with a general medical ward. 48

Level 2++

**Death or dependency**

7.1.4.5 When comparing all patients with acute ischemic stroke, three studies reported statistically differences in favour of stroke units for the outcome of combined death or dependency or measures of disability or dependency. 52, 53, 47

7.1.4.6 A further three studies reported statistical differences in favour of stroke units for these outcomes but only for specific groups. 54, 55, 57

Level 3

7.1.4.7 The study on intracerebral haemorrhage reported no statistical differences for a stroke unit compared with a general medical
ward with respect to number of patients discharged home or to institutionalised care (NS).48

Level 2++

7.1.4.8 A further study reported there was no statistical difference at six months on quality of life measures when comparing patients admitted to a stroke unit compared with those to a general medical ward (NS) 50.

Level 2+

Length of stay

7.1.4.9 The Cochrane review and three other studies found no significant differences in the duration of hospital stay for patients on stroke units compared with general wards.45, 47, 52, 48 One study reported a statistically shorter duration of hospital stay associated with stroke unit care 53 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.57

Level 3

Diagnostic procedures and treatment

7.1.4.10 One study found no processes of care (including setting, staffing, protocols, mobilisation and diagnostic exams available) were associated with outcome.52 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 46. There was limited evidence to suggest that patients admitted to stroke units underwent diagnostic tests more frequently or more quickly 47 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 admission directly to a stroke unit.56, 47, 48

Level 3

7.1.5. Health economic evidence statement

Randomised evidence

7.1.5.1 Patel et al. (2004)60 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.

7.1.5.2 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.

7.1.5.3 When the stroke unit was compared to domiciliary care, the incremental cost for an additional 1% of deaths/institutionalisations avoided was £496 (excluding costs of informal care), which related to an incremental cost per QALY of £64,097.

Observational evidence

7.1.5.4 Moodie et al. (2006)\textsuperscript{59} 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

7.1.6.1 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.

7.1.6.2 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.

7.1.6.3 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.

7.1.6.4 The 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 would seem to imply that stroke units are not cost-effective compared with domiciliary care, 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 alternative cost-effectiveness ratio of £496 per death/institutionalisation avoided, suggests that stroke units are likely to be highly cost-effective with a more reasonable time horizon. Stroke unit care was not found to be statistically significantly more expensive than care given by mobile stroke teams on general medical wards but even if the cost difference is real, at £24,000 per QALY gained stroke units might be considered cost-effective even with the conservative one-year time horizon.

7.1.7. Recommendations

7.1.7.1 All people with suspected stroke should be admitted directly to a specialist acute stroke unit.

7.2. Brain imaging in people with acute stroke

7.2.1. Clinical introduction

7.2.1.1 Brain imaging is essential in stroke to exclude haemorrhage and stroke mimics. The National Clinical Guidelines for Stroke (2004) recommend scanning within 24 hours of onset of symptoms to confirm diagnosis. Only 42% of patients in the 2006 Sentinel Audit 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.

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

7.2.2. Clinical methodological introduction

7.2.2.1 No relevant papers were identified

7.2.3. Health economic methodological introduction

7.2.3.1 Two economic evaluations were identified that address early brain imaging following an acute stroke
7.2.3.2 An evaluation in the US of the HE of early scanning assessed usual US practice with practice based on NINDS recommendations on time from arrival to hospital to scanning.62

7.2.3.3 A UK study63 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, excluding subarachnoid haemorrhage.

**7.2.4. Health economic evidence statements**

7.2.4.1 Both strategies in the Stahl et al62 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

7.2.4.2 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.

7.2.4.3 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.

7.2.4.4 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.

7.2.4.5 Wardlaw et al (2004)63 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**

7.2.5.1 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. The strong clinical consensus of the GDG was that this includes 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 urgent (next available slot or within one hour; within one hour out of hours) brain imaging. 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

7.2.6.1 Brain imaging should be performed immediately (ideally the next slot and definitely within 1 hour, whichever is sooner) for people with acute stroke who have:

- indications for thrombolysis or early anticoagulation, or
- been taking anticoagulant treatment, or
- a known bleeding tendency, or
- a depressed level of consciousness, or
- unexplained progressive or fluctuating symptoms, or
- papilloedema, neck stiffness or fever, or
- severe headache at onset of stroke.

7.2.6.2 For all people with acute stroke without indications for immediate brain imaging, scanning should be performed as soon as possible (at most within 24 hours of onset of symptoms).

8. Pharmacological treatments for people with acute stroke

8.1. Aspirin and anticoagulant treatment in people with acute ischaemic stroke

8.1.1. Clinical introduction

8.1.1.1 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. Thrombotic stroke tends to be associated with platelet emboli in contrast to cardioembolic stroke which may be associated with blood clot.

8.1.1.2 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 two weeks after presentation. Antiplatelet agents and anticoagulants may increase the risk of haemorrhagic transformation of cerebral infarction.

8.1.1.3 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.

8.1.1.4 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.

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

8.1.2. Clinical methodological introduction

8.1.2.1 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 ischemic 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.

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

**Antiplatelet agents vs. placebo**

8.1.2.3 For the comparison antiplatelet agents versus placebo one Cochrane systematic review was identified.\(^{64}\) One RCT was not considered further due to methodological limitations.\(^{65}\)

**Level 1++**

8.1.2.4 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\(^{5}\) (N=40850) and aspirin plus 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 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 dipyridamole with control the doses were 330mg and 75 mg eight hourly, respectively. The follow-up period ranged from four weeks to six months.

**Level 1++**

**Anticoagulants vs. placebo**

8.1.2.5 For the comparison anticoagulants versus placebo one Cochrane systematic review (N=23547)\(^ {66}\) and one RCT (N=418)\(^ {67}\) 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 two weeks of stroke onset. The follow-up period ranged from seven days to one year. The RCT compared patients with acute non-lacunar hemispheric cerebral infarction treated with five days of unfractionated heparin (24 000 IU/day) or saline with a follow-up period of 90 days. After five days, both groups were prescribed aspirin 100mg/day or oral anticoagulants.

**Level 1++**

**Antiplatelet agents vs. anticoagulants**

8.1.2.6 For the comparison of antiplatelet agents versus anticoagulants one Cochrane systematic review (N=16558)\(^ {68}\) and one RCT

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\(^{5}\) Placebo (one RCT), Factorial design of aspirin, heparin both or neither (one RCT) and no treatment (one RCT)
(N=353) were identified. One RCT 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 ten days to six months. The RCT compared LMWH with aspirin administered within 48 hrs of symptom onset in patients with large artery occlusive disease. The follow-up period was six 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.69

Level 1++
8.1.3. Health economic methodological introduction

8.1.3.1 Of the papers appraised four were not considered to be of good quality. Marissal et al (2004)\textsuperscript{74} and Shah et al (2000)\textsuperscript{72} 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.

8.1.3.2 Matchar et al (2005)\textsuperscript{73} 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.

8.1.3.3 Six other papers were identified which were appraised. Beard et al. (2004)\textsuperscript{74} 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.

8.1.3.4 The health technology appraisal, Jones et al (2004)\textsuperscript{75}, 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.

8.1.3.5 The evaluation presented in Chambers et al. (1999)\textsuperscript{76} was updated in Chambers et al (2002)\textsuperscript{77}. In both versions the cohort was 30-day survivors of an initial ischaemic stroke in the UK. The 1999 evaluation compared no anti-platelet therapy, low-dose aspirin, MR dipyridamole, and a coformulation of low-dose aspirin plus modified-release dipyridamole. In the 2002 version aspirin plus dipyridamole was compared to aspirin alone.

8.1.3.6 Schleinitz et al. (2004)\textsuperscript{78} and Sarasin et al (2000)\textsuperscript{79} were both conducted in the USA. Schleinitz et al. (2004)\textsuperscript{78} compared of aspirin with clopidogrel in patients with peripheral arterial disease, a previous nonhaemorrhagic stroke, or a previous myocardial infarction. Sarasin et al (2000)\textsuperscript{79} compared aspirin, clopidogrel and dipyridamole in patients who have experienced stroke or TIA.

8.1.3.7 Moodie et al. (2004)\textsuperscript{80} 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.

8.1.4. Clinical evidence statements

\textit{Antiplatelet agents vs. placebo}
8.1.4.1 The Cochrane systematic review\textsuperscript{64} reported that aspirin therapy compared to control was associated with a significant reduction in the number of patients who were died or dependent or who experienced symptomatic pulmonary embolism or recurrent stroke. However, there was a small but statistical increase in the number of symptomatic intracranial haemorrhages and major extra-cranial haemorrhages. Overall, the small RCT comparing aspirin plus dipyridamole vs control reported no statistical differences between the two treatments. See table below for a summary of the results.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin vs. control</th>
<th>Aspirin plus dipyridamole vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or dependence at final follow-up (one month or more after randomisation)</td>
<td>↓Aspirin</td>
<td>NE</td>
</tr>
<tr>
<td>Death from all causes during the scheduled treatment period</td>
<td>↓Aspirin</td>
<td>NS</td>
</tr>
<tr>
<td>Death from all causes at follow-up</td>
<td>↓Aspirin</td>
<td>NS</td>
</tr>
<tr>
<td>Deep vein thrombosis during the treatment period</td>
<td>NE</td>
<td>↓Aspirin plus dipyridamole</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism during the treatment period</td>
<td>↓Aspirin</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrent ischaemic stroke or recurrent stroke of unknown pathological type during the treatment period</td>
<td>↓Aspirin</td>
<td>NS</td>
</tr>
<tr>
<td>Symptomatic intracranial haemorrhage during the treatment period</td>
<td>↑Aspirin</td>
<td>NS</td>
</tr>
<tr>
<td>Any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period and during long term follow up</td>
<td>↓Aspirin</td>
<td>NS</td>
</tr>
<tr>
<td>Major extracranial haemorrhage during the treatment period</td>
<td>↑Aspirin</td>
<td>NS</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>↑Aspirin</td>
<td>NE</td>
</tr>
</tbody>
</table>
denotes a significant decrease ↑ denotes a significant increase NS non significant NE not evaluated

**Anticoagulants vs. placebo**

8.1.4.2 The Cochrane review\(^{66}\) reported no statistically 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 DVTs and 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++

8.1.4.3 The RCT reported no statistical differences associated with UFH compared saline on the number of deaths at follow-up (NS) but there was a statistically significant increase in the number of patients in the UFH group who were ‘self-sufficient’ (score of zero to two on the modified Rankin Scale) at the end of follow-up. Significantly more symptomatic intracranial haemorrhages were associated UFH\(^{67}\). See table below for a summary of the results.

Level 1++

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Anticoagulants vs. control (^{66})</th>
<th>Unfractionated heparin (UH) vs. saline (^{67})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or dependence at final follow-up</td>
<td>NS</td>
<td>Death: NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Self-sufficiency: ↑ UFH</td>
</tr>
<tr>
<td>Death from all causes during the scheduled treatment period</td>
<td>NS</td>
<td>NE</td>
</tr>
<tr>
<td>Death from all causes at follow-up greater than one month after randomisation</td>
<td>NS</td>
<td>NE</td>
</tr>
<tr>
<td>Deep vein thrombosis (DVTs) during the treatment period</td>
<td>↓ Anticoagulants</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>Note: the majority of DVT’s detected were subclinical or asymptomatic</td>
<td></td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism during the</td>
<td>↓ Anticoagulation</td>
<td>NE</td>
</tr>
<tr>
<td>treatment period</td>
<td>(\Downarrow)Anticoagulation</td>
<td>NE</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------</td>
<td>----</td>
</tr>
<tr>
<td>Recurrent ischaemic stroke or recurrent stroke of unknown pathological type during the treatment period</td>
<td>(\Downarrow)Anticoagulation</td>
<td>NE</td>
</tr>
<tr>
<td>Symptomatic intracranial haemorrhage (SIH) during the treatment period</td>
<td>(\Uparrow)Anticoagulation</td>
<td>NE</td>
</tr>
<tr>
<td>Any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period and during long term follow up</td>
<td>NS</td>
<td>Symptomatic: (\Uparrow) UFH Asymptomatic NS</td>
</tr>
<tr>
<td>Major extracranial haemorrhage during the treatment period</td>
<td>(\Uparrow)Anticoagulation</td>
<td>NS (treatment and follow-up)</td>
</tr>
</tbody>
</table>

\(\Downarrow\) denotes a significant decrease \(\Uparrow\) denotes a significant increase NS non significant NE not evaluated

**Antiplatelet agents vs. anticoagulants**

8.1.4.4 The Cochrane review reported that anticoagulant therapy compared with antiplatelet therapy was associated with a significant increase in the number of deaths, symptomatic intracranial haemorrhage and major extracranial haemorrhages and a statistically 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 below for a summary of the results.

1++

8.1.4.5 The RCT reported no statistical differences between patients treated with LMWH and aspirin on the primary outcome of the Barthel Index (NS) measured at six months but a significantly greater proportion of patients had a good recovery as measured on the modified Rankin Scale (score 0 to 1 compared with \(\geq 2\) only). The rate of haemorrhagic transformation and severe adverse events were similar in both groups (NS). \(^{69}\)

1++

<p>| Anticoagulants versus antiplatelet agents | Anticoagulants versus antiplatelet agents (Berge et al., 2002) | UFH plus aspirin vs. aspirin alone (Berge et al., 2002) |</p>
<table>
<thead>
<tr>
<th>Event</th>
<th>Anticoagulants</th>
<th>UFH plus aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or dependence at final follow-up</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Death from all causes during the scheduled treatment period</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Death from all causes at follow-up</td>
<td>↑Anticoagulants</td>
<td>NS</td>
</tr>
<tr>
<td>Deep vein thrombosis during the treatment period</td>
<td>↓Anticoagulants</td>
<td>NE</td>
</tr>
<tr>
<td>Symptomatic pulmonary embolism during the treatment period</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Progression of symptoms during the treatment period</td>
<td>NS</td>
<td>NE</td>
</tr>
<tr>
<td>Recurrent ischemic stroke or recurrent stroke of unknown pathological type during the treatment period</td>
<td>NS</td>
<td>↓UFH plus aspirin</td>
</tr>
<tr>
<td>Symptomatic intracranial haemorrhage (SIH) during the treatment period</td>
<td>↑Anticoagulants</td>
<td>↑UFH and aspirin</td>
</tr>
<tr>
<td></td>
<td>↑High dose</td>
<td>↑High dose</td>
</tr>
<tr>
<td></td>
<td>↑Low dose</td>
<td>Low dose NS</td>
</tr>
<tr>
<td>Any recurrent stroke or symptomatic intracranial haemorrhage during the treatment period</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Major extracranial haemorrhage during the treatment period</td>
<td>↑Anticoagulants</td>
<td>↑UFH plus aspirin</td>
</tr>
<tr>
<td></td>
<td>↑High dose</td>
<td>↑High dose</td>
</tr>
<tr>
<td></td>
<td>Low dose NS</td>
<td></td>
</tr>
</tbody>
</table>

↓ denotes a significant decrease  ↑ denotes a significant increase  NS non significant  NE not evaluated.
8.1.5. Health economic evidence statements

8.1.5.1 Beard et al. (2004) and Chambers et al (2002) both had a 5 year time horizon. Beard et al found the combination of aspirin plus 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.

8.1.5.2 Schleinitz et al. (2004) and Sarasin et al (2000) 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 dipyridamole was more effective and less expensive aspirin or clopidogrel.

8.1.5.3 Over a 40 year time horizon if treatment effects on non-vascular deaths were included, Jones et al (2004) found that aspirin was more effective and less expensive than clopidogrel, aspirin plus modified release dipyridamole, or modified release dipyridamole in patients who had a previous stroke or TIA. If treatment duration was taken to be only 2 years (rather than for the duration of the patients' remaining lifetimes as in the base-case) then aspirin plus modified release dipyridamole had a cost per QALY of £5,500 and clopidogrel was more expensive and less effective than aspirin.

8.1.6. From evidence to recommendations

8.1.6.1 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.

8.1.6.2 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 – 300mg were reported as being equally effective and this was specified within the recommendation. 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 12-48h and found no significant difference. .

8.1.6.3 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.

8.1.6.4 In the 2 largest RCT’s, CAST and IST, aspirin therapy was continued for 2-4 weeks post stroke onset. These RCT’s 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.

8.1.6.5 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 contra-indications should take aspirin with proton pump inhibitor cover where appropriate. Genuine aspirin intolerance defined by the NICE vascular disease TA as people with proven hypersensitivity to aspirin-containing medicines or history of severe dyspepsia induced by low-dose aspirin. The NICE vascular disease TA recommends that these people should be offered an alternative antiplatelet agent e.g. clopidogrel. Patients who have not previously tolerated high doses of aspirin may be able to tolerate low dose aspirin.

8.1.6.6 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. It was agreed on the basis of the evidence presented that anticoagulant therapy confers no additional benefit over antiplatelet agents in acute stroke. It was noted that there was no evidence available on long term morbidities associated with DVT following stroke.

8.1.7. Recommendations

8.1.7.1 All people presenting with acute stroke who have had a diagnosis of primary intracerebral haemorrhage excluded by brain imaging should be given:

- aspirin 150–300 mg orally if they are not dysphagic.
- aspirin rectally or by enteral tube if they are dysphagic.

And thereafter

- aspirin 150–300 mg should be continued until 2 weeks post-stroke, at which time definitive long-term antithrombotic treatment should be prescribed.
8.1.7.2 Any person with acute ischaemic stroke who reports previous dyspepsia associated with aspirin should be given a proton pump inhibitor in addition to aspirin.

8.1.7.3 Any person with acute ischaemic stroke who is allergic to or genuinely intolerant of aspirin should be given an alternative antiplatelet agent (e.g. clopidogrel)**.

8.1.7.4 Anticoagulation should not be used routinely for the treatment of acute ischaemic stroke.

8.2. Antiplatelet and anticoagulant treatment in people with acute venous stroke

8.2.1. Clinical introduction

8.2.1.1 Venous stroke (ie 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 provides more accurate diagnosis, although in some cases angiography may be necessary to confirm the diagnosis. D-dimer may sometimes be elevated but a normal D-dimer does not exclude the diagnosis. 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 anti-coagulant treatment acutely.

8.2.2. Clinical methodological introduction

8.2.2.1 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.

Level 1++

8.2.3. Health economic methodological introduction

8.2.3.1 No papers were identified

** Aspirin intolerance is defined as either of the following:
- proven hypersensitivity to aspirin-containing medicines
- history of severe dyspepsia induced by low-dose aspirin.
8.2.4. Clinical evidence statements

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

8.2.4.1 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%).

Level 1++

8.2.4.2 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%).

Level 1++

**Confirmed pulmonary embolism**

8.2.4.3 There were no cases of confirmed pulmonary embolism.

Level 1++

**Symptomatic intracranial haemorrhage (ICH)**

8.2.4.4 There were no cases of new symptomatic ICH after initiation of anticoagulant therapy.

Level 1++

**Major extracranial haemorrhage**

8.2.4.5 One patient on anticoagulant therapy experienced a major non-fatal gastro-intestinal haemorrhage (RR 2.9; CI 0.12 to 68.5).

Level 1++

8.2.5. From evidence to recommendations

8.2.5.1 The evidence supports early anticoagulation in confirmed venous stroke with a reduction in death and dependency without a significant increase in intracranial or extracranial haemorrhage. It should be noted that other complications of the stroke (seizures, oedema) should be treated appropriately.

8.2.6. Recommendations

8.2.6.1 People diagnosed with cerebral venous sinus thrombosis (including those with secondary cerebral haemorrhage) should be treated with full-dose anticoagulation (INR 2–3) unless there are comorbidities that preclude its use.
8.3. **Antiplatelet and anticoagulant treatment in people with stroke due to arterial dissection**

### 8.3.1. Clinical introduction

8.3.1.1 Acute dissection of a cervical artery (carotid or more commonly vertebrobasilar) is a not uncommon cause of stroke. 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.

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

### 8.3.2. Clinical methodological introduction

8.3.2.1 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 antiplatelets agents versus anticoagulant comparison). Two further retrospective case series studies were also identified. Three studies were excluded due to methodological limitations.

Level 3

8.3.2.2 One study \(^85\) (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) \(^86\) reviewed the records of patients with internal carotid artery dissection. Of these, 19 (31.7%) patients received antiplatelets agents (aspirin) and 34 (56.7%) patients received anticoagulant therapy.
(intravenous heparin and/or oral anticoagulants) (7 (11.6%) received no specific treatment).

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

8.3.3. Health economic methodological introduction

8.3.3.1 No papers were identified.

8.3.4. Evidence statements

Carotid artery dissection

Death and disability

8.3.4.1 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).\textsuperscript{90,85}

Level 3

Recanalisation

8.3.4.2 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).\textsuperscript{85, 86}

Level 3

Vertebral artery dissection

Death and dependency

8.3.4.3 No patients died during treatment with antiplatelet agents or whilst having anticoagulant therapy\textsuperscript{85}.

Level 3

Recanalisation

8.3.4.4 For complete recanalisation, there was a statistically significant difference in favour of anticoagulant therapy compared with antiplatelets agents but there was no statistical differences for the rates of partial recanalisation (NS).\textsuperscript{85}

Level 3

Recurrent strokes

8.3.4.5 There was no statistical difference for the number of recurrent strokes when comparing antiplatelets agents with anticoagulant therapy (NS).\textsuperscript{85}

Level 3
8.3.5. From evidence to recommendations

8.3.5.1 From the evidence presented the GDG noted that there was no significant difference between 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.

8.3.6. Recommendations

8.3.6.1 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.

8.4. Antiplatelet and anticoagulant treatment in people with acute stroke due to antiphospholipid syndrome

8.4.1. Clinical introduction

8.4.1.1 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, thrombocytopenia and livedo reticularis. 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?

8.4.2. Clinical methodological introduction

8.4.2.1 No papers were identified.

8.4.3. Health economic methodological introduction

8.4.3.1 No papers were identified.

8.4.4. From evidence to recommendation

8.4.4.1 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.

8.4.5. Recommendations

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

8.5. Thrombolysis in people with acute ischaemic stroke

8.5.1. Clinical introduction

8.5.1.1 Thrombolysis with alteplase in acute ischaemic stroke has been shown to significantly improve outcome in selected patients treated within three hours of onset of symptoms. It has been reviewed in detail in NICE Technology Appraisal (TA122) so 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).

8.5.1.2 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 (ref or website). One series of 1135 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. 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 three 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.

8.5.2. Recommendations

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

8.5.2.2 Alteplase should only be administered within a well organised stroke service with:
- staff trained in the delivery of thrombolysis and monitoring for post-thrombolysis complications
- 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.

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

8.6. Statin treatment in people with acute stroke

8.6.1. Clinical Introduction

8.6.1.1 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.\textsuperscript{93} 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.\textsuperscript{94} A reduction in concentration of LDL cholesterol by 1 mmol/L with statins over a 5 year period reduced the relative risk of any vascular event by 20% in a prospective meta analysis of 14 statin trials in 90 056 individuals\textsuperscript{95} 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.\textsuperscript{96} The recent SPARCL (Stroke Prevention by Aggressive reduction in Cholesterol Levels) trial\textsuperscript{97} addressed the issue of the safety and efficacy of statin treatment with more recent TIA or non cardio embolic stroke. Patients were randomized between 1 and 6 months after non-disabling TIA or stroke to atorvastatin 80mg vs placebo and treated for a median of 4.9 years. A reduction in LDL of 1.4mmol/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.98 Statins may have a neuroprotective effect99; they are anti-inflammatory100 and have beneficial effects on endothelial function and haemostasis. A retrospective analysis of a consecutive case series of 155 patients who received intravenous t-PA for middle cerebral artery ischaemic stroke101 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 syndromes102 with a reduction in inflammatory markers.103 A pilot study of acute treatment with statins (MISTICS) following stroke has reported interim results.104 The FASTER study study planned to assess the efficacy of early anti-platelets and statins, was halted because of increased statin use pre-stroke.105 The clinical question to be addressed is whether patients with acute stroke should be give early treatment with statins.

8.6.2. Clinical methodological introduction

**Statin withdrawal**

8.6.2.1 One RCT (N=89) was identified and this reported on the influence of statin pre-treatment and its withdrawal on the outcome of acute ischemic stroke patients.106

Level 1+

8.6.2.2 Patients were admitted within 24 hrs of symptom onset. Patients on statins prior to the stroke were randomised to ‘statin withdrawal’ for the first three days after admission or to immediately receive atorvastatin 20mg/day (non-statin withdrawal).106

Level 1+

**Pre-morbid statin treatment**

8.6.2.3 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.107, 108, 109 None of the three studies identified were RCTs. One cross-sectional/cohort study compared patients with ischemic stroke or TIA who were on statins prior to the index event (N=152) with those that were not on statins (N=1539).107 One retrospective case-referent study compared patients with ischemic or haemorrhagic stroke who were on statins (N=125) and those that were not on
statins (N=250). A third study prospectively evaluated ischemic stroke patients (of less than 24 hrs in duration) on statins prior to the event (N=30) with those that were not (N=137).

Level 2+

8.6.3. Health economic methodological introduction

8.6.3.1 No papers were identified.

8.6.4. Clinical evidence statements

Statin withdrawal

8.6.4.1 At three 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 of dependency at three 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.

Level 1+

Pre-morbid statin treatment

Mortality

8.6.4.2 One study reported on this outcome. After adjusting for the uneven distribution of co-morbidity 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).

Level 2+

Disability

8.6.4.3 One study reported that at one week follow-up, statin treatment was significantly associated with stroke severity only if the event was severe (modified Rankin Score (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 is no longer a statistical effect (NS).

Level 2+
8.6.4.4 A further study reported that at three 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 Bathel Index 95 to 100 but not mRS.109

Level 2+

**Stroke type**

8.6.4.5 One study reported that lacunar strokes were statistically more frequent in the statin group than the no statin group.109

Level 2+

8.6.5. From evidence to recommendations

8.6.5.1 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. There is clearly benefit from initiation of statins after the acute phase of stroke in vascular risk reduction.

8.6.6. Recommendations

8.6.6.1 Immediate initiation of lipid lowering agents is not recommended following acute stroke.

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

8.6.6.3 People with acute ischaemic stroke and a total cholesterol of 3.5 mmol/l or greater should be initiated on statins prior to discharge.

8.7. Reversal of anticoagulation in people with haemorrhagic stroke

8.7.1. Clinical introduction

8.7.1.1 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.\textsuperscript{110} 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.\textsuperscript{111} The incidence of intracerebral haemorrhage in patients on warfarin is around 1.6%\textsuperscript{112} and increases dramatically in those patients with INR >4.\textsuperscript{113} 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; the effect was sustained 24 hours later. In two patients given PCC without IV vitamin K INR dropped rapidly but increased 12-24 hr later. Treatment with IV vitamin K alone reduced the INR but only after 24-48 hours\textsuperscript{114}; haematoma expansion occurred only in those patients with INR > 2.0.\textsuperscript{115} 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.\textsuperscript{116} However, there have as yet been no randomized controlled trials to assess outcome.

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

8.7.2. Clinical methodological introduction

8.7.2.1 No RCTs were identified which explored the efficacy of vitamin K, fresh frozen plasma (FFP) or prothrombin complex (PCC) or a combination of these interventions. Two short-term follow-up case series were identified, one prospective\textsuperscript{117} and one retrospective.\textsuperscript{118} Two long-term follow-up retrospective case series were also identified.\textsuperscript{119, 120}

Level 3

8.7.2.2 Two small studies compared PPC plus vitamin K with FFP plus vitamin K, one with a follow up of 180 minutes (N=12)\textsuperscript{117} and one 12 hours (N=17).\textsuperscript{118} A further study with a three month
follow-up compared FFP with vitamin K. 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 one year.

Level 3

8.7.2.3 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

8.7.3. Health economic methodological introduction

8.7.3.1 No papers were identified.

8.7.4. Clinical evidence statements

Prothrombin time

8.7.4.1 Two case series reported a greater reduction in INR values and a more rapid correction time in patients treated with PCC compared with FFP.117, 118

Level 3

8.7.4.2 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 hrs) compared with FFP and Vitamin K alone.120

Level 3

8.7.4.3 A further case series investigated the how time to 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 FPP administration was independently associated with a 20% decrease in the probability of a successful INR reversal within 24 hrs. A similar effect was reported for vitamin K.119

Level 3

Haematoma growth

8.7.4.4 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)**

8.7.4.5 Two case series studies reported no associated between functional outcome and treatment interventions at discharge or at 12 month follow-up. One study compared PCC with FFP (NS) 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).

Level 3

**8.7.5. From evidence to recommendations**

8.7.5.1 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 randomized controlled trial evidence on which to base a recommendation. Prothrombin complex conjugate and fresh frozen plasma 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 prothrombin complex conjugate and fresh frozen plasma is not sustained unless IV vitamin K is also added.

8.7.6. Recommendations

8.7.6.1 People admitted with a primary intracerebral haemorrhage and who are receiving anticoagulation therapy should have their clotting levels returned to normal as soon as possible, by reversing the effects of the anticoagulation treatment.

**8.8. Anticoagulation for other comorbidities in people with acute stroke**

8.8.1. Clinical introduction

8.8.1.1 Current National Clinical guidelines recommend aspirin for the treatment of acute ischaemic stroke (up to day 14) in patients both in atrial fibrillation (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 randomized controlled trial.
Insertion of an 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\textsuperscript{121,122} but increase the risk of DVT and have not been proven
to affect mortality\textsuperscript{123}; a recent review confirmed that there is no
RCT evidence to clarify optimum treatment in these patients.\textsuperscript{124}

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

8.8.2. Clinical methodological introduction

Atrial Fibrillation

8.8.2.1 One meta analysis on a sub group of patients with atrial
fibrillation extracted from three RCTs\textsuperscript{125, 126, 127, 128} was
identified.\textsuperscript{129} One of these three trials was conducted in a
Chinese population.\textsuperscript{127} The studies compared aspirin,
heparin/heparinoid or both. Treatment was initiated within 30 to
48 hrs of stroke onset.\textsuperscript{129} An additional prospective case series
was identified (N=386) that compared aspirin 75 to 300 mg with
adjusted-dose warfarin.\textsuperscript{130}

Level 1+

Prosthetic Heart Valves

8.8.2.2 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) both
looking at outcomes associated with warfarin cessation and
recommencement.\textsuperscript{131, 132}

8.8.2.3 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.\textsuperscript{132}

Level 3

8.8.2.4 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.\textsuperscript{131}

Level 3

**DVT’s and PE**

*Anticoagulants versus placebo*

8.8.2.5 For the comparison anticoagulants versus placebo one Cochrane systematic review was identified.\textsuperscript{66} The review included 22 RCTs testing UFH, LMWH, heparinoids, oral anticoagulants and thrombin inhibitors. All patients were started on treatment within two weeks of stroke onset. The follow-up period ranged from seven days to 1 year.

Level 1++

*Anticoagulants versus antiplatelet agents*

8.8.2.6 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 ten days to 6 months.\textsuperscript{68}

Level 1++

**8.8.3. Health economic methodological introduction**

8.8.3.1 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)\textsuperscript{133} included a subgroup of patients with a history of stroke or TIA but did not report the results separately. Wade (1998)\textsuperscript{134} did not include any details of the costs, and the time horizon was only 14 days.

8.8.3.2 The third paper identified, Gage et al. (1995)\textsuperscript{135} 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.

**8.8.4. Clinical evidence statements**

*Atrial Fibrillation*

1.0 Mortality
8.8.4.1 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).\textsuperscript{129, 130}

Level 3

1.2 Recurrent strokes

8.8.4.2 Two of the three trials\textsuperscript{127, 128} in the meta analysis reported no statistical differences in the incidence of ischemic recurrent stroke when comparing either LMWH with aspirin or aspirin with placebo\textsuperscript{129}. One trial\textsuperscript{125, 126} reported a significantly higher recurrent ischemic stroke rate in patients on ‘no heparin’ compared with those on heparin (but see 1.3).\textsuperscript{129}

Level 1+

8.8.4.3 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).\textsuperscript{130}

Level 3

1.3 Intracerebral haemorrhage

8.8.4.4 The trial in meta analysis reporting a reduced incidence of recurrent ischemic stroke associated with unfractionated heparin (UFH) also reported an increased incidence of hemorrhagic stroke in these patients compared with those on no heparin\textsuperscript{125, 126}. There was no statistical difference in the incidence of haemorrhagic stroke for aspirin in comparison with either placebo or control (NS)\textsuperscript{129}

Level 1+

8.8.4.5 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)\textsuperscript{130}

Level 3

1.4 Disability/functional outcome

8.8.4.6 One trial\textsuperscript{125, 126} in the meta analysis evaluated this outcome and no statistically significant differences between anticoagulants and antiplatelet agents on the number of patients ‘alive and independent’ (NS)\textsuperscript{129}

Level 1+
Prosthetic Heart Valves

1.1 Mortality and adverse events

8.8.4.7 The prospective case series study reported the Kaplan-Meier survival estimate for the probability of having ischemic events at seven 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 seven and 14 respectively. There were no cases of recurrent intracerebral haemorrhage during hospitalization.132

Level 3

8.8.4.8 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.131

Level 3

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

Anticoagulants versus placebo

8.8.4.9 The Cochrane systematic review reported the following results66:

1.1 Deep vein thrombosis during the treatment period (ten trials)

8.8.4.10 Anticoagulants were associated with a highly significant reduction in the odds of DVT although the majority of DVT’s detected were subclinical or asymptomatic (note there was significant heterogeneity between the trials).66

Level 1++

1.2 Symptomatic pulmonary embolism (PE) (fourteen trials)

8.8.4.11 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%126 to 7%.136, 137, 66

Level 1++

Anticoagulants versus antiplatelet agents
8.8.4.12 The Cochrane systematic review reported the following results.

2.1 Deep vein thrombosis

8.8.4.13 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 statistical difference (NS).

Level 1++

2.2 Pulmonary embolisms

8.8.4.14 The incidence of symptomatic pulmonary embolism during the treatment period was non significant (NS).

Level 1++

8.8.5. Health economic evidence statements

8.8.5.1 Gage et al. (1995) 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 quality adjusted life year of $8,000.

8.8.6. From evidence to recommendations

Atrial Fibrillation

8.8.6.1 In a meta-analysis of two large RCT’s, there was no statistically significant difference in the number of aspirin-treated compared with no aspirin/control treated patients who died and a RCT comparing a low molecular weight heparin (LMWH) with aspirin also reported no significant difference in mortality rates at 14 days and 3 months. National Stroke guidelines recommend the avoidance of anticoagulants in AF for two 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.

8.8.6.2 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 anti-platelet 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 two weeks following stroke before starting or restarting anticoagulation.

**Heart valves**

8.8.6.3 Patients with prosthetic heart valves in situ may require long term anticoagulation 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 RCT’s 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 dipyridamole to anticoagulation should be considered in patients who suffer systemic embolism despite adequate intensity of anticoagulation.

**Deep vein thrombosis (DVTs) and Pulmonary Emboli (PE)**

8.8.6.4 No evidence was found on the safety and efficacy of anticoagulant agents versus placebo for patients with acute stroke who may require anticoagulation for co-morbidities 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 RCT’s 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 subclinical. 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. However, the GDG felt that in the absence of RCT evidence it was reasonable to assume that anticoagulation and antiplatelets would be equally effective in prevention and in treatment.

8.8.6.5 The GDG did not review any evidence on the safety and efficacy of treatment with caval filters.

8.8.6.6 The GDG agreed that 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.

8.8.7. Recommendations

8.8.7.1 People admitted with disabling ischaemic stroke who are in atrial fibrillation should be treated with aspirin 150–300 mg for the first 2 weeks before considering anticoagulation.

8.8.7.2 People with prosthetic valves who have disabling cerebral infarction and who are at significant risk of haemorrhagic transformation should have their anticoagulation treatment stopped for 14 days and aspirin 150–300 mg substituted.

8.8.7.3 People with ischaemic stroke and symptomatic deep vein thrombosis (DVTs) or pulmonary embolisms (PEs) should receive anticoagulation in preference to treatment with aspirin unless there are other contraindications.

8.8.7.4 People with haemorrhagic stroke and symptomatic DVTs or PEs should have treatment to prevent further PE using either anticoagulation or caval filter.

9. Maintenance or restoration of homeostasis

9.1. Supplemental oxygen therapy

9.1.1. Clinical introduction
9.1.1.1 Oxygen supplementation by mask is usual practice in emergency prehospital and hospital care in acutely ill patients after appropriate assessment. 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.

9.1.1.2 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

9.1.2.1 Two studies were identified that reported on the affect of supplemental oxygen in patients with acute stroke (time from symptom onset to presentation 14 days or less). One of these studies was excluded due to methodological limitations.

Level 1+

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

Level 1+

9.1.3. Health economic methodological introduction

9.1.3.1 No papers were identified

9.1.4. Clinical evidence statements

Mortality, neurological impairment and disability

9.1.4.1 At one year follow-up, there were no statistical differences between patients given oxygen therapy compared with control.

‡‡ 33 patients in the treatment group did not receive supplemented oxygen as described (not given such treatment or were treated for less than 24 hrs) and 66 patients in the control group were given oxygen but for a lot less than 24 hrs.
patients in terms of mortality or neurological impairment (Scandinavian Stroke Score, SSS) or disability (Barthel Index) (NS)\(^{140}\).

Level 1+

**Stroke severity**

9.1.4.2 The one year survival rate for patients with moderate or mild strokes (SSS score $\geq 40$ on admission) was higher in the control group than patients who received supplemental oxygen. There were no 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)\(^{140}\).

Level 1+

9.1.5. From evidence to recommendations

9.1.5.1 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 discussed.

9.1.6. Recommendations

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

9.2. Blood sugar control

9.2.1. Clinical introduction

9.2.1.1 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.\(^{142}\) 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. The GIST-UK study is a randomised controlled trial of an intervention (variable dose insulin GKI infusion) vs. saline (control) in patients with all types of acute stroke.

9.2.1.2 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

9.2.2.1 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=2355). Level 1++

9.2.2.2 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 hypoglycaemia (admission glucose range 6.0 to 17 mmol). GKI was administered for a minimum of 24 hrs to maintain capillary blood glucose concentration at 4-7 mmol/L. Trial hypoglycaemia 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. Level 1++

9.2.2.3 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 HbA1c (< 6.2%), 191 (31.4%) had an acceptable percentage (HbA1c 6.2 to 7.5%) and 83 (13.7%) had a high percentage (HbA1c > 7.5%). Level 1++

9.2.3. Health economic methodological introduction

9.2.3.1 No papers were identified

9.2.4. Clinical evidence statements

Mortality & Disability
9.2.4.1 At 90 days, there were no statistical differences in mortality rates between those patients given GKI and placebo patients (NS)\textsuperscript{145}.

Level 1++

9.2.4.2 At 90 days, there were no statistical differences on the modified Rankin Scale (mRS), Barthel Index or the European Stroke Scale (ESS) between the GKI and placebo treated patients (NS)\textsuperscript{145}.

Level 1++

9.2.4.3 Overall, 73 (15\%) GKI-treated patients required rescue intravenous glucose treatment for hypoglycaemia (capillary glucose \(\leq 4\) mmol/L persisting more than 30 min after temporary discontinuation of the GKI infusion. There were no statistical differences in the mortality rates when patients receiving rescue dextrose and the other GKI patients (NS)\textsuperscript{145}.

Level 1++

\textit{Time from symptom onset.}

9.2.4.4 At 90 days, there was no statistical difference in mortality for those patients treated within 6 hrs of stroke onset compared with patients in the placebo group (NS)\textsuperscript{145}.

Level 1++

\textit{Complications}

9.2.4.5 At 72 hrs, there were no statistical differences between the two groups with respect to the number of complications at 72 hrs (NS)\textsuperscript{145}.

Level 1++

\textbf{9.2.5. From evidence to recommendations}

9.2.5.1 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 10 mmol/l following stroke should be treated. The Type 2 diabetes guidelines recommend 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 where possible between 4-11 mmol/l.

**9.2.6. Recommendations**

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

9.2.6.2 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)

**9.3. Blood pressure control**

**9.3.1. Clinical introduction**

9.3.1.1 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 (ref) had systolic blood pressure $>160$ mm Hg. 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 strokeiv. 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.
9.3.1.2 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

9.3.2.1 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=7521, 28 trials) and one glyceryl trinitrate (GTN) (N=227, two trials). Four additional RCTs were identified (N=265), (N=454), (N=302), (N=339).

9.3.2.2 The studies on calcium antagonists initiated therapy from between six hours or less to 72 hrs from stroke onset.

9.3.2.3 The remaining Cochrane review reported on glyceryl trinitrate (GTN) compared with control/placebo. In the studies included, therapy was initiated between four to five days from stroke onset.

9.3.2.4 One phase II RCT compared an angiotensin II antagonist with placebo in patients who had a ≥ 200 mm Hg systolic and/or ≥ 110 mm Hg diastolic 6 to 24 hrs after admission or ≥ 180 mm Hg systolic and/or ≥ 105 mm Hg diastolic 24 to 36 hrs after admission.

9.3.2.5 An RCT conducted in patients with hemispheric stroke (conscious and able to swallow) sustained within 48 hours, compared β blockers with placebo initiated four to five days from stroke onset.

9.3.3. Health economic methodological introduction

9.3.3.1 No papers were identified

9.3.4. Clinical evidence statements

*Calcium antagonists*
9.3.4.1 The Cochrane review included patients with acute ischemic 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)\textsuperscript{146}.

Level 1++

9.3.4.2 One additional RCT reported on a combination of intravenous and oral nimodipine (1 mg/hr (low dose), 2 mg/hr (high dose) both for five days plus oral nimodipine 120 mg for 16 days). All of the patients had ischemic stroke and were randomised within 24 hrs of stroke onset\textsuperscript{148}.

Level 1+

9.3.4.3 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 six hours of stroke onset and the duration of treatment was 10 days\textsuperscript{149}.

Level 1+

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

9.3.4.4 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)\textsuperscript{146}. One of the separate RCTs reported a similar finding for nimodipine compared with placebo (NS)\textsuperscript{149}.

Level 1++

9.3.4.5 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\textsuperscript{148}.

Level 1+

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

9.3.4.6 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)\textsuperscript{146}. One RCT also reported no statistical differences (NS)\textsuperscript{149}.

Level 1++

9.3.4.7 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 148.

**Level 1+**

**Recurrent stroke**

9.3.4.8 The Cochrane review found no statistical differences when patients on calcium antagonists were compared with control/placebo (NS) 146.

**Level 1++**

**Time to treatment**

9.3.4.9 The Cochrane review reported no statistical difference in outcomes between early treatment (\(\leq 12\) 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 hrs (NS) 146.

**Level 1++**

9.3.4.10 *Route of administration (intravenous versus oral)*

The Cochrane review reported no statistical difference in outcomes when comparing intravenous and oral nimodipine (NS) 146.

**Level 1++**

**Adverse events**

9.3.4.11 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) 148, 149.

**Level 1+**

**Transdermal glyceryl trinitrate (GTN)**

9.3.4.12 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 ischemic and N=10 haemorrhagic stroke) 147.

**Level 1+**

**Blood pressure**
9.3.4.13 GTN significantly lowered 24 hr ambulatory systolic blood pressure. There was no statistical difference for diastolic blood pressure (NS)\(^{147}\).

**Level 1++**

**Mortality and deterioration**

9.3.4.14 At three 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)\(^{147}\).

**Level 1++**

**Angiotensin II antagonist**

9.3.4.15 One RCT reported on patients who were treated with candesartan cilexetil 4 mg on day one increasing to 8 or 16 mg on day two if blood pressure exceeded 160 mm Hg systolic or 100 mm Hg diastolic. The treatment was targeted to a blood pressure reduction of 10 to 15% within 24 hrs\(^{151}\).

**Level 1+**

**Blood pressure**

9.3.4.16 During the placebo-controlled phase in the first seven 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 seven due to a hypertensive 24-hour blood pressure profile\(^{151}\).

**Level 1+**

**Mortality and vascular events**

9.3.4.17 There was no statistical difference in the cumulative 12-month mortality for candesartan cilexetil versus placebo (NS)\(^{151}\).

**Level 1+**

9.3.4.18 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\(^{151}\).

**Level 1+**

**Functional outcome**
9.3.4.19 There were no statistical differences between candesartan cilexetil and placebo on the Barthel Index at three months (NS)\(^{151}\).

Level 1+

**Concomitant medication, drug tolerance, adverse events**

9.3.4.20 There were no statistical differences between candesartan cilexetil and placebo regarding the use of concomitant medication, drug tolerance or adverse events during follow-up\(^{151}\).

Level 1+

**β blockers**

9.3.4.21 An RCT compared two β blockers, namely atenolol 50 mg daily, propranolol slow release 80 mg daily, with placebo\(^{150}\).

Level 1+

**Neurological changes (based on neurological assessment)**

9.3.4.22 When patients given propranolol or atenolol were combined and compared with placebo, there was a statistical higher number of mean neurological changes associated with placebo compared to beta-blockers at one day to one week and one day to one month\(^{150}\).

Level 1+

**Functional outcome (activities of daily living)**

9.3.4.23 At one 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 one week or six months (NS)\(^{150}\).

Level 1+

**Rate of discharge**

9.3.4.24 There was no statistical difference in the rate of hospital discharge (NS)\(^{150}\).

Level 1+

**Adverse events**

9.3.4.25 Eight patients experienced definite side effects from beta blockers\(^{150}\).

Level 1+
9.3.5. From evidence to recommendations

9.3.5.1 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 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 SCAST trial (which is due to report in 2009).

9.3.5.2 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 may be indicated. The effects of this on acute stroke are unknown.

9.3.5.3 The GDG acknowledged that the SCAST trial results will not be available until 2009

9.3.6. Recommendations

9.3.6.1 Blood pressure manipulation in people with acute stroke is not recommended except where there is a hypertensive emergency or any 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 >200 mmHg.

10. Hydration and nutrition

10.1. Oral nutritional supplementation

10.1.1. Clinical introduction

10.1.1.1 Adequate 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. In addition poor nutritional status is linked to poorer outcome after stroke. 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. It should however be noted that a significant proportion of patients with stroke are malnourished on admission and all patients should be weighed and have their nutritional state assessed and treated where appropriate.

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

10.1.2. Clinical methodological introduction

10.1.2.1 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=4023) on patients with first or recurrent stroke, and who were admitted to hospital within seven days of stroke onset. 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 yrs. 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 six months.¹⁵³

Level 1++

10.1.2.2 An additional single blind RCT (N=42) was identified comparing oral food supplementation in additional to a NHD with patients receiving NHD only. The mean age was 79 yrs. The follow-up was 12 weeks.¹⁵⁴

Level 1+

10.1.3. Health Economic methodological introduction

10.1.3.1 No papers were identified.

10.1.4. Clinical evidence statements

Mortality & disability
10.1.4.1 There were no statistical differences in the mortality rate as measured by Kaplan-Meier survival curves or disability on the modified Rankin Scale between the patients who received a NHD plus supplementation compared with those on a NHD (NS).\textsuperscript{153}

Level 1++

10.1.4.2 The remaining study reported no statistical differences between the two groups for mortality or disability (Barthel score) (NS).\textsuperscript{154}

Level 1+
**In-hospital complications**

10.1.4.3 There were no hospital complications thought to be related to intervention.\(^{153}\).  
Level 1++

**Discharge destination and length of hospital stay**

10.1.4.4 Both studies reported no significant differences in the discharge destination (NS) or the length of hospital stay.\(^{153},^{154}\)  
Level 1+

**Quality of life (EuroQol)**

10.1.4.5 There were no significant differences between the treatment groups on the EuroQol, mobility, self-care, usual activities, pain/discomfort and anxiety/depression in the open label RCT (NS).\(^{153}\) The remaining study did not report on this outcome.\(^{154}\)  
Level 1+

**Weight gain**

10.1.4.6 One study reported on this outcome: no statistical differences between the two groups were found.\(^{154}\)  
Level 1+

**Adverse events**

10.1.4.7 There were no serious life-threatening events. One patient had petite mal fits thought to be related to the oral supplementation inhibiting the absorption of phenytoin.\(^{153}\) None were reported in the remaining study.\(^{154}\)  
Level 1+

**10.1.5. From evidence to recommendations**

10.1.5.1 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 review Potter et al\(^{155}\) of benefits of nutritional supplementation in malnourished elderly people. All stroke patients should be weighed regularly and have nutritional screening.

**10.1.6. Recommendations**

10.1.6.1 All hospital inpatients on admission and all outpatients at their first clinic appointment should be screened for malnutrition and
the risk of malnutrition. Screening should be repeated weekly for inpatients and when there is clinical concern for outpatients. (NICE Nutrition Support recommendation)\textsuperscript{156}

10.1.6.2 Screening should assess body mass index (BMI) and percentage unintentional weight loss and should also consider the time over which nutrient intake has been unintentionally reduced and/or the likelihood of future impaired nutrient intake. The Malnutrition Universal Screening Tool (MUST), for example, may be used to do this. (NICE Nutrition Support recommendation)\textsuperscript{156}

10.1.6.3 Screening for malnutrition and the risk of malnutrition should be carried out by healthcare professionals with appropriate skills and training. (NICE Nutrition Support recommendation)\textsuperscript{156}

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

10.2. Assessment of swallowing function

10.2.1. Clinical introduction

10.2.1.1 Dysphagia (swallowing difficulty) is common after acute stroke with reported incidence varying in different studies depending on definition but commonly quoted at around 40\%.\textsuperscript{157} 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 functionally, however, a proportion will have persistent abnormal swallowing physiology and aspiration at six months despite resuming oral intake.\textsuperscript{158} 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 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.\textsuperscript{16} 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 health care 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. Patients who fail a swallow screen should be referred for a more comprehensive swallowing assessment. This 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.

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

10.2.2. Clinical methodological introduction

*Accuracy of bedside swallowing assessment vs. video fluoroscopy vs. fiberoptic endoscopic*

10.2.2.1 Five studies were identified that reported the diagnostic of bedside swallowing assessment (BSA), video fluoroscopy (VF) and fiberoptic endoscopic evaluation of swallowing (FEES)\(^1\)\(^{159, 160, 161, 162, 163}\). One addition study was on a newly developed screening tool, the Guggling Swallowing Screen (GUSS)\(^1\)\(^{164}\). 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\(^1\)\(^{161, 162}\). Three studies investigated the reliability of BSA\(^1\)\(^{160, 161, 162}\). One study was excluded due to methodological limitations\(^1\)\(^{165}\). The GUSS was compared with FEES\(^1\)\(^{164}\).
10.2.2.2 One study (N=60) looked at the sensitivity and specificity of BSA for predicting aspiration on VF of swallowing. 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.

Level 1b++

10.2.2.3 One study (N=128) looked at the diagnostic accuracy of BSA compared with VF, and one the interobserver agreement for swallowing disorders and aspiration admitted to an acute stroke unit.

Level 1b++

10.2.2.4 A small study (N=49) compared BSA with FEES and a further study (N=20) reported the inter- and intra-judge reliability of a BSA.

Level 1b++

10.2.2.5 The GUSS (N=19 and N=30) is a simple stepwise bedside screen that assesses nonfluid 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.

Level 1b++

10.2.2.6 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 yrs).

Level 2+

10.2.2.7 One study included patients within 24 hrs of stroke onset and one seven days or less. The remaining three studies included patients up to six weeks post-stroke, but the significant majority were examined within two weeks.

Level 1b++

**Effect on clinical outcomes**

10.2.2.8 Overall, six studies were identified. Three studies compared patients with and without swallowing impairment using a bedside swallowing assessment (BSA), one a measurement scale and video fluoroscopy (VF) [Power] and two BSA and VF. Follow-up periods ranged from discharge to five years.

Level 3+
10.2.3. Health economic methodological introduction

10.2.3.1 No papers were identified.

10.2.4. Clinical evidence statements

Accuracy of bedside swallowing assessment vs. video fluoroscopy vs. fiberoptic endoscopic
Bedside swallowing assessment (BSA) and video fluoroscopy (VF)

10.2.4.1 One study on patients with acute stroke reported that BSA under estimated the frequency of dysphagia and over estimated the frequency of aspiration when compared with VF. The table below reports the data for any clinical evidence of dysphagia or aspiration \( ^{159} \).

Level 1b++

10.2.4.2 Two studies reported on the accuracy of a BSA at predicting aspiration on VF \( ^{161} \), \( ^{162} \), one of these was a follow-up study \( ^{162} \). Only the results of a global judgement of aspiration from the 3-oz swallow test are reported here (see table 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 \( ^{162} \).

Level 1b++

<table>
<thead>
<tr>
<th></th>
<th>Incidence on VF</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>82/128 (64%)</td>
<td>73% (62 to 82%)</td>
<td>89% (76 to 96%)</td>
<td>92% (83 to 97%)</td>
<td>65% (52 to 77%)</td>
</tr>
<tr>
<td>Mann et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td>28/128 (22%)</td>
<td>93% (76 to 99%)</td>
<td>63% (53 to 72%)</td>
<td>41% (29 to 54%)</td>
<td>97% (89 to 100%)</td>
</tr>
<tr>
<td>McCullough et al. (2001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td>22/60 (37%)</td>
<td>68%¹  77%²</td>
<td>82%  63%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>McCullough et al. (2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td>43/165 (26%)</td>
<td>54%³  89%</td>
<td>62%  86%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR Not reported ¹ Spontaneous cough on trial swallow ² Overall estimate of aspiration. No other signs of measures met the criteria for sensitivity of specificity (60% or more) \( ^{161} \). ³ Global measure of aspiration \( ^{162} \).

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

10.2.4.4 The accuracy of BSA was sensitivity 86%, specificity 30%, positive predictive value 73% and negative predictive value 73%. These results indicate that BSA under estimated aspiration risk when compared with FEES and over estimated aspiration risk in patients who did not exhibit aspiration risk 163.

Level 1b++

**GUSS compared with FEES**

10.2.4.5 The table 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>
<thead>
<tr>
<th>GUSS</th>
<th>FEES, highest score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspiration risk, PAS (5 to 8)</td>
</tr>
<tr>
<td>First sample (N=19)</td>
<td>Aspiration risk (0 to 14)</td>
</tr>
<tr>
<td></td>
<td>No aspiration risk (15 to 20)</td>
</tr>
<tr>
<td>Second sample (N=30)</td>
<td>Aspiration risk (0 to 14)</td>
</tr>
<tr>
<td></td>
<td>No aspiration risk (15 to 20)</td>
</tr>
</tbody>
</table>

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

**Inter- and intra- judge reliability**

10.2.4.7 Four studies study reported on the reliability of a BSA 159, 160, 161, 162.

Level 1b++

10.2.4.8 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\textsuperscript{159}.

Level 1b++

10.2.4.9 The inter- and intrajudge reliability for a 3-oz swallow test and an overall measure of the presence or absence of aspiration was good (significant Kappa measure)\textsuperscript{161}; McCullough, 2005 2531 /id}. Inter- and intrajudge reliability for relating the presence of absence of aspiration from VF was significant\textsuperscript{161}. An additional study reported relatively low intrajudge reliability between two speech-language pathologists on the 3-oz swallow and an overall rating of dysphagia but good interjudge reliability\textsuperscript{160}.

Level 1b++

10.2.4.10 The interrater reliability of the GUSS performed by two ‘therapists’ with a maximum of two hours between the two assessments (first sample N=19) was excellent\textsuperscript{164}.

Level 1b++
Effect on clinical outcomes

10.2.4.11 Overall, swallowing impairments were associated with increased mortality [Power] \(^{167, 169, 166}\). Three studies reported that a statistically higher proportion of patients with aspiration compared to those without had an episode of pneumonia or a chest infection [Power]; \(^{167, 170}\). 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 [Power]. Three studies reported an association with measures of disability and dysphagia \(^{167, 169, 166}\).

Level 2+

10.2.4.12 Two studies reported that dysphagia was statistically associated with a longer stay in hospital [Power]; \(^{167}\). Two studies reported that one patients with dysphagia were statistically more likely to be discharged to institutional care \(^{167}\) or were living in a nursing home at a follow-up \(^{169}\).

Level 2++

10.2.4.13 In four studies, multivariate analysis reported that dysphagia or swallowing impairment at baseline was an independent predictor of outcome, namely mortality \(^{168, 166, 167}\), disability \(^{166}\), chest infection \(^{158}\).

Level 2++

10.2.5. From evidence to recommendations

10.2.5.1 Swallow screening is useful in determining early management of feeding after stroke, however, but 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.

10.2.5.2 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.

10.2.5.3 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.

10.2.5.4 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.

10.2.5.5 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 that it is commenced as soon as possible. There was concern from the group that the recommendation was based on relatively little evidence.

10.2.6. Recommendations

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

10.2.6.2 People with acute stroke for whom the admission screen indicates problems with swallowing should have a specialist assessment of swallowing early after stroke.

10.2.6.3 People with suspected aspiration on specialist assessment or who require tube feeding or dietary modification for 3 days should then be re-assessed and be considered for instrumental examination.

10.3. Timing of feeding by nasogastric and percutaneous endoscopic gastrostomy / jejunostomy tubes

The GDG felt that early was defined as preferably within 24 hours of, and no more than 72 hours after, admission.
10.3.1. Clinical introduction

10.3.1.1 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 nasogastric or percutaneous endoscopic gastrostomy/jejunostomy (PEG/PEJ) 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. 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.

10.3.1.2 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.

10.3.2. Clinical methodological introduction

Early versus late initiation of tube feeding

10.3.2.1 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 follow-up period was a median 6.5 months for the avoid tube feeding and 6.8 months in the early tube feeding.

Level 1++

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

10.3.2.2 Two studies were identified which addressed the question of whether NG compared with PEG is associated with reduced mortality and morbidity. One of these was excluded due to methodological limitations.

Level 1++

10.3.2.3 The included study was an open label RCT (N=321) on patients admitted to hospital with a first or recurrent within seven
days of stroke onset. The RCT compared feeding by nasogastric (NG) with percutaneous endoscopically guided gastrostomy (PEG). Patients could be randomized up to 30 days of hospital admission. Patients were followed-up at six months by a person blinded to the intervention they had received.\(^{153}\)

Level 1++

10.3.3. Health economic methodological introduction

10.3.3.1 No papers were identified.

10.3.4. Clinical evidence statements

**Early versus late initiation of tube feeding**

*Mortality and disability*

10.3.4.1 There were no significant differences between the two groups in terms of mortality or death or poor outcome combined (modified Rankin Scale 3 to 5) (NS)\(^{153}\). There was no statistical difference between the two groups on the Kaplan-Meier survival curves (NS)\(^{153}\).

Level 1++

*In-hospital complications*

10.3.4.2 There was a statistically higher proportion of gastrointestinal haemorrhages in the early tube group compared with the avoid tube group\(^{153}\).

Level 1++

*Discharge destinations*

10.3.4.3 There was no statistical difference between the groups on discharge destinations (NS) or residence at final follow-up (NS)\(^{153}\).

Level 1++

*Quality of life (EuroQol)*

10.3.4.4 There was no statistical difference between the two groups on a measure of quality of life (NS)\(^{153}\).

Level 1++

*Adverse events*

10.3.4.5 There were no apparent differences in the number of recorded adverse events between the two groups, but statistical analyses were not performed\(^{153}\).

Level 1++
Nasogastric (NG) vs. percutaneous endoscopically-guided gastrostomy (PEG)

**Mortality and disability**

10.3.4.6 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.

Level 1++

**In-hospital complications**

10.3.4.7 There was a significantly higher incidence in the number of gastrointestinal haemorrhages in the NG group compared with the PEG group.

Level 1++

**Discharge destinations**

10.3.4.8 There was no statistical difference between the groups on discharge destinations (NS) or residence at final follow-up (NS).

Level 1++

**Quality of life**

10.3.4.9 There was no statistical difference between the two groups on a measure of quality of life (NS).

Level 1++

**Adverse events**

10.3.4.10 There were no apparent differences between the two groups in terms of the number of adverse events reported, but no statistical analyses were performed.

Level 1++

10.3.5. From evidence to recommendations

10.3.5.1 The 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.

10.3.5.2 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.

10.3.5.3 Better functional outcomes were associated with feeding via NG tube than PEG tube. 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 PEG should be the intervention of choice if it is impractical to use a NG tube.

10.3.6. Recommendations

10.3.6.1 People with acute stroke who are unable to take adequate nutrition and fluids orally should receive early*** tube feeding with a NG tube.

11. Mobilisation

11.1. Early mobilisation and optimum positioning in people with acute stroke

11.1.1. Clinical introduction

11.1.1.1 Mobilisation of patients is a cornerstone of modern acute stroke care. Although most therapy interventions have not been subjected to randomised control 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\(^1\), 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.\(^2\) The details of the interventions most likely to improve outcome are not known, and the time at which early mobilisation should start is unclear.

11.1.1.2 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.

*** The GDG felt that early was defined as within 24 hours of admission.
11.1.2. Clinical methodological introduction

Early mobilisation

11.1.2.1 Two single-blind RCTs were identified that looked at the association between early mobilisation and morbidity or mortality.

11.1.2.2 One study from China evaluated physiotherapy initiated within one week of stroke onset. The intervention consisted of one 45 min session a day, five days a week for a total of four 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 patients (35.9%) of patients were lost to follow-up in the physiotherapy arm.

Level 1+

11.1.2.3 One study 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 hrs per day in the early intense and later less-intense traditional therapy respectively.

Level 1+
Positioning patients

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

Level 3

11.1.2.5 The studies were highly variable with respect to design, interventions and outcomes.

11.1.3. Health economic methodological introduction

11.1.3.1 No papers were identified.

11.1.4. Clinical evidence statements

Early mobilisation

Activities of daily living

11.1.4.1 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 early therapy. At six months this difference was no longer significant (NS).

Level 1+

Gait velocity

11.1.4.2 The study on gait training reported at six 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 three and six months post stroke.

Level 1+

Functional scores

11.1.4.3 Both studies reported no statistical differences between the interventions on 'functional' outcomes e.g., the Fugl-Meyer Score (NS); Richards, 1993 2579.

Level 1+

Positioning patients

Oxygen desaturation
11.1.4.4 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 statistical 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 statistically associated with decreased oxygen saturation 175.

Level 3

**Upper airway obstruction**

11.1.4.5 In a study on prevalence of upper airway obstruction in the first 24 hrs 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) 176.

Level 3

**11.1.5. From evidence to recommendations**

11.1.5.1 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 DVT’s, early access to water and fluids (thus improving hydration) and access to nutrition. The consensus was that these potential advantages out weighed 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.

11.1.5.2 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 mobilisation 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**

11.1.6.1 People with acute stroke should be mobilised as soon as possible following an assessment (e.g. sitting balance and falls
12. Avoidance of complications

12.1. Aspiration pneumonia

12.1.1. Clinical introduction

12.1.1.1 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.

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

12.1.2. Clinical methodological introduction

12.1.2.1 One RCT was identified that compared acute stroke patients within three 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. Level 1+

12.1.2.2 The patient population had a mean age of 77 yrs. 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 focal folds.
12.1.2.3 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**

12.1.3.1 No papers were identified.

**12.1.4. Clinical evidence statements**

*End point of no thin aspiration*

12.1.4.1 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)\(^{177}\).

Level 1+

*Daily intake of liquids*

12.1.4.2 Patients on thickened liquids only had a statistical higher intake of thickened liquids compared to those on thickened liquids with additional water\(^{177}\).

Level 1+

*Follow-up videofluoroscopic evaluations*

12.1.4.3 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)\(^{177}\).

Level 1+

*Complications*

12.1.4.4 No patients developed pneumonia, dehydration, or complications during the course of the study or at 30 day follow-up\(^{177}\).

Level 1+

**12.1.5. From evidence to recommendations**

12.1.5.1 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 there insufficient evidence on which a recommendation could be made.

12.1.6. Recommendations

12.1.6.1 No recommendation was made by the group.

13. Surgery for people with acute stroke

13.1. Surgical referral for acute intracerebral haemorrhage

13.1.1. Clinical introduction

13.1.1.1 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 over 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. This is likely to be due to anti-thrombotic 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. 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 anti-coagulation 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

13.1.2.1 This question address 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†††

13.1.2.2 Two RCTs were identified that compared surgery with medical treatment for primary intracerebral haemorrhage (PICH) \(^{180, 181}\). One multicentre RCT, the International Surgical Trial in Intracerebral Haemorrhage (STICH) (N=1033), compared early surgery (N=503) (within 24 hrs of randomisation) plus medical treatment with initial conservative therapy (N=530) (medical treatment) although some patients went on to surgery later \(^{180}\). Eligibility criteria included CT evidence of a spontaneous PICH that had arisen in the past 72 hrs. Patients were admitted to the trial if the neurosurgeon felt there was equipoise regarding the benefits of either treatment.

Level 1++

13.1.2.3 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 hrs. Only univariate analyses were reported and this combined with the small sample size limits the generalisability of these results \(^{181}\).

Level 1+

13.1.3. Health economic methodological introduction

13.1.3.1 No papers were identified.

13.1.4. Clinical evidence statements

Mortality and function outcome

13.1.4.1 The STICH showed that the mortality rate at six months was not statistically different for the early surgery and conservative treatment (NS). On prognosis-based indices of the extended Glasgow outcome scale, there was no statistical difference between the early surgery and conservative treatment group.

††† Outcomes associated with surgery are reported for completeness
(NS). With the prognosis-based modified Rankin Scale, there was no statistical difference at six months when comparing the early surgery group with conservative treatment (NS) $^{180}$.

Level 1++

13.1.4.2 In the trial comparing endoscopic intervention with medical treatment, during the first week significantly fewer patients treated surgically died compared with those treated medically. 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 six months, the mortality rate was significantly lower in the surgically treated patients compared with those treated medically $^{181}$.

Level 1++

Clinical and demographic factors

13.1.4.3 The STICH showed that if the haematoma was 1cm or less from cortical surface, a significantly more unfavourable outcome was associated with early surgery compared with conservative management. 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) $^{180}$.

Level 1++

13.1.4.4 For the study on endoscopic intervention, surgery was associated with significantly lower mortality compared with medical treatment for the following factors: age < 60 yrs, haematoma > 50 cu cm; preoperative status of somnolent or alert and a subcortical haematoma $^{181}$.

Level 1+

13.1.4.5 For the study on endoscopic, surgery was associated with a significantly higher incidence of good outcome compared with medical treatment for the following factors: age < 60 yrs; haematoma <50 cu cm; preoperative status of somnolent or alert and a subcortical haematoma $^{181}$.

Level 1+
13.1.5. From evidence to recommendations

13.1.5.1 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 co morbidities, and patients with a Glasgow outcome scale (GCS) score of lower than 8 were unlikely to benefit from surgery. There were no RCT’s 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.

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

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

13.1.6. Recommendations

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

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

13.1.6.3 Previously fit people should be considered for surgical intervention following primary intracranial haemorrhage if they:

- have a lobar haemorrhage with hydrocephalus or
• are deteriorating neurologically.

13.1.6.4 People with any of the following rarely require surgical intervention and should receive medical treatment initially:
• small deep haemorrhages
• lobar haemorrhage without hydrocephalus or rapid neurological deterioration
• a large haemorrhage and significant prior comorbidities
• a GCS of less than 8.

13.2. Surgical referral for decompressive craniectomy

13.2.1. Clinical introduction

13.2.1.1 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%\(^{182}\) and usually presents within 2-5 days of stroke onset. It is commonest 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

13.2.2.1 Two studies were identified that addressed the question of which patients should be referred urgently for decompressive surgery\(^{183}, 184\).

13.2.2.2 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)\(^{184}\). All of the RCTs randomised patients to either surgery (N=51) or conservative management (N=42). Data was included only for patients aged 18 to 60 yrs treated within 48 hrs 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 cm³ on MRI. Exclusion criteria for the pooled analysis included a prestroke score on the modified Rankin Scale of ≤ 2 and a life expectancy of less than three years.

Level 1++

13.2.2.3 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 ¹⁸³. Patients were included if the infarct involved the MCA plus another vascular territory. A dictomotimised 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

13.2.3.1 No papers were identified.

13.2.4. Clinical evidence statements

Mortality and functional outcome

13.2.4.1 In the pooled analysis, at twelve months, surgery compared with conservative management was associated with a lower mortality rate. A smaller proportion of patients with a mRS of five or more or greater than three ¹⁸⁴.

Level 1++

13.2.4.2 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% ¹⁸³

Level 3

Prognostic indicators

13.2.4.3 For the pooled analysis of the RCT data, surgery was beneficial (mRS score of four or less) for the predefined subgroups of age (above or below 50 yrs), aphasia (above or below 24 hrs) and time to randomisation (above and below 24 hrs) ¹⁸⁴.

Level 1++

13.2.4.4 For the pooled analysis of the case series data, a significantly higher proportion of patients older than 50 years compared with those 50 yrs or less were severely disabled or dead after
surgery. The mortality rate was also significantly higher after surgery in patients older than 50 yrs compared with those 50 yrs or less. 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 hrs compared with those who underwent surgery after 24 hrs (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).

Level 3

13.2.5. From evidence to recommendations

13.2.5.1 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 study 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. The data from a large non randomised series suggested that outcome is substantially improved if treatment is initiated within 24 hour 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 referred immediately to a neurosurgical centre.

13.2.6. Recommendations

13.2.6.1 People with middle cerebral artery (MCA) infarction who meet all of the criteria defined 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 up to 60 years.
- 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 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 cm$^3$ as shown on MR with DWI.

13.2.6.2 People who are referred for decompressive hemicraniectomy should be monitored by appropriately trained professionals skilled in neurological assessment.
14. Research Recommendations

Does free access to water vs. withdrawal or oral modification of liquids prevent aspiration pneumonia following an acute stroke?

RCT to compare aspirin with other antiplatelet agents (e.g. modified release dipyridamole, clopidogrel) in acute ischaemic stroke

RCT to compare maintaining the same dose of aspirin in patients who have a stroke whilst on aspirin, versus increasing the dose.

What is the safety and efficacy of very early mobilisation after stroke delivered by appropriately trained professionals?

The safety and efficacy of the early manipulation of blood pressure after stroke should be evaluated.
APPENDICES
### Appendix A: Clinical question and search strategies

<table>
<thead>
<tr>
<th>Question ID</th>
<th>Question wording</th>
<th>Study Type Filters used</th>
<th>Databases and Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question ID</td>
<td>Question wording</td>
<td>Study Type Filters used</td>
<td>Databases and Years</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>PHAR6</td>
<td>What is the safety and efficacy of anticoagulants versus antiplatelet agents or placebo for patients with acute stroke who may require anticoagulation for co-morbidities (e.g. atrial fibrillation, prosthetic heart valve [mitral/aortic], deep vein thrombosis or pulmonary embolism)?</td>
<td>Systematic reviews, RCTs, Observational studies</td>
<td>Medline 1950-2007 Embase 1980-2007 Cinahl 1982-2007 Cochrane 1800-2007</td>
</tr>
</tbody>
</table>
| STAT1       | a)What is the safety and efficacy for patients with acute stroke (including haemorrhagic) of i) initiating statin therapy, ii) continuing statin therapy  
<p>| ADM1        | In patients with suspected stroke what are the benefits of being admitted to specialist care versus a non-specialised unit in terms of recovery time, morbidity and mortality?                                                                                           | Systematic reviews, RCTs, Observational studies | Medline 1950-2007 Embase 1980-2007 Cinahl 1982-2007 Cochrane 1800-2007 |</p>
<table>
<thead>
<tr>
<th>Question ID</th>
<th>Question wording</th>
<th>Study Type Filters used</th>
<th>Databases and Years</th>
</tr>
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<tbody>
<tr>
<td>IMAG1</td>
<td>After TIA which modality (MRI or CT) should be used?</td>
<td>Systematic reviews, RCTs, Observational studies</td>
<td>Medline 1950-2007 Embase 1980-2007 Cinahl 1982-2007 Cochrane 1800-2007</td>
</tr>
<tr>
<td>Question ID</td>
<td>Question wording</td>
<td>Study Type Filters used</td>
<td>Databases and Years</td>
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<tr>
<td>NUTRI1</td>
<td>In patients with acute stroke a) what is the accuracy of i) bedside swallowing assessment ii) video fluoroscopy iii) fibreoptic endoscopic evaluation of swallowing, and b) how do the results of these assessments affect clinical outcomes?</td>
<td>Systematic reviews, RCTs, Observational studies</td>
<td>Medline 1950-2007 Embase 1980-2007 Cinahl 1982-2007 Cochrane 1800-2007</td>
</tr>
<tr>
<td>NUTRI3</td>
<td>In patients with acute stroke, who are unable to take adequate fluids orally, does a) early versus late initiation of tube feeding, or b) nasogastric (NG) versus percutaneous endoscopically-guided gastrostomy (PEG) reduce mortality and morbidity?</td>
<td>Systematic reviews, RCTs, Observational studies</td>
<td>Medline 1950-2007 Embase 1980-2007 Cinahl 1982-2007 Cochrane 1800-2007</td>
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<tr>
<td>Question ID</td>
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NOTE: The final cut-off date for all searches was 31 October 2007
Appendix B: Scope and referral from the Department of Health

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

Guideline title

Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA).

Short title

Stroke

Background

a) The National Institute for Health and Clinical Excellence (‘NICE’ or ‘the Institute’) has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on acute stroke and TIA for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute’s clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

c) In parallel to the development of the Institute’s Acute Stroke and TIA clinical guideline the Royal College of Physicians’ Intercollegiate Stroke Working Party (ICSWP) will also be updating their guideline to focus on longer-term management and rehabilitation. The developers will work
closely with the ICSWP to ensure continuity and to avoid any overlapping or gaps.

d) The Department of Health are developing a National Stroke Strategy to be published in 2007. This will be addressing many of the issues regarding service models, structures and staffing. Where possible this guideline will work closely with the Stroke Strategy Project Executive.

e) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

**Clinical need for the guideline**

a) Stroke is the third most common cause of death in the UK, and one of the most important causes of significant adult disability. Each year in the UK, approximately 120,000 people have a first stroke, 30% of whom die within a month. In addition about 30,000 recurrent strokes occur. The risk of having a stroke before the age of 85 years is one in four for men, and one in five for women.

b) Stroke is a medical emergency and brain damage can be reduced if stroke is identified early enough.

c) Stroke and transient ischaemic attack (TIA) are very similar, the only difference being that the symptoms of TIA resolve completely within 24 hours, and stroke symptoms and signs persist. With refined sensitive imaging techniques it has been clearly shown that many people who have experienced a TIA have sustained significant permanent cerebral damage. TIA is not, therefore, a benign condition. Stroke and TIA management depends upon accurate diagnosis of the underlying pathology and aetiology.
d) The risk of stroke within the first month after a TIA can be as high as 32% for some patient groups. With effective diagnosis, investigation and treatment, many strokes could be prevented.

e) The recent National Audit Office report ‘Reducing brain damage: faster access to better stroke care’ identified major problems with the consistent delivery of high-quality stroke care to all patients in England. Evidence clearly demonstrating that stroke is both a preventable and treatable disease has accumulated rapidly over recent years, but health services have been slow to reflect this.

f) The National Sentinel Audit in 2006 covering all hospitals in England, Wales and Northern Ireland showed that 78% of hospitals have a neurovascular clinic and only 35% of these patients are seen within 7 days. Few hospitals had protocols agreed between the ambulance service and the acute trust to ensure rapid transfer of patients with stroke to casualty, and access to brain scans remains difficult for some particularly outside normal working hours.

g) The cost of stroke care is high, with an estimate in the National Audit Office report of £7 billion per year. Much of this is spent on providing longer-term healthcare, social services and financial support to people with residual disability. More effective acute treatment would save lives and money.

The guideline

a) The guideline development process is described in detail in two publications which are available from the NICE website (see ‘Further information’). ‘The guideline development process: an overview for stakeholders, the public and the NHS’ describes how organisations can become involved in the development of a guideline. ‘The guidelines manual’ provides advice on the technical aspects of guideline development.
This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

c) The areas that will be addressed by the guideline are described in the following sections.

**Population**

**Groups that will be covered**

a) Patients with transient ischaemic attacks (TIAs) or completed strokes, that is, an acute neurological event presumed to be vascular in origin and causing cerebral ischaemia, cerebral infarction or cerebral haemorrhage. This includes:

- first and recurrent events
- thrombotic and embolic events
- primary intracerebral haemorrhage of any cause, including venous thrombosis

**Groups that will not be covered**

a) Specific issues relating to the general management of underlying conditions will not be considered, but the immediate management to reduce the extent of brain damage will be included.

b) Subarachnoid haemorrhage

c) Children (16 and under)

**Healthcare setting**

Primary and secondary NHS healthcare settings, including referral to tertiary care.

Pre-hospital emergency care settings, including ambulance services..


**Clinical management**

The purpose of the guideline is to describe the initial and early management (without specifying a fixed time) aimed at reducing the ischaemic brain damage, and in the case of TIA’s, preventing subsequent stroke.

a) The rapid recognition of symptoms and diagnosis

b) Initial and early management of stroke and TIA

c) Diagnostic procedures aimed to delineate the nature and location of the pathology

d) Treatment interventions that aim to minimise the pathology

e) Management and maintenance of homeostasis (including fluids, nutrition and oxygen therapy)

f) Initial and early pharmacotherapies including thrombolysis. (Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use the ‘Summary of product characteristics’ to inform their decisions for individual patients.)

g) Management of complications where these are likely to affect the area of brain damage (for example, the early use of anticoagulants for venous thrombo-embolism in acute stroke).

h) Non-pharmacological management, including the role of early mobilisation and positioning

i) Indications for referral for specific interventions (for example, carotid angioplasty, carotid endarterectomy).

j) Identification of people who need continuing or early anticoagulation,
Status

Scope

This is the final version of the scope. It has been out for consultation, modified in response to comments received and signed off by one of NICE’s independent Guidelines Review Panels.

The guideline will incorporate the following technology appraisals:


Guideline

The development of the guideline recommendations will begin in November 2006.

Further information

Information on the guideline development process is provided in:

- The guideline development process: an overview for stakeholders, the public and the NHS.

- The guidelines manual.

These booklets are available as PDF files from the NICE website ([www.nice.org.uk/guidelinesmanual](http://www.nice.org.uk/guidelinesmanual)). Information on the progress of the guideline will also be available from the website.
Referral from the Department of Health

The Department of Health asked the Institute:

‘To prepare a clinical guideline on the diagnosis and acute management of stroke and transient ischaemic attack, concentrating on initial treatment.’
Appendix C: Model to determine the cost-effectiveness of immediate specialist assessment in a stroke unit compared to specialist assessment at a weekly clinic or no specialist assessment

**Questions:**
ASM 1 What is the accuracy of a pre-hospital health professional assessment tool/checklist for identifying signs and symptoms of suspected stroke/TIA?

ASM 2 How accurately do scoring systems predict which patients with suspected TIA need to be referred urgently to a specialist assessment?

ASM 3 In patients with a suspected minor stroke/TIA, does early versus late expert assessment reduce mortality or morbidity?

ADM 2 Does rapid admission to a hyperacute stroke unit reduces mortality, morbidity and length of hospital stay?

**Background:**
The risk of developing a stroke after hemispheric TIA can be as high as 30% within the first month, with the greatest risk being within the first 72 hours.‡‡‡ It is considered that effective management of patients with TIA or minor stroke requires identification of individuals at the highest risk and then appropriate early intervention. 185

The ABCD² score aims to identify individuals at high-risk of stroke and who may require emergency intervention. The score is based on known clinical predictors of stroke:

- **Age**
  - < 60 years=0
  - ≥ 60=1

- **BP**
  - systolic ≤140mm Hg and/or diastolic ≤90 mm Hg=0
  - systolic >140 mm Hg and/or diastolic >90mm Hg =1

- **clinical features**
  - unilateral weakness=2
  - speech disturbance without weakness=1
  - other symptom=0

- **duration of symptoms**
  - <10 mins =0

The subgroup of patients with carotid stenosis account for the highest proportion of early recurrent strokes. Carotid endarterectomy reduces the risk of stroke in patients with recently symptomatic stenosis. For neurologically stable patients with TIA and minor stroke, benefit from endarterectomy is greatest if performed within 2 weeks of the event and falls rapidly with increasing delay.\textsuperscript{186}

**Aim:**
Population: Patients with a TIA or minor stroke identified by a GP, in the A&E, or by an ambulance crew.

To evaluate the relative cost-effectiveness of assessing TIA or minor stroke patients:
- immediately at a specialist stroke unit’ or
- within 7 days at a weekly specialist stroke unit clinic, or
- by the patient’s GP.

We assess cost-effectiveness of each strategy both for all minor stroke / TIA patients but also broken down by ABCD\textsuperscript{2} score group.

**General methods:**
The cost-effectiveness of the different strategies was estimated using a simple decision analysis.

The NICE reference case was followed:
- Costs are measured from the perspective of the NHS and personal social services (PSS) perspective 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). Where one QALY is equal to one year of full health (or two years at half health, etc).
- A 3.5\% discount rate was applied to both costs and effects. The discount rate reflects that people prefer to receive a benefit earlier and to incur a cost later, even in a world with zero inflation and no bank interest\textsuperscript{187}.

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.\textsuperscript{37}.

**The model:**
A decision tree is used to represent the model (Figure 1, Figure 2, Figure 3).

The decision model seeks 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>=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 life time.

The effect of different treatment strategies is first modelled in terms of effect on stroke incidence. Patients are then divided in to 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 health care 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.
Figure 1: Decision tree arm for no specialist assessment
Figure 2: Decision tree arm for specialist assessment at a weekly clinic (the positive and negative scan results include true and false results)
DRAFT FOR CONSULTATION

Figure 3: Decision tree arm for immediate specialist assessment (the positive and negative scan results include true and false results)
Age/sex distribution of TIAs and stroke mimics
The incidence of TIAs and minor strokes in a population of 500,000 people was reported in Wardlaw et al. which used data from the Oxford Vascular Study (OXVASC) data.

Table 1: Wardlaw et al. Expected number of TIAs and minor strokes per annum in a standard population of 500,000 people.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>55-64</th>
<th>65-74</th>
<th>75-84</th>
<th>≥85</th>
<th>Total</th>
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<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.5 (5%)</td>
<td>66.3 (14%)</td>
<td>63.4 (13%)</td>
<td>25.7 (5%)</td>
<td>177.9 (36%)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.1 (6%)</td>
<td>65.3 (13%)</td>
<td>130.7 (27%)</td>
<td>86 (18%)</td>
<td>312.1 (64%)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>52.3 (11%)</td>
<td>131.7 (27%)</td>
<td>194.2 (40%)</td>
<td>111.6 (23%)</td>
<td>490</td>
</tr>
</tbody>
</table>

The base case for this model assumes that all patients have a TIA or a minor stroke. The GDG felt this was unlikely to be the situation in practice as a high proportion of patients suspected as having a TIA would be being discharged when found to have a TIA mimic. TIA mimics include epilepsy, migraines and brain tumours. The impact of these additional patients will be explored by doubling the cost of initial assessment in each strategy to reflect a ratio of 1:1 of patients with actual TIA or minor stroke to stroke mimics who are discharged without further treatment for stroke prevention.

Incidence of stroke after TIA
Johnston et al (2007) reported the incidence of stroke up to 90 days after a TIA, by ABCD² score (Table 2). They had reviewed the evidence from six cohorts of patients from the England and the USA totalling 4799 patients. Taking the aggregate figures across all six cohorts we estimated stroke rates (Table 2) for each ABCD² score group using the following formula:

\[ m = \frac{1}{t} \ln \left( \frac{S}{S_0} \right) \]

Where t is the number of days of follow-up since the TIA, S=the number of patients who survived the follow-up period without a stroke and S₀=the total number of patient in the group.

Table 2: Stroke incidence after TIA, by ABCD² score

| ABCD² score | All Stroke by day 2 Stroke by day 7 Stroke by day 90 Stroke rate days 1-2 Stroke rate days 3-7 Stroke rate days 8-90 |
|-------------|----------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 0           | 47 0 0 0                                              | 0.00%                          | 0.00%                          | 0.00%                          |
| 1           | 191 0 0 4                                             | 0.00%                          | 0.00%                          | 0.03%                          |
| 2           | 543 7 8 17                                           | 0.65%                          | 0.30%                          | 0.04%                          |
| 3           | 847 10 12 29                                         | 0.59%                          | 0.29%                          | 0.04%                          |
| 4           | 1165 41 60 93                                        | 1.79%                          | 1.10%                          | 0.11%                          |
Accuracy of carotid ultrasound scan

It was assumed that all patients assessed at a specialist stroke unit will have a carotid ultrasound scan (U/S).

- If the scan is positive (carotid stenosis ≥50%) patients will have surgery (endarterectomy) in addition to medical treatment.

- If the carotid scan is negative (carotid stenosis<50%), patients will be treated with medical treatment alone.

Wardlaw et al. 37 reported that 10% of all patients with TIAs had a carotid stenosis level of 50-99% (using NASCET criteria) which should be treated with surgery.

**Table 3: Wardlaw et al. 37 Distribution of patients with TIA and minor stroke between stenosis bands**

<table>
<thead>
<tr>
<th>Stenosis level</th>
<th>% of all TIAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-99%</td>
<td>6%</td>
</tr>
<tr>
<td>50-69%</td>
<td>4%</td>
</tr>
<tr>
<td>0-49%, 100%</td>
<td>90%</td>
</tr>
</tbody>
</table>

The sensitivities and specificities of U/S for detecting carotid stenosis were also reported by Wardlaw et al. 37. Surgery is recommended for patients with a stenosis level of ≥50%. Wardlaw et al. also reported the distribution of misdiagnosis by band, which is shown in Table 5: Misdiagnosis distribution for ultrasound by stenosis level.

**Table 4: Sensitivity and Specificity of ultrasound by stenosis level 37**

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-99%</td>
<td>0.89 (0.85 to 0.92)</td>
<td>0.84 (0.77 to 0.89)</td>
</tr>
<tr>
<td>50-69%</td>
<td>0.36 (0.25 to 0.49)</td>
<td>0.91 (0.87 to 0.94)</td>
</tr>
<tr>
<td>0-49%</td>
<td>0.83 (0.73 to 0.90)</td>
<td>0.84 (0.62 to 0.95)</td>
</tr>
</tbody>
</table>

**Table 5: Misdiagnosis distribution for ultrasound by stenosis level 37**

<table>
<thead>
<tr>
<th>Misdiagnosed stenosis band</th>
<th>0-49%</th>
<th>50-69%</th>
<th>70-99%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-49%</td>
<td>N/A</td>
<td>0.24</td>
<td>0.13</td>
</tr>
<tr>
<td>50-69%</td>
<td>0.36</td>
<td>N/A</td>
<td>0.87</td>
</tr>
<tr>
<td>70-99%</td>
<td>0.64</td>
<td>0.76</td>
<td>N/A</td>
</tr>
</tbody>
</table>

The associations between the ABCD² score and presence of carotid stenosis ≥50% were studied by Koton and Rothwell, but no clear relationship was found. Wardlaw et al. reported a 0.53% relative risk of stroke in patients with stenosis level <70% compared to ≥70% 37. By using this relative risk and
keeping the proportion of patients with ≥70% stenosis constant in each group (6%), we were able to estimate stroke risk by both ABCD² score and stenosis level as follows:

Table 6: Baseline stroke risk, by ABCD² score and level of stenosis

<table>
<thead>
<tr>
<th>ABCD² Score</th>
<th>All (see Table 2)</th>
<th>Stenosis&gt;=70</th>
<th>Stenosis&lt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroke rate days 1-2</td>
<td>Stroke rate days 3-7</td>
<td>Stroke rate days 8-90</td>
</tr>
<tr>
<td>0</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
<tr>
<td>1</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.03%</td>
</tr>
<tr>
<td>2</td>
<td>0.65%</td>
<td>0.30%</td>
<td>0.04%</td>
</tr>
<tr>
<td>3</td>
<td>0.59%</td>
<td>0.29%</td>
<td>0.04%</td>
</tr>
<tr>
<td>4</td>
<td>1.79%</td>
<td>1.10%</td>
<td>0.11%</td>
</tr>
<tr>
<td>5</td>
<td>2.47%</td>
<td>1.49%</td>
<td>0.17%</td>
</tr>
<tr>
<td>6</td>
<td>4.41%</td>
<td>2.77%</td>
<td>0.29%</td>
</tr>
<tr>
<td>7</td>
<td>3.23%</td>
<td>2.41%</td>
<td>0.37%</td>
</tr>
<tr>
<td>All</td>
<td>2.00%</td>
<td>1.19%</td>
<td>0.13%</td>
</tr>
</tbody>
</table>

Effectiveness of Carotid Endarterectomy
The table 7 below gives the absolute risk reduction in stroke or death for patients having surgery compared to medical treatment by time to surgery and stenosis level.

Table 7: Absolute risk reduction per 100 patients with surgery in 5-year actuarial risk of ipsilateral carotid ischemic stroke and any stroke or death within 30 days after trial surgery from the pooled analysis of the RCTs 39.

<table>
<thead>
<tr>
<th>Factor</th>
<th>50 to 69% stenosis</th>
<th>≥ 70% stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since last event</td>
<td>Surgical vs medical (ARR; 95%CI)</td>
<td>Surgical vs medical (ARR; 95%CI)</td>
</tr>
<tr>
<td>(weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>17/158 vs 34/150</td>
<td>23/167 vs 54/149</td>
</tr>
<tr>
<td></td>
<td>(14.8; 6.2 to 23.4)</td>
<td>(23.0; 13.6 to 32.4)</td>
</tr>
<tr>
<td>2 to 4 weeks</td>
<td>21/135 vs 20/110</td>
<td>10/133 vs 24/105</td>
</tr>
<tr>
<td></td>
<td>(3.3; -6.3 to 13.0)</td>
<td>(15.9; 6.6 to 25.2)</td>
</tr>
</tbody>
</table>

In the base case analysis it was assumed that 80% of patients who were assessed immediately and had a stenosis level of ≥50% would have surgery within 2 weeks of their TIA. For patients having specialist assessment at a weekly clinic, only 25% were assumed to have surgery within 2 weeks. All other patients with a stenosis level of ≥50% would have surgery from 2 to 4 weeks after their TIA.
These were tested in a sensitivity analysis. For immediate assessment, 50% to 100% of surgery would happen within 2 weeks of TIA. For assessment at a weekly clinic, 0 to 50% of surgery would happen within 2 weeks of TIA.

**Effectiveness of medical treatment**

The following data was based on the QRESEARCH database that was supplied for a modelling project being carried out in Birmingham. This data was drawn from 463 practices which use the EMIS clinical system (most common (>50%) primary care computer system)\(^{189}\). It shows that most patients are prescribed aspirin but only a small proportion of patients are prescribed appropriate combination medication post-TIA.

**Table 8 Prescriptions given by a GP at 1 month following a TIA (3366 people were coded as suffering a TIA)**

<table>
<thead>
<tr>
<th>Drug prescribed or over the counter</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelets/anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2144 (64%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>171 (5%)</td>
</tr>
<tr>
<td>Statins</td>
<td>1244 (37%)</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide</td>
<td>585 (17%)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme (ACEI)</td>
<td>672 (20%)</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker (ARB)</td>
<td>174 (5%)</td>
</tr>
<tr>
<td><strong>Combinations</strong></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agent/warfarin + statin + ACEI + thiazide*</td>
<td>153 (5%)</td>
</tr>
<tr>
<td>Antiplatelet agent/warfarin + statin + any hypertensive</td>
<td>742 (22%)</td>
</tr>
</tbody>
</table>

*gold standard

Wardlaw et al.\(^{37}\) included relative risk reductions associated with various drugs given as treatment for TIA or minor stroke (Table 9). We assumed that all three groups would benefit from aspirin, but our baseline risk data (Table 2 and Table 6) almost certainly already accounts for aspirin use. Our treatment effect is therefore a 15% reduction in the 90-day stroke risk for patients being assessed by specialists due to prescribing of dipyridamole. Patients going immediately to the specialist clinic get this benefit from day 1, whereas patients being sent to the weekly clinic are assumed to get this effect from day 4.

**Table 9 Wardlaw et al.\(^{37}\) Risk of stroke in medically-treated patients by time after TIA or minor stroke and stenosis band.**

<table>
<thead>
<tr>
<th>Time since initiation of medical therapy</th>
<th>Reduction in stroke risk</th>
<th>Drugs assumed to affecting risks</th>
</tr>
</thead>
</table>

\(^{555}\) QRESEARCH relies on GP Read codes and so are representative of people thought to have had a TIA in primary care – roughly half referred to specialist clinics with suspected TIA (OXVASC) are subsequently thought to have had a TIA.
<3 months 15% dipyridamole  
<3 months 33% Aspirin and dipyridamole  
3-6 months 25% Aspirin and dipyridamole  
6-12 months 47% Aspirin, dipyridamole and blood pressure-lowering drugs  
1 year and beyond 55% Aspirin, dipyridamole, blood pressure-lowering drugs and lipid-lowering drugs

**Stroke-related health status**

The outcome of a stroke occurring less that 90 days after a first TIA (Table 10) was taken from the Express study (personal communication from Peter Rothwell). A low Rankin score (0-2) was considered an independent health state. A higher score (3-5) was considered a dependent state requiring long-term nursing care.

**Table 10: Outcome of stroke within 90 days of first TIA**

<table>
<thead>
<tr>
<th>Health State</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent after stroke</td>
<td>11 (29%)</td>
</tr>
<tr>
<td>Independent after stroke</td>
<td>18 (47%)</td>
</tr>
<tr>
<td>Dead</td>
<td>9 (24%)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td><strong>38 (100%)</strong></td>
</tr>
</tbody>
</table>

**Life Expectancy**

The life expectancy was derived from data for the general population in England & Wales from the Office for National Statistics for 2003-2005. Based on the age-sex profile of patients (Table 1) the average life expectancy for a TIA patient who does not have a follow-up stroke within 90 days was estimated to be 10.8 years. It was assumed that a TIA patient who had a stroke which resulted in an independent health state would have half the life expectancy, 5.4 years. If the stroke resulted in a dependent health state then their life expectancy would be a third, 3.6 years.

**Utilities**

Utilities are the name given to generic measures of (health-related) quality of life measured on 0-1 scale. Health-related utilities scores are on a scale from 0 to 1, with 0 representing death and 1 representing perfect health. The utilities used in this model relate to each stroke-related health state and were taken from Wardlaw et al. 37

**Table 11: Utility scores for each outcome for the model**

<table>
<thead>
<tr>
<th>Health State</th>
<th>Utility score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent after a stroke</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Calculation of QALYs
For each stroke-related outcome the utility value was multiplied by the corresponding life expectancy to calculate the number of QALYs (Table 12). The QALYs were then discounted by 3.5% per year. Since we did not have data on stroke incidence up to 5 years for all patient groups, the QALYs gained attributable to averting strokes due to surgery were calculated separately but in the same manner (Table 13).

Table 12: Calculation of QALYs, based on stroke outcome within 90 days of TIA

<table>
<thead>
<tr>
<th>Health state at 90 days</th>
<th>Utility</th>
<th>Life expectancy</th>
<th>QALYs</th>
<th>Discounted QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>dependent after a stroke within 90 days</td>
<td>0.31</td>
<td>3.6</td>
<td>1.116</td>
<td>1.06</td>
</tr>
<tr>
<td>independent after a stroke with 90 days</td>
<td>0.71</td>
<td>5.4</td>
<td>3.834</td>
<td>3.54</td>
</tr>
<tr>
<td>fully recovered after TIA / no stroke at 90 days</td>
<td>0.88</td>
<td>10.8</td>
<td>9.504</td>
<td>8.05</td>
</tr>
<tr>
<td>fatal stroke by 90 days / surgical death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 13: Calculation of QALYs gained from surgery, based on averting strokes up to 5 years

<table>
<thead>
<tr>
<th>Type of stroke averted</th>
<th>Life expectancy</th>
<th>LE - no stroke</th>
<th>LYG</th>
<th>Utility - no stroke</th>
<th>QALYs gained</th>
<th>Discounted QALYs gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>dependent after a stroke</td>
<td>1.6</td>
<td>8.8</td>
<td>7.2</td>
<td>0.88</td>
<td>6.336</td>
<td>3.95</td>
</tr>
<tr>
<td>independent after a stroke</td>
<td>3.5</td>
<td>8.8</td>
<td>5.3</td>
<td>0.88</td>
<td>4.664</td>
<td>2.66</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0</td>
<td>8.8</td>
<td>8.8</td>
<td>0.88</td>
<td>7.744</td>
<td>6.31</td>
</tr>
</tbody>
</table>

Costs
The cost of assessment at a stroke unit was taken from costs for a one-stop TIA clinic, which includes staffing, overhead costs, imaging and labs. A range of costs were collected from various centres in the UK to be used to develop a new unit cost for the department of health. The highest cost reported was used for immediate assessment (£410) and the mean cost was used for a weekly clinic (£316). These costs were varied in the probabilistic sensitivity analysis and the cost of immediate assessment at a stroke unit was doubled in a one-way sensitivity analysis. It was assumed that a patient who did not receive specialist assessment would have two GP consultations within the first month, at £25 per 10 minute consultation.

Table 14: Costs of one-stop TIA clinics in the UK
<table>
<thead>
<tr>
<th>Specialist assessment costs</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate - daily clinic</td>
<td>£410</td>
</tr>
<tr>
<td>Weekly clinic</td>
<td>£316</td>
</tr>
<tr>
<td>GP clinic</td>
<td>£50</td>
</tr>
</tbody>
</table>

Table 15: Costs of surgery and outcomes of stroke by dependency

<table>
<thead>
<tr>
<th>Cost of Endarterectomy *</th>
<th>Mean</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£3,442</td>
<td>£2,525</td>
<td>£4,360</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke (dependent health state) unit cost for first year of treatment **</th>
<th>Mean</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£22,255</td>
<td>£16,691</td>
<td>£27,819</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>rehabilitation cost per year for dependent health state (subsequent years)</th>
<th>Mean</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£11,292</td>
<td>£8,469</td>
<td>£14,115</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke (independent health state) unit cost for first year of treatment</th>
<th>Mean</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£3,716</td>
<td>£2,787</td>
<td>£4,645</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>average annual cost of long-term care for independent health state (subsequent years) ***</th>
<th>Mean</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>£876</td>
<td>£657</td>
<td>£1,095</td>
</tr>
</tbody>
</table>

*cost per inpatient day £407 and average length of stay (LOS) in the hospital is 6 days

**mean LOS of 51 days inpatient, rehabilitation cost of £763 and average annual cost of £11,292

***mean LOS of 14 days inpatient, rehabilitation cost of £40 and average annual cost of long-term care of £876

The most commonly prescribed drugs and their doses were taken from the Prescription Pricing Authority (PPA) (Table 16).

Table 16: Most commonly cardiovascular prescribing taken from the Prescription Pricing Authority website

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Used in base case analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspirin</td>
<td>75mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Simvastatin*</td>
<td>[40mg]*</td>
<td>Yes</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10mg</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole**</td>
<td>[2×200mg]**</td>
<td>Yes</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75mg</td>
<td></td>
</tr>
<tr>
<td>lisinopril</td>
<td>10mg</td>
<td>Yes</td>
</tr>
<tr>
<td>bendrofluazide</td>
<td>2.5mg</td>
<td>Yes</td>
</tr>
<tr>
<td>losartan</td>
<td>50mg</td>
<td></td>
</tr>
<tr>
<td>Perindopril*</td>
<td>20mg</td>
<td></td>
</tr>
</tbody>
</table>

* The dose of simvastatin was thought to be too low by the GDG (15mg) and this was changed to 40mg.
** The GDG thought it was more likely that modified release dipyridamole would be prescribed in doses of 200mg, rather than 4 doses of 100mg a day as reported by the PPA.

For the base case analysis it was assumed that patients assessed at the specialist clinic would be prescribed aspirin, a statin an ace inhibitor and thiazide all for life plus dipyridamole for two years. Whereas for the GP assessed patients only 14% would get this combination (minus dipyridamole) and the rest would get only aspirin (based on the Oxford data – see Table 8 above).

Drug prices are shown in Table 17.

**Table 17: Drug prices used in the model**

<table>
<thead>
<tr>
<th>BNF March 2007</th>
<th>Annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (non-prop) 75mg 28-tabs</td>
<td>£1.89</td>
</tr>
<tr>
<td>Bendroflumethiazide (non-prop) 2.5mg 28-tabs</td>
<td>£1.15</td>
</tr>
<tr>
<td>Lisinopril (ACEi) (non-prop) 10mg 28 tabs</td>
<td>£1.54</td>
</tr>
<tr>
<td>Simvastatin (non-prop) 40mg 28 tabs</td>
<td>£3.40</td>
</tr>
<tr>
<td>Persantin Retard (dipyridamole) (Boehringer Ingelheim), 200mg 60-cap</td>
<td>£8.38</td>
</tr>
</tbody>
</table>

**Lifetime costs**

Both drug costs and long-term care costs after stroke are calculated over the patient’s lifetime (Table 18). The total costs differ between the alternative assessment strategies because assessment and surgery costs differ but also because strokes incidence will differ due to the different treatments given.

**Table 18: Lifetime treatment costs*, by stroke-related health state**

<table>
<thead>
<tr>
<th></th>
<th>Life expectancy</th>
<th>Lifetime costs</th>
<th>Discounted lifetime cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>dependent after a stroke within 90 days</td>
<td>3.6</td>
<td>51,614</td>
<td>49,684</td>
</tr>
<tr>
<td>independent after a stroke with 90 days</td>
<td>5.4</td>
<td>7,570</td>
<td>7,214</td>
</tr>
<tr>
<td>fully recovered after a TIA / no stroke at 90 days (i.e. drug costs only)</td>
<td>10.8</td>
<td>798</td>
<td>674</td>
</tr>
<tr>
<td>- GP assessment</td>
<td>10.8</td>
<td>1,327</td>
<td>1,152</td>
</tr>
<tr>
<td>- specialist assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fatal stroke by 90 days / surgical death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* not including the one-off costs of assessment and surgery

**Sensitivity Analyses**

One-way sensitivity analyses were carried out to test the robustness of the results to changes in the key parameters/assumptions.

**Results**
For each strategy, the number of strokes, deaths and QALYs resulting from each strategy are presented in Table 19 – immediate specialist assessment had the least number of strokes and the most QALYs. GP care had the most strokes and least QALYs. The breakdown of costs is shown in Table 21 – weekly specialist assessment was most costly and GP care least costly.

### Table 19: Base case results: events per 1000 TIA patients

<table>
<thead>
<tr>
<th>90 day outcome</th>
<th>Immediate specialist assessment</th>
<th>Weekly specialist assessment</th>
<th>GP care</th>
</tr>
</thead>
<tbody>
<tr>
<td>alive no stroke</td>
<td>837</td>
<td>831</td>
<td>814</td>
</tr>
<tr>
<td>Stroke</td>
<td>160</td>
<td>167</td>
<td>186</td>
</tr>
<tr>
<td>dependent stroke</td>
<td>46</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>independent stroke</td>
<td>75</td>
<td>78</td>
<td>87</td>
</tr>
<tr>
<td>Stroke death</td>
<td>38</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Surgical death</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>All patients</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>Additional strokes averted by surgery beyond 90 days</td>
<td>17</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>QALYs</td>
<td>7,123</td>
<td>7,062</td>
<td>6,920</td>
</tr>
</tbody>
</table>

### Table 20: Base case results: cost per 1000 TIA patients

<table>
<thead>
<tr>
<th></th>
<th>Immediate specialist assessment</th>
<th>Weekly specialist assessment</th>
<th>GP care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment</td>
<td>£410,000</td>
<td>£301,508</td>
<td>£50,000</td>
</tr>
<tr>
<td>Surgery</td>
<td>£846,725</td>
<td>£797,775</td>
<td>£0</td>
</tr>
<tr>
<td>Drugs</td>
<td>£964,621</td>
<td>£957,201</td>
<td>£548,797</td>
</tr>
<tr>
<td>Stroke care (independent)</td>
<td>£821,591</td>
<td>£855,484</td>
<td>£954,681</td>
</tr>
<tr>
<td>Stroke care (dependent)</td>
<td>£3,336,510</td>
<td>£3,474,151</td>
<td>£3,876,994</td>
</tr>
<tr>
<td>Stroke care (Strokes averted by surgery)</td>
<td>£-275,459</td>
<td>£-186,662</td>
<td>£0</td>
</tr>
<tr>
<td>Total cost</td>
<td>£6,103,988</td>
<td>£6,199,458</td>
<td>£5,430,472</td>
</tr>
</tbody>
</table>

When all patients were assessed in the same way regardless of ABCD² score, immediate specialist assessment was the most cost-effective option. Immediate specialist assessment dominated weekly specialist assessment, it was more effective and less expensive than weekly specialist assessment.

### Table 21: Base case results: cost-effectiveness

<table>
<thead>
<tr>
<th></th>
<th>Mean QALYs</th>
<th>Mean Cost</th>
<th>ICER (vs GP care)</th>
<th>ICER (vs Weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP care</td>
<td>6.92</td>
<td>£5,430</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly specialist assessment</td>
<td>7.06</td>
<td>£6,199</td>
<td>£5,412</td>
<td></td>
</tr>
<tr>
<td>Immediate specialist</td>
<td>7.12</td>
<td>£6,104</td>
<td>£3,332</td>
<td>Immediate</td>
</tr>
</tbody>
</table>
Using the ABCD² Score

The number of strokes averted in the first 90 days after TIA varied greatly by ABCD² score group (Table 1). However, immediate specialist assessment was still the most cost-effective strategy for all groups except 0 and 1 (Table 23). For group zero the GP assessment was optimal and for group 1 it was either immediate assessment or GP care depending on whether the £20,000 or £30,000 per QALY threshold was used.

Table 22: Strokes by 90 days per 1000 patients, by ABCD² score group

<table>
<thead>
<tr>
<th>ABCD² score</th>
<th>Immediate specialist assessment</th>
<th>Weekly specialist assessment</th>
<th>GP care</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>52</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>53</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>143</td>
<td>149</td>
<td>166</td>
</tr>
<tr>
<td>5</td>
<td>203</td>
<td>210</td>
<td>234</td>
</tr>
<tr>
<td>6</td>
<td>325</td>
<td>337</td>
<td>371</td>
</tr>
<tr>
<td>7</td>
<td>338</td>
<td>347</td>
<td>385</td>
</tr>
<tr>
<td>All</td>
<td>160</td>
<td>167</td>
<td>186</td>
</tr>
</tbody>
</table>
Table 23: Cost-effectiveness by ABCD² score group

<table>
<thead>
<tr>
<th>ABCD² score</th>
<th>ICER (weekly vs GP)</th>
<th>ICER (Immediate vs GP)</th>
<th>ICER (Immediate vs weekly)</th>
<th>Optimal strategy at £20,000 per QALY gained</th>
<th>Optimal strategy at £30,000 per QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50,625</td>
<td>31,397</td>
<td>1,231</td>
<td>GP</td>
<td>GP</td>
</tr>
<tr>
<td>1</td>
<td>27,819</td>
<td>20,579</td>
<td>1,231</td>
<td>Immediate dominates</td>
<td>Immediate</td>
</tr>
<tr>
<td>2</td>
<td>18,014</td>
<td>11,849</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>3</td>
<td>17,286</td>
<td>11,662</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>4</td>
<td>6,398</td>
<td>3,989</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>5</td>
<td>3,630</td>
<td>2,120</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>6</td>
<td>1,108</td>
<td>269</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>7</td>
<td>652</td>
<td>149</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>All</td>
<td>5,412</td>
<td>3,332</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
</tbody>
</table>

ICER=Incremental cost-effectiveness ratio (£ per QALY gained).

One-way sensitivity analyses
The results of the sensitivity analyses are presented in Table 24. These analyses are described below.

Table 24: Results of one-way sensitivity analyses

<table>
<thead>
<tr>
<th>Sensitivity analysis</th>
<th>ICER (weekly vs GP)</th>
<th>ICER (Immediate vs GP)</th>
<th>ICER (Immediate vs weekly)</th>
<th>Optimal strategy at £20,000 per QALY gained</th>
<th>Optimal strategy at £30,000 per QALY gained</th>
<th>Result by ABCD² score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>5,412</td>
<td>3,332</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
<td>See Table 23</td>
</tr>
<tr>
<td>A</td>
<td>7,524</td>
<td>5,360</td>
<td>264</td>
<td>Immediate</td>
<td>Immediate</td>
<td>GP care is now optimal for groups 2 and 3</td>
</tr>
<tr>
<td>B</td>
<td>6,383</td>
<td>4,682</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
<td>Immediate is now optimal for group 1</td>
</tr>
<tr>
<td>C</td>
<td>2,553</td>
<td>1,275</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
<td>No change</td>
</tr>
<tr>
<td>D</td>
<td>10,885</td>
<td>7,234</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
<td>No change</td>
</tr>
<tr>
<td>E</td>
<td>4,403</td>
<td>1,503</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
<td>No change</td>
</tr>
<tr>
<td>F</td>
<td>5,526</td>
<td>3,820</td>
<td>Immediate dominates</td>
<td>Immediate</td>
<td>Immediate</td>
<td>Immediate is now optimal for group 1</td>
</tr>
</tbody>
</table>

ICER=Incremental cost-effectiveness ratio (£ per QALY gained).
Sensitivity analysis A
The GDG commented that for every suspected TIA patient who has had a TIA or minor stroke, one patient will have had a TIA mimic. It is difficult to estimate the consequences for these patients. To reflect this the costs of specialist assessment, were doubled assuming that for each patient treated for a TIA the cost of another patient would be incurred who was discharged after assessment. This is a very conservative assumption since the model does not estimate the health gain (and possibly cost savings) attained by these patients from getting an improved diagnosis. Immediate specialist assessment remains the most cost-effective strategy for ABCD² scores 2-7 and overall.

Similarly, the addition of the cost of brain scan would also not affect which strategy is most cost-effective.

Sensitivity analysis B
In the base case analysis, it was assumed that the proportion of patients with stenosis was constant across the ABCD² score groups and that the absolute risk reduction from surgery was constant across the ABCD² score groups. However, it is likely that the risk reduction is smaller for patients in the lower ABCD² score groups. For this sensitivity analysis we estimated the health gain using relative risk instead of absolute risk reductions (estimated from the same data - Table 7). The relative risk reductions (e.g. 65%RRR for stenosis>=70%) were applied to the 90 day stroke rates.

Sensitivity analysis C
In terms of medication, the base case analysis is rather conservative in that the patients undergoing specialist assessment are assumed to be prescribed a number of drugs and yet the health effects of these drugs are not modelled. In this sensitivity analysis we calculate only the cost of aspirin and dipyridamole for 90 days. The other drug costs are removed and we no longer cost the drugs over the lifetime. The results were largely unchanged.

Sensitivity analysis D
In the base case only patients receiving specialist assessment receive dipyridamole. In this sensitivity analysis, we assume that 50% of patients receiving GP care are prescribed dipyridamole. The cost-effectiveness results were largely unchanged.

Sensitivity analysis E
We changed the life expectancy of a dependent stroke patient from 1/3 of normal to 2/3. And then the life expectancy of an independent stroke patient was changed from 1/2 of normal to 3/4. The cost-effectiveness results were largely unchanged.

Sensitivity analysis F
We changed the life expectancy of a dependent stroke patient from 1/3 of normal to 1/6. And then the life expectancy of an independent stroke patient...
was changed from 1/2 of normal to 1/4. The cost-effectiveness results were largely unchanged.

**Discussion**
The most cost-effective strategy overall appears to be immediate specialist assessment. This strategy was optimal for all ABCD² score groups apart from 0 and 1. And the results appear to be robust to changes in key parameters.

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 appear even more cost-effective.

The main driver for the cost-effectiveness of immediate assessment appears to be getting patients on effective medication faster which improves their outcomes.

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 so caution should be applied when using these results. However, the results of this analysis reinforce the conclusions of other 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. 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.

Finally, another cost-effective model comparing different assessment strategies has also found that same day clinics are cost-effective compared with weekly clinics for every ABCD² score group.

In conclusion, referral of suspected TIA patients for immediate specialist assessment appears to be cost-effective for all but the lowest risk patients because it supports timely prescribing of effective drugs and selection of patients for effective surgery.
### Appendix D: GDG members’ declaration of interests

<table>
<thead>
<tr>
<th>Name &amp; date of signature on DoI form</th>
<th>Personal pecuniary interest</th>
<th>Personal family interest</th>
<th>Non-personal pecuniary interest</th>
<th>Personal non-pecuniary interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLISON Rhoda</td>
<td>None</td>
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<td>None</td>
<td>None</td>
</tr>
<tr>
<td>BARKER Julie</td>
<td>None</td>
<td>Husband works for Xansa-SBS who contract out financial functions of some NHS Trusts</td>
<td>None</td>
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<tr>
<td>BOWMASTER Alan</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>DAY Diana</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>FORD Gary</td>
<td>Honoraria from Boehringer Ingelheim, Astra Zeneca for educational activities and advisory boards.</td>
<td>Family ownership of Glaxo Smith Kline shares</td>
<td>Research grants to institution or/and unrestricted educational grants from Boehringer #Ingelheim, Lundbeck, ...illegible...(see form) and Astra Zeneca</td>
<td>Director UK Stroke Research Network</td>
</tr>
<tr>
<td>HATTON Steve</td>
<td>None</td>
<td>None</td>
<td>Company director at BPA/College of Paramedics</td>
<td>None</td>
</tr>
<tr>
<td>Name</td>
<td>Conflict of Interest 1</td>
<td>Conflict of Interest 2</td>
<td>Conflict of Interest 3</td>
<td>Conflict of Interest 4</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
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<tr>
<td>KORNER Joseph</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<td>Form signed 15/11/07</td>
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<td>LAMONT Peter</td>
<td>None</td>
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<tr>
<td>McMANUS Richard</td>
<td>None</td>
<td>None</td>
<td>In the last 5 years Dr McManus has participated in research funded by: Pfizer, Sanofi – Aventis and A. Menarini Pharma and funding to attend a research conference from MSD.</td>
<td>None</td>
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<tr>
<td>MORSE Mariane</td>
<td>None</td>
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<tr>
<td>POTTER John</td>
<td>Received lecture and research funding from various pharma more directly related to this GDG</td>
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<td>RUDD Anthony</td>
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<tr>
<td>TYRRELL Pippa</td>
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<td>None</td>
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