NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review of Clinical Guideline (CG68) – Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)

Background information

Guideline issue date: 2008

3 year review: 2011

National Collaborating Centre: National Collaborating Centre for Chronic Conditions

Review recommendation

- The guideline should not be updated at this time.
- The guideline should be amended to align it with the updated Technology Appraisal: Vascular disease - clopidogrel and dipyridamole (TA210).
- The guideline should cross refer to the new Technology Appraisal: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (TA 249).
- The guideline should be reviewed again pending the publication of the Technology Appraisals (due to be published in 2012/2013) for new oral anticoagulants rather than in three years time.

Factors influencing the decision

Literature search

1. An assessment of abstracts from a high-level randomised control trial (RCT) search revealed new evidence relating to the following clinical areas within the guideline:
    - The rapid recognition of symptoms and diagnosis
    - Pharmacological treatments for people with acute stroke
    - Maintenance or restoration of homeostasis
    - Early mobilisation and optimum positioning of people with acute stroke
    - Nutrition and hydration
    - Surgery for people with acute stroke
    - Neuroprotectants

2. A sufficient number of studies (159) relevant to the above clinical areas were identified to allow an assessment and review proposal. No new evidence was identified in these areas which would change the direction of current guideline recommendations.

3. Intelligence gathering; high level RCT abstracts, and feedback from other NICE departments and the Guideline Development Group indicated that there were no additional clinical areas that required further focused literature searches.
4. However, the guideline needs to be amended to reflect changes in the updated technology appraisal 210: Vascular disease - clopidogrel and dipyridamole (2010) and to cross refer to the new Technology Appraisal: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (TA 249).

5. It should also be noted that due to a license extension of alteplase, Technology Appraisal 122: Ischaemic stroke (acute) – alteplase (2007) is under review.

6. There are several new oral anticoagulants being evaluated as technology appraisals in 2012/2013 that may impact on the section in the guideline relating to reversal of anticoagulation treatment in people with haemorrhagic stroke.
    - Atrial fibrillation (stroke prevention) - rivaroxaban May 2012
    - TA Venous thromboembolism (prevention) – rivaroxaban TBC
    - TA Venous thromboembolism (treatment and long term secondary prevention) - rivaroxaban July 2012
    - Stroke and systemic embolism (prevention, non-valvular atrial fibrillation) - apixaban February 2013

7. Several ongoing clinical trials (publication dates unknown) were identified focusing on thrombolysis, neuroprotectants, antiplatelet medications, acute rehabilitation, nutrition, mechanical clot retrieval and homeostasis.

8. New evidence was identified which directly answered research recommendations in the original guideline relating to:
    - Blood pressure control
    - Early mobilisation and optimum positioning of people with acute stroke
    - Aspirin and anticoagulant treatment for acute ischaemic stroke

Guideline Development Group questionnaire and National Collaborating Centre perspective

9. A questionnaire was distributed on two occasions to GDG members and the National Collaborating Centre (NCC) to consult on the need for an update of the guideline. Respondents highlighted that since publication of the guideline more literature has become available on specialist stroke units and homeostasis. It was also noted that the Royal College of Physicians are currently updating their Stroke guideline (publication expected in 2012).

10. The pharmacological treatment of acute stroke by thrombolysis (TA122) was suggested to be in need of update due to new relevant data been published from various trials (including CLOTs2, AVERT3 and IST3) that may result in changes to current recommendations.

11. In addition, a clinical advisor stressed that the use of new oral anticoagulants (rivaroxaban, dabigatran and apixaban) by patients with atrial fibrillation may impact on the use of thrombolysis drugs in patients with acute stroke or on the reversal of anticoagulation treatment in people with haemorrhagic stroke. However, at present the evidence base in these areas appears to be limited.

12. Ongoing research in areas relevant to the guideline was highlighted by GDG members including:
    - oxygen therapy
    - blood pressure early mobilisation,
    - prophylactic antibiotic use
    - thrombolysis for patients with acute stroke

13. The majority of respondents felt that there is insufficient variation in current practice supported by adequate evidence at this time to warrant an update of the current guideline.

Implementation and post publication feedback

14. In total 82 enquiries were received from post-publication feedback, most of which were routine.

15. Feedback from the NICE implementation team identified six audits. These indicate an improving service for acute stroke delivery with more hospitals providing stroke units and having access to appropriate care. Conversely, limited numbers of patients are not receiving thrombolysis and stroke care within the time frame recommended by CG68, particularly in relation to operations. However, consecutive

yearly audits indicate that progress is been made with average times to intervention reducing year on year.

16. Qualitative input from the implementation field team suggested that the guidance should focus on the time from door to scan for stroke patients. It was also reported that whilst the stroke guideline is important, it is proving very difficult for a small trust to implement it due to the resources required for MRI scanning and thrombolysis for relatively small numbers of patients. In addition, it was highlighted that commissioners are taking different approaches to developing stroke centres which may impact on another aspects of service delivery especially ambulance policy across service areas.

17. Stakeholder comments from The National Quality Board quality standards engagement exercise (August -October 2011) indicated that there is inconsistency between the recommendations in CG68 and the Accelerating Stroke Improvement stroke metric timeframe for thrombolysis. TA122-Alteplase 2007 is currently being updated and considering this issue.

Relationship to other NICE guidance

18. NICE guidance related to CG68 can be viewed in Appendix 1.

Summary of Stakeholder Feedback

Review proposal put to consultees:
The guideline should not be updated at this time.
The guideline will be reviewed again according to current processes.

19. In total 13 stakeholders commented on the review proposal recommendation during the 2 week consultation period. The table of stakeholder comments can be viewed in Appendix 2.

20. Ten stakeholders agreed with the review proposal. Two stakeholders did not state a definitive decision and one stakeholder disagreed.

21. The stakeholder that disagreed with the review proposal commented that:

The guideline does not currently mention neurothrombectomy but the National Stroke Strategy 2007 and management of patients with Stroke or TIA SIGN 108 (2008) identified that there may be a role for neurointerventional treatment in stroke patients. The stakeholder commented that they would like to see the guideline encourage clinicians to participate in their trial of a revascularization device in comparison to alteplase that is currently in use in England for stroke treatment. It should, however be noted that the current evidence with regard to neurothrombectomy devices is limited and insufficient to establish the role of these interventions in routine clinical practice for acute ischemic stroke. Some of the procedures still require RCT based evidence whilst others are equivocal to their effectiveness. This area will be examined again in the future review of the guideline.

It may be of interest to the stakeholder to note that the Interventional Procedures Programme within NICE publishes guidance in relation to new procedures that are available within the NHS or be about to be used for the first time in the NHS, outside formal research. In addition the Medical Technologies Evaluation Programme produces guidance on technologies based on a manufacturers submission, expert opinion and the completion of an external assessment report for medical technologies where it is believed that, following evaluation, they have the potential to offer substantial benefits to patients and/or the NHS and are more likely to be adopted consistently and more quickly.

22. During consultation, one stakeholder suggested a new area to consider in a future update of the guideline:

- neurothrombectomy

Anti-discrimination and equalities considerations

23. No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope is inclusive of all patients over 16 years with TIAs or completed strokes. This includes people with first and recurrent events, thrombotic and embolic events and primary intracerebral haemorrhage of any cause, including venous thrombosis. The following group and clinical area were specifically outside of the scope: patients with subarachnoid haemorrhage and specific issues relating to the general management of underlying conditions. The guideline covers the initial and early management aimed at reducing the ischaemic brain damage, and in the case of TIAs, preventing subsequent stroke in primary, secondary and tertiary NHS care settings including pre-hospital emergency and ambulance services.

Conclusion

24. The evidence and intelligence identified through the update review process suggests that the guideline (CG68) does not need updating at this stage.

25. One recent, updated Technology Appraisal was identified: TA 210 Vascular disease - clopidogrel and dipyridamole (2010). The guideline (CG68) should be amended to align it with the changes in the updated TA 210 that alter recommendations with regard to these pharmacological treatments.

26. One new Technology Appraisal was identified: TA249 Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (March 2012). The guideline CG68 should cross refer to TA 249.

27. Technology Appraisal 122: Ischaemic stroke (acute) – alteplase 2007 is in review due to a license extension of this agent. The guideline (CG68) will need to reflect any changes made to recommendations in the updated version of this technology appraisal.

28. Lastly, a number of Technology Appraisals either recently published or in development for new oral anticoagulants were identified. The current guideline CG68 refers to reversal of anticoagulation for people with haemorrhagic stroke treated with warfarin. However, it appears that there is currently no data relating to reversal of anticoagulation of Dabigatran etexilate in patients with acute stroke. This are should be considered in the next update review. Therefore, the guideline should be reviewed again pending the publication of the Technology Appraisals (due to be published in 2012/2013) for new oral anticoagulants rather than in three years time.

29. The Stroke guideline (CG68) should not be updated at this time.

Relationship to quality standards

30. This guideline relates to a published quality standard on stroke.

31. The update of the TAs within CG68: Stroke may impact on the published quality standard: Stroke (see Appendix 3).

32. This topic is part of the library of NICE Quality Standard NHS healthcare topics.

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Centre for Clinical Practice
10 April 2012

Appendix 1

The following NICE guidance is related to CG68:

Guidance	Review date
Ischaemic stroke (acute) - alteplase (TA122) 2007	Currently under review as an STA due to a license extension. Publication expected late 2012
Vascular disease - clopidogrel and dipyridamole (TA210) 2010	This MTA was a review of previous technology appraisals and was only published in December 2010. Not scheduled for review until July 2013
Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (TA 249) March 2012	2015
CG 36 Atrial fibrillation 2006	Currently scheduled for update (2011)
CG 92 Venous thromboembolism: reducing the risk 2010	2013
CG127 Hypertension: clinical management of primary hypertension in adults. 2011 updates and replaces NICE clinical guideline 34 (published June 2006)	2014
CG67 Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. 2008	Currently scheduled for update (2011)
IPG388 Carotid artery stent placement for asymptomatic	

extracranial carotid stenosis	
IPG389 Carotid artery stent placement for symptomatic extracranial carotid stenosis	
Related NICE guidance in progress	
CG Stroke rehabilitation	TBC
TA Atrial fibrillation (stroke prevention) - rivaroxaban	May 2012
TA Venous thromboembolism (prevention) - rivaroxaban	TBC
Stroke and systemic embolism (prevention, non-valvular atrial fibrillation) - apixaban	February 2013
Related NICE quality standard	
Stroke Quality Standard 2010	TBC

Appendix 2

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Stroke Guideline Review Consultation Comments Table

5 March - 19 March 2012

Stakeholder	Agree ?	Comments Please insert each new comment in a new row.	Comments on areas excluded from original scope	Comments on equality issues	Response
East Midlands Ambulance Service NHS Trust	Agree	I am wondering if there would be an acceptable form of assessment that could be considered for the Ambulance Service and JRCAL which would mirror the same in A&E as per statement on page 5? “Current recommendations within CG 68 state that people admitted to A&E with a suspected stroke or TIA should be diagnosed rapidly using a validated tool/scoring system such as ABCD2. The new evidence identified supports the recommendations in CG 68”			Thank you for your comment. Evidence relating to pre-hospital tools for recognition of stroke are reviewed in section 5.1 of CG68. The ABCD2 validated tool/scoring system is used as a means to assess the risk level of patients for subsequent strokes.
The		The Department of Health has no			Thank you for your comment.

Stakeholder	Agree ?	Comments Please insert each new comment in a new row.	Comments on areas excluded from original scope	Comments on equality issues	Response
Department of Health		substantive comments to make, regarding this consultation.			
Pfizer	Agree	We agree with the proposal that "The guideline should be not considered for an update at this time"			Thank you for your comment.
Pfizer	Agree	We agree with the GDG's comments on development due to occur in 2012/13 that will impact the CG68 and need to be considered in the next version of the guideline such as the Royal College of Physicians Stroke Guideline update and new oral anticoagulants being reviewed by NICE such as rivaroxaban, dabigatran and apixaban.			Thank you for your comment.
NHS Direct	Agree				Thank you for your comment.
RCN	Agree	There are no further comments to add at this stage on proposals not to update this guideline at this time. It is noted that the guideline will be reviewed again in accordance with current processes.			Thank you for your comment.
Royal College of Physicians (RCP)	Agree	The RCP is grateful for the opportunity to respond. Our experts believe that the proposal appears to be comprehensive and appropriate.			Thank you for your comment.
Welsh Association of Stroke		**Clinical area 1: The rapid recognition of symptoms and diagnosis**			Thank you for your comment. Current guideline recommendations indicate

Stakeholder	Agree ?	Comments Please insert each new comment in a new row.	Comments on areas excluded from original scope	Comments on equality issues	Response
Physicians (WASP)		1. TIA Rapid assessment - more efficient, cost effective but equal outcomes [ref 60] Stroke/TIA services are struggling to provide 7 day a week assessment in many centres in the country. Could the emphasis be put on the urgent initiation of treatment; urgent assessment of high risk and crescendo TIA would of course still apply.			that assessment should be made in defined time frames according to patients' signs, symptoms and risk strata. The clinical introduction to chapter 6 Imaging in TIA and non-disabling stroke states that, 'it is important that brain scanning does not delay the institution of optimum secondary prevention'
Welsh Association of Stroke Physicians (WASP)		**Urgent carotid imaging and surgery** 1. CTA probably should be recommended only in case of a doubt regarding degree of stenosis or morphology. 2. A statement re: method of measurement (ECST or NACET criteria) would be helpful. Quite a few vascular labs in the UK use NACET method to measure the level of stenosis although majority use ECST criteria. Labs should state the method			Thank you for your comments. The choice of carotid imaging type was not assessed in CG68. CG68 gives thresholds relating to both ECST and NACET criteria.

Stakeholder	Agree ?	Comments Please insert each new comment in a new row.	Comments on areas excluded from original scope	Comments on equality issues	Response
		used in their reporting.			
Welsh Association of Stroke Physicians (WASP)		**Anticoagulation treatment for comorbidities in people with acute stroke** **Patient with acute ischaemic stroke** 1. Patients with AF and minor stroke with no or very small ischaemic area might benefit from early anticoagulation (by avoiding risk of early recurrence). Although there is no RCT in this area clinicians feel uncomfortable in leaving such patients unprotected. A statement to acknowledge the difficulty and explicit recommendation of early anticoagulation in such patients with (possibly use brain imaging as further guide) until further evidence become available would be helpful to a practicing clinician.			Thank you for your comment. The guideline recommendations strive to be evidence based wherever possible. No evidence relating to patients with AF and a minor stroke and early anticoagulation was identified. We will examine this area in the next review of the guideline.
Bayer plc	Agree				Thank you for your comment.

Stakeholder	Agree ?	Comments Please insert each new comment in a new row.	Comments on areas excluded from original scope	Comments on equality issues	Response
College of Occupational Therapists	Agree	As this is a guideline about TIA & Early Stroke the only information that is relevant is around early mobilisation. This area is specific to Physiotherapy; however as Occupational Therapists we would want to support it and encourage our members to do the same.			
RCGP	Agree	Agree with the recommendations from NICE			Thank you for your comment.
BDA	Agree				Thank you for your comment.
NHS Sickle Cell & Thalassaemia Screening Programme	Agree	We are very supportive of a Review of Clinical Guidelines on Stroke by NICE. However there seem to be no references to patients with sickle cell disease (including children) where stroke is often a co-morbidity. A&E staff and stroke wards/units should be aware that stroke patients may also have sickle cell disease particularly if they are of African or African/Caribbean background. Please note that the NCEPOD report ("A Sickle Crisis?" 2008) highlighted the lack of knowledge about sickle amongst many healthcare professionals. In addition Liverpool Reviews and		(1) stroke treatments should be culturally and linguistically sensitive for stroke patients with sickle cell disease, many of whom come from BME backgrounds; (2) stroke treatments should also be age-specific for children with sickle cell disease	Thank you for your comments. CG68 specifically excluded children in its scope and therefore makes recommendations for individuals with acute stroke >18 years of age. A sickle cell acute painful episode clinical guideline is due to be published later in 2012.

Stakeholder	Agree ?	Comments Please insert each new comment in a new row.	Comments on areas excluded from original scope	Comments on equality issues	Response
		Implementation Group (LRiG) are due to publish their report (commissioned by the NIHR HTA Programme) in July 2012 – "The clinical and cost effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation". The report concludes that the use of TCD scanning to identifying children at high risk of stroke and treating these children with prophylactic blood transfusion appears to be both clinically and cost effective.		who have one (or more) strokes.	
ev3 (Covidien)	Disagree		Clinical area 8: Surgery for people with acute stroke – Neurothrombectomy: • The National Stroke Strategy of 2007 identifies that there may be a role for neurothrombectomy devices in stroke treatment • "Patients should have access to a stroke service with		Thank you for your comments. The current evidence with regard to neurothrombectomy devices is limited and insufficient to establish the role of these interventions in routine clinical practice for ischemic. Some of the procedures still require RCT based evidence whilst others are equivocal to their effectiveness. However, we will examine this area again in the next review of the guideline.

Stakeholder	Agree ?	Comments Please insert each new comment in a new row.	Comments on areas excluded from original scope	Comments on equality issues	Response
			neurointerventional capacity” • “There may be a role for interventional neuroradiology in the management of basilar thrombosis” • The Guideline in Scotland SIGN 108 (2008) (Section 5.7 Mechanical Reperfusion – 5.7.1 Clot Retrieval) refers to neurothrombectomy devices in the treatment of stroke. It states that: “Mechanical clot retrieval may be an alternative to drug therapies in patients with contraindications to IV thrombolysis”. ev3 manufactures and		The Interventional procedures Programme within NICE may be a more appropriate means to assess the efficacy and safety of the device you refer to as they publish guidance that aims to ensure that: • patients and carers are reassured that new interventional procedures are being assessed to protect patient safety, and that they have access to information about procedures • clinicians, healthcare organisations and the NHS will be supported in the process of introducing new procedures • innovation is fostered by facilitating data collection and analysis, arranging systematic reviews, recommending

Stakeholder	Agree ?	Comments Please insert each new comment in a new row.	Comments on areas excluded from original scope	Comments on equality issues	Response
			markets Solitaire™ FR Revascularization Device and is one of many unique mechanical neurothrombectomy devices, CE marked and currently in use in England for stroke treatment. We would like to see the guideline encourage clinicians to participate in the upcoming UK multicenter RCT – Pragmatic Ischemic Stroke Thrombectomy Evaluation (PISTE) to evaluate the value of mechanical thrombectomy devices against tPA in stroke treatment. We feel that neurothrombectomy devices should be mentioned within the NICE CG68 since they are being used to treat certain patients for stroke.		training and providing advice on the efficacy and safety of new procedures.

Appendix 3. Quality Standard Stroke

There are 5 quality statements within the Stroke quality standard that are within the scope of CG68. Four of the quality standards are unlikely to be affected by changes in the technology appraisals 122 or 210:

Ambulance screening and transfer to an acute stroke unit

- **Quality statement**- People seen by ambulance staff outside hospital, who have sudden onset of neurological symptoms, are screened using a validated tool to diagnose stroke or transient ischaemic attack (TIA). Those people with persisting neurological symptoms who screen positive using a validated tool, in whom hypoglycaemia has been excluded, and who have a possible diagnosis of stroke, are transferred to a specialist acute stroke unit within 1 hour. Not likely to affected by changes in TAs

Neuro-imaging

- **Quality statement**-Patients with acute stroke receive brain imaging within 1 hour of arrival at the hospital if they meet any of the indications for immediate imaging

Swallowing screening and nutrition management

- Quality statement-Patients with acute stroke have their swallowing screened by a specially trained healthcare professional within 4 hours of admission to hospital, before being given any oral food, fluid or medication, and they have an ongoing management plan for the provision of adequate nutrition

Assessment and management of patients with stroke

Quality statement- Patients with stroke are assessed and managed by stroke nursing staff and at least one member of the specialist rehabilitation team within 24 hours of admission to hospital, and by all relevant members of the specialist rehabilitation team within 72 hours, with documented multidisciplinary goals agreed within 5 days

However the quality statement below will be directly affected.

Admission of patients with suspected stroke

Quality statement- Patients with suspected stroke are admitted directly to a specialist acute stroke unit and assessed for thrombolysis, receiving it if clinically indicated.

Quality measure

Denominator: the number of patients with suspected stroke ad mitted to hospital.
(b) Proportion of patients with suspected stroke assessed for thrombolysis who receive it in accordance with NICE technology appraisal guidance 122 (2007) and NICE clinical guideline CG68 (2008).
Numerator: the number of patients who received thrombolysis in accordance with NICE technology appraisal guidance 122 (2007) and NICE clinical guideline CG68 (2008).
Denominator: the number of patients with suspected stroke assessed to require thrombolysis.