TITLE: Appropriateness of CT Imaging to Support the Diagnosis of Stroke: A Review of the Clinical Evidence

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CONTEXT AND POLICY ISSUES

In Canada, stroke is the third most common cause of death[1] with an estimated incidence of approximately 50,000 cases each year.[2] The majority of strokes are ischemic (80%) and are a result of interruption of blood flow to the brain caused by a blood clot.[3] Transient Ischemic Attack (TIA) is defined as "a transient episode of neurodysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction".[4] Approximately 15,000 Canadians experience a TIA each year[5] and are five times more likely to suffer from a stroke in the following two years when compared to the general population.[6] The need for an accurate and timely diagnostic test is therefore needed, as the risk of recurrent stroke within 90 days after a TIA is between 10% to 20%.[6]

The combination of imaging modalities, laboratory tests, and clinical features provide a comprehensive diagnosis for stroke.[7] Advances in imaging technology such as computed tomography (CT) and magnetic resonance imaging (MRI) have allowed for the distinction between hemorrhagic and ischemic strokes, providing clinicians with greater certainty whether to administer thrombolysis.[7] With rapid scan times and ease for detecting intracranial hemorrhage, CT has shown to be a preferred diagnostic technology.[8] MRI has been shown to easily detect ischemia with diffusion-weighted imaging and also detects hyperacute hemorrhage with proper sequences.[8] MRI is not as widely available as CT and is typically more costly.[9]

With no single gold standard for the diagnosis of stroke, uncertainty regarding the appropriateness of solely using CT or expert clinical assessment remains. Furthermore, current clinical practice guidelines state that CT tests must be performed, though this technology is not always available in rural or remote emergency departments. The objective of this review is to summarize recent clinical evidence of CT and expert clinical assessment to support the diagnosis of stroke and TIAs.

RESEARCH QUESTIONS

1. What is the clinical evidence regarding the necessity and appropriateness of Computerized Axial Tomography to support a diagnosis of stroke or transient ischemic attack?

2. What is the clinical evidence regarding the use of expert clinical assessment without further information obtained from diagnostic imaging testing to support a diagnosis of stroke or transient ischemic attack?

KEY FINDINGS

Diagnostic imaging with CT appears to be an appropriate method to support a diagnosis for stroke or TIA. No evidence was identified to determine whether a comprehensive clinical assessment of symptoms is sufficient to support a diagnosis of stroke or TIA. Better designed clinical diagnostic trials for CT are needed.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. The search was also limited to English language documents published between Jan 1, 2008 and Oct 24, 2013.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of relevant titles and abstracts were retrieved and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with acute stroke symptoms or transient ischemic attack (TIA) symptoms presenting to the hospital
Intervention	Q1: Computerized Axial Tomography (CT Scanning) to support the diagnosis of stroke Q2: interventions and tests other than CT and other diagnostic imaging modalities.
Comparator	Other related medical imaging diagnostic tests including chest x-ray (CxR), MRI, etc., to support diagnosis of ischemic stroke or TIA
Outcomes	Diagnostic value during early symptom presentation Change in patient outcomes Impact on patient outcomes, change in treatment pathway
Study Designs	Health technology assessment, systematic reviews, meta-analyses, randomized and non-randomized controlled trials

Exclusion Criteria

For the first research question, studies were excluded if they did not evaluate the diagnostic value, change in patient outcomes, and impact on patient outcomes with standard CT Scanning for stroke or TIA. For the second research question, studies that did not evaluate the diagnostic value, change in patient outcomes, and impact on patient outcomes with clinical expert assessment or diagnostic imaging modalities other than CT were excluded. Studies were excluded if they were described in a systematic review included in this report.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised and summarized narratively. The methods used when conducting the literature search, study selection, quality assessment, data extraction, and summarizing the data were appraised for systematic reviews. The systematic review was appraised using the AMSTAR instrument.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 509 citations. Upon screening titles and abstracts, 484 citations were excluded and 25 potentially relevant articles were retrieved for full-text review. 3 additional potentially relevant reports were retrieved from the grey literature and by hand search. Of the 28 potentially relevant reports 27 were excluded. One systematic review,[7] published in 2009, met the inclusion criteria. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

1. What is the clinical evidence regarding the necessity and appropriateness of Computerized Axial Tomography to support a diagnosis of stroke or transient ischemic attack?

One systematic review was retrieved and is described in Appendix 2. The systematic review by Brazzelli and colleagues (2009)[7] included seven non-randomized studies, published between 1996 and 2007, consisting of 226 patients for detection of ischemic stroke comparing diffusion-weighted MRI (DWI) with CT performed within 12 hours of stroke onset versus a reference standard of clinical diagnosis and imaging follow-up. The authors performed a meta-analysis using maximum likelihood estimations of a random-effects model to pool logit transformed proportions. Sensitivity and specificity of each diagnostic technology were reported.

2. What is the clinical evidence regarding the use of expert clinical assessment without further information obtained from diagnostic imaging testing to support a diagnosis of stroke or transient ischemic attack?

   Based on the selection criteria (Table 1), no evidence was found regarding the use of expert clinical assessment without further information obtained from diagnostic imaging testing to support a diagnosis of stroke or transient ischemic attack.

Summary of Critical Appraisal

The strengths and limitations of included studies are presented in Appendix 3.

Clinical studies

The systematic review by Brazzelli and colleagues[7] was well designed and of high methodological quality. The authors used rigorous methods to search, select, appraise and synthesize the studies. An 'a priori' design was provided and three independent data extractors were used for the study selection. A comprehensive literature search was performed which included grey literature. A list of both included and excluded studies was provided. The methodological quality of the seven included studies for ischemic stroke varied based on Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.[10] The key limitations of the lower quality studies were the lack of a representative spectrum, the sequence of tests was not determined at random, and there was uncertainty regarding the blinding of the reference standard. Furthermore, three of the seven studies had scans that were read without knowledge of clinical information.

Summary of Findings

Necessity and appropriateness of Computerized Axial Tomography to support a diagnosis of stroke or transient ischemic attack

The overall results from the systematic review from Brazzelli and colleagues[7] suggest that DWI appears to be more sensitive than CT in regards to diagnostic accuracy for acute ischemic stroke (Appendix 4). Seven non-randomized trials (n=226) provided data for CT sensitivity (0.39, 95% confidence interval [CI]: 0.16 to 0.69), CT specificity (1.00, 95% CI: 0.94 to 1.00), DWI sensitivity (0.99, 95% CI: 0.23 to 1.00), and DWI specificity (0.92, 95% CI: 0.83 to 0.97). The systematic review did not provide results for change or impact on patient outcomes with standard CT Scanning for stroke or TIA. The number participants who were true positives were

73 and 147, false positives were 0 and 5, false negatives were 88 and 14, and true negatives were 65 and 60 with CT and DWI respectively.

Limitations

The methodological quality of the seven included studies in the systematic review varied. The results of the systematic review were limited as the methodological and clinical sources of heterogeneity were not investigated due to the limited number of included studies (n=7), with small sample sizes. Non-English articles were excluded from the systematic review. In addition, DWI and CT were evaluated in a highly selected patient sample (high probability of stroke) and not representative of a typical patient population presenting to an emergency department. The results should therefore be interpreted with caution.

In the included systematic review,[7] the authors identified expert clinical assessment coupled with clinical and imaging follow-up as an appropriate reference standard for diagnosing stroke. However, no other evidence for the use of clinical expert clinical assessment was found.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited evidence suggests that DWI is more sensitive than CT for the early detection of stroke in highly selected patients. Based on clinical practice guidelines,[9,11-15] the use of diagnostic imaging, whether with CT or MRI, appears to be an appropriate method to support a diagnosis for stroke or TIA.

The American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend that patients with TIA should preferably undergo neuroimaging evaluation within 24 hours of symptom onset. MRI, including DWI, was the preferred brain diagnostic imaging modality. If MRI is not available, cranial CT was recommended.[9] The Brazilian Stroke Society (SBDCV) guidelines state that cranial CT is essential in the emergency assessment of patients with acute ischemic stroke. Both cranial CT and MRI (including diffusion and gradient echo sequences) are recommended for patients with acute stroke, though the recommendation for brain CT is based on a higher level of evidence. The guidelines further state that multimodal neuroimaging can be useful for selecting patients for thrombolytic therapy with onset of symptoms with an indefinite duration or beyond 4.5 hours.[11] The South African Stroke Society (SASS) guidelines recommend the use of cranial CT or MRI for patients with suspected stroke or TIA. The cranial CT recommendation was based on a higher level of evidence compared with MRI. According to the guidelines, CT brain scans can accurately determine the type and anatomy of the stroke. They further stated that if a CT scan is not feasible, patients may be required to be referred to another centre that is able to perform a CT or MRI scan.[12] The National Collaboration Centre for Chronic Conditions (NCC-CC) guidelines state that patients with suspected TIA, for whom vascular territory or pathology is uncertain, should undergo DWI. Furthermore, the authors state that CT scanning should be used when MRI is contraindicated (for example, patients with a pacemaker, shrapnel, brain aneurysm clips and heart valves, metal fragments in eyes, or severe claustrophobia). Brain scanning with MRI with DWI should be performed within 24 hours following TIA.[13] The European Stroke Organisation (ESO) guidelines recommend brain imaging with CT or MRI in all suspected stroke or TIA patients. The use of urgent cranial CT had a recommendation based on a higher level of evidence compared with MRI. The guidelines stated that a 24-hour CT scan should be available for centres managing acute stroke patients.[14] The Institute for Clinical Systems Improvement (ICSI) guidelines state that patients presenting less than 24 hours since the initial clinical TIA should not leave the

emergency department until undergoing or scheduling brain imaging with MRI or CT. MRI was described as the preferred diagnostic procedure as diffusion-weighted sequences may identify patients at particularly high risk of early major recurrence.[15] With varying recommendations regarding the preferred diagnostic imaging modality, it is still unclear whether patients with suspected acute stroke or TIA should undergo MRI versus CT scans. While this does not represent a comprehensive search for clinical practice guidelines for stroke diagnosis, further detail regarding the recommendations for diagnostic imaging for stroke from these guidelines is included in Appendix 5.

Evidence regarding the use of expert clinical assessment is limited, thus further research is needed to identify if a comprehensive clinical assessment of symptoms is sufficient to support a diagnosis of stroke or TIA. While expert clinical assessment was used as the reference standard in each diagnostic imaging study included in this review, no literature on the use of expert clinical assessment for stroke diagnosis was identified. AHA/ASA guidelines state that patients with stroke should undergo clinical assessment along with neurological examination, and that a stroke rating scale preferably the National Institutes of Health Stroke Scale (NIHSS), should be used.[9] Similarly other guidelines recommend the use of validated tools, such as the Recognition of Stroke in the Emergency Room (ROSIER) tool[16] to evaluate patients suspected of stroke. The ICSI guidelines[15] recommend that a qualified clinician should evaluate patients with TIA or minor stroke symptoms and initiate risk factor assessment and counseling. However, while tools to support clinical assessment have been recommended by various guideline groups, recommendations for the use of clinical assessment, without accompanying diagnostic imaging, appear to be lacking.

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REFERENCES

1. Leading causes of death in Canada, 2009 [Internet]. Ottawa: Statistics Canada; 2012. Highlights. [cited 2013 Nov 22]. Available from: http://www.statcan.gc.ca/pub/84-215-x/2012001/hl-fs-eng.htm

2. Hakim AM, Silver F, Hodgson C. Organized stroke care: a new era in stroke prevention and treatment. CMAJ [Internet]. 1998 Sep 22 [cited 2013 Nov 13];159(6 Suppl):S1. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1255890/pdf/cmaj0159006000S1.pdf

3. Heart & Stroke Foundation. Statistics [Internet]. Ottawa: The Foundation; 2013. [cited 2013 Nov 13]. Available from: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3483991/k.34A8/Statistics.htm#stroke

4. Caplan LR. Overview of the evaluation of stroke. 2013 Mar 22. In: UpToDate [Internet]. Version 22.0. Waltham (MA): UpToDate; 1992 - . Available from: www.uptodate.com Subscription required.

5. Field TS, Green TL, Roy K, Pedersen J, Hill MD. Trends in hospital admission for stroke in Calgary. Can J Neurol Sci [Internet]. 2004 Aug [cited 2013 Nov 13];31(3):387-93. Available from: http://cjns.metapress.com/content/lv9twred80u74f2d/fulltext.pdf

6. The Quality of stroke care in Canada [Internet]. Ottawa: Canadian Stroke Network; 2011. [cited 2013 Nov 13]. Available from: http://www.canadianstrokenetwork.ca/wp-content/uploads/2011/06/QoSC-EN1.pdf

7. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, et al. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. Cochrane Database Syst Rev. 2009;(4):CD007424.

8. Cutlip D, Abbott JD. Coronary artery stent types in development. 2013 Sep 19 [cited 2013 Nov 15]. In: UpToDate [Internet]. Version 22.0. Waltham (MA): UpToDate; 1992 - . Available from: www.uptodate.com Subscription required.

9. Jauch EC, Saver JL, Adams HP, Jr., Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke [Internet]. 2013 Mar [cited 2013 Nov 21];44(3):870-947. Available from: http://stroke.ahajournals.org/content/early/2013/01/31/STR.0b013e318284056a.full

10. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol [Internet]. 2003 Nov 10 [cited 2013 Nov 15];3(25). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC305345

11. Oliveira-Filho J, Martins SC, Pontes-Neto OM, Longo A, Evaristo EF, Carvalho JJ, et al. Guidelines for acute ischemic stroke treatment: part I. Arq Neuropsiquiatr [Internet]. 2012

Aug [cited 2013 Oct 30];70(8):621-9. Available from: http://www.scielo.br/pdf/anp/v70n8/v70n8a12.pdf

12. Bryer A, Connor M, Haug P, Cheyip B, Staub H, Tipping B, et al. South African guideline for management of ischaemic stroke and transient ischaemic attack 2010: a guideline from the South African Stroke Society (SASS) and the SASS Writing Committee. S Afr Med J. 2010 Nov;100(11 Pt 2):747-78.

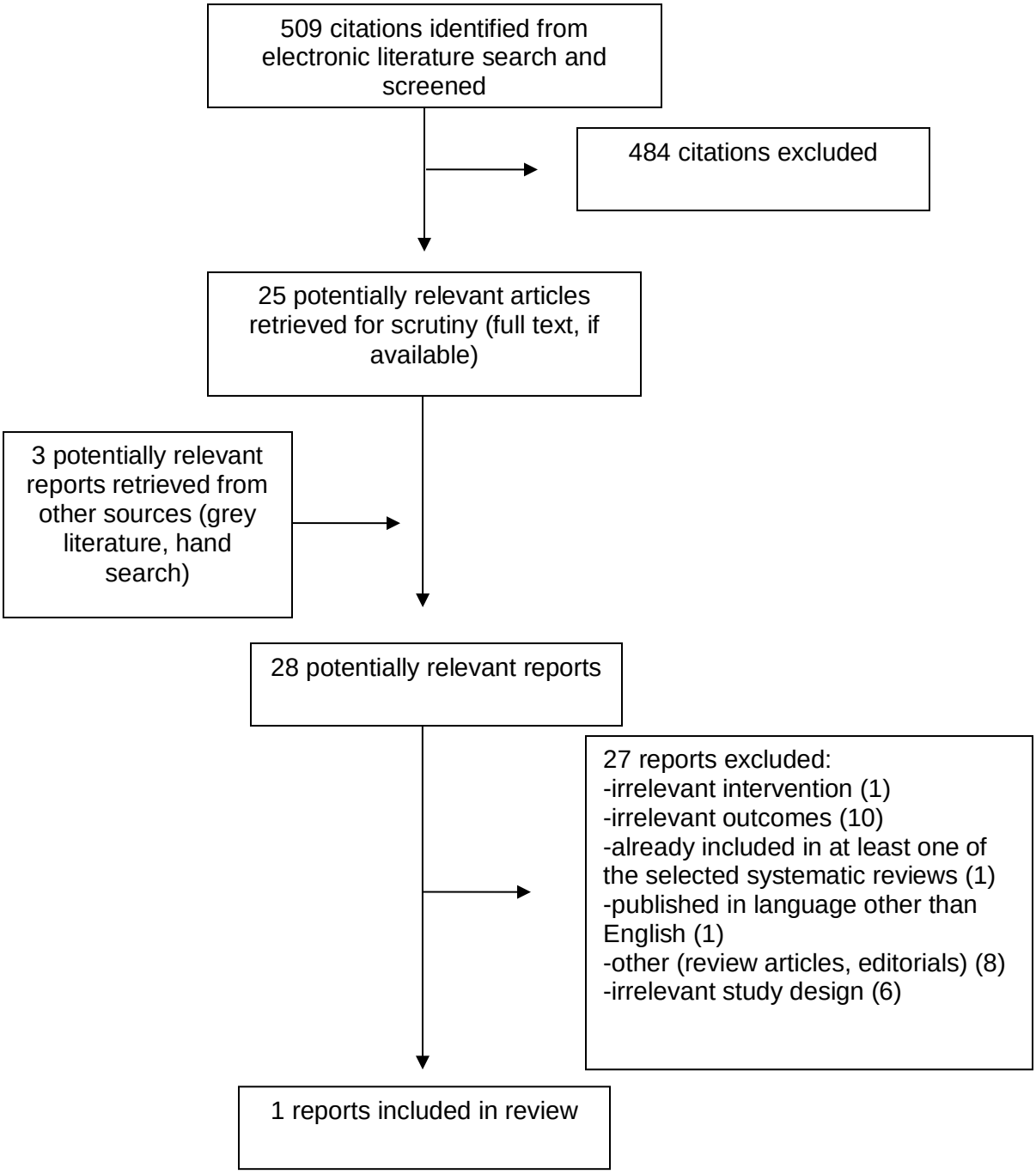
13. The National Collaborating Centre for Chronic Conditions. Stroke: national clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) [Internet]. London: Royal College of Physicians; 2008. [cited 2013 Nov 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK53295/pdf/TOC.pdf

14. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457-507.

15. National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); [1997] -. Guideline summary: Diagnosis and initial treatment of ischemic stroke; 2013 [cited 2013 Nov 13]. Available from: http://www.guideline.gov/content.aspx?id=38254

16. Nor AM, Davis J, Sen B, Shipsey D, Louw SJ, Dyker AG, et al. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. Lancet Neurol. 2005 Nov;4(11):727-34.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Systematic Review

Author, year, funding source	Key inclusion criteria, N studies	Interventions	Outcomes
Brazzelli et al., 2009[7] Unknown source of funding	RCTs (cut-off March 2009); assessing the diagnostic accuracy for acute ischemic stroke 7 non-randomized studies (226 patients)	• Diffusion-weighted MRI • Computed tomography	• Sensitivity • Specificity

MRI= magnetic resonance imaging

APPENDIX 3: Critical Appraisal of Systematic Reviews

Author, year	Strengths	Limitations
Systematic reviews		
Brazzelli et al., 2009[7]	• High quality systematic review • Comprehensive literature search was performed • The scientific quality of included studies was assessed • Independently extracted by three reviewers	• Methodological and clinical sources of heterogeneity were not investigated due to the limited number of included studies (n=7) with small sample sizes • Non-English articles were excluded • DWI and CT were evaluated in a highly selected patient sample (high probability of stroke) and not representative of a typical patient population presenting to an emergency department

CT= computed tomography; DWI= diagnostic accuracy of diffusion-weighted magnetic resonance imaging

APPENDIX 4. Summary of Findings from Brazzelli et al., 2009[7]

Outcome	Number of trials	Total number of participants (n)	Number of participants with CT (n)	Number of participants with DWI (n)	Summary effect (95% CI)
True positive	7	226	73	147	DWI sensitivity 0.99 (0.23 to 1.00)
False positive	7	226	0	5	DWI specificity 0.92 (0.83 to 0.97)
False negative	7	226	88	14	CT sensitivity 0.39 (0.16 to 0.69)
True negative	7	226	65	60	CT specificity 1.00 (0.94 to 1.00)

CI=confidence interval; CT= computed tomography; DWI= diffusion-weighted magnetic resonance imaging

APPENDIX 5. Summary of Recommendations from Clinical Practice Guidelines

Author, year, country	Recommendation	Rating of Evidence
American Heart Association/American Stroke Association (AHA/ASA, United States),[9]	**CT Scanning** "Patients with TIA should preferably undergo neuroimaging evaluation within 24 hours of symptom onset. MRI, including DWI, is the preferred brain diagnostic imaging modality. If MRI is not available, cranial CT should be performed" pg. 19	Strong recommendation based on a single high quality RCT or nonrandomized study
	Tests other than CT (diagnostic imaging) "Patients with stroke should have a careful clinical assessment, including neurological examination" pg. 13 "The use of a stroke rating scale, preferably the National Institutes of Health Stroke Scale (NIHSS), is recommended" pg. 13	Strong recommendation based on a single high quality RCT or nonrandomized study
Brazilian Stroke Society (SBDCV, Brazil),[11]	**CT Scanning** "For patients with acute stroke, an urgent non-contrast cranial CT is recommended (preferred) or, alternatively, cranial MRI with the inclusion of diffusion and gradient echo sequences." pg. 625	Strong recommendation based on high quality systematic reviews and studies
	Tests other than CT (diagnostic imaging) "Perform laboratory tests for exclusion of differential diagnoses and therapeutic decision aid" pg. 624	Weak recommendation based on expert opinion
South African Stroke Society (SASS, South Africa),[12]	**CT Scanning** "For patients with suspected stroke or TIA, urgent cranial CT (preferred) or MRI is recommended " pg. 764	Strong recommendation based on high quality studies
	Tests other than CT (diagnostic imaging) For patients with suspected stroke or TIA, blood glucose, full blood count, urea, creatinine, electrolytes tests are recommended (pg. 762)	Weak recommendation based on uncontrolled studies, case reports or expert opinion
National Collaboration Centre for Chronic Conditions (NCC-CC, United Kingdom),[13]	**CT Scanning** "People who have had a suspected TIA who need brain imaging (that is, those in whom vascular territory or pathology is uncertain) should undergo MRI with DWI except where contraindicated, in which case computed tomography (CT) scanning should be used." pg. 44	Weak recommendation based on non-analytic studies
	Tests other than CT (diagnostic imaging) "People who are admitted to accident & emergency (A&E) with a suspected stroke or TIA should have the diagnosis established rapidly using a validated tool, such as Recognition of Stroke in the Emergency Room (ROSIER)." pg. 28	Strong recommendation based on high quality systematic reviews and studies

European Stroke Organisation (ESO, Europe),[14]	**CT Scanning** In all suspected stroke patients, brain imaging such as CT or MRI are recommended (pg. 462)	Weak recommendation based on uncontrolled studies, case reports or expert opinion
	Tests other than CT (diagnostic imaging) In all suspected stroke patients, complete blood count and platelet count, prothrombin time, partial thromboplastin time, serum electrolytes, blood glucose, C-reactive protein or sedimentation rate, hepatic and renal chemical analysis (pg. 462)	Weak recommendation based on uncontrolled studies, case reports or expert opinion
Institute for Clinical Systems Improvement (ICSI, United States).[15]	**CT Scanning** "Patients presenting less than 24 hours since initial clinical TIA with high risk generally not leave the emergency department until brain imaging: MRI (preferred) or CT are completed or scheduled within the next few hours on an inpatient basis." (pg. 24) "If MRI is not available, a CT of the head is indicated." (pg. 24)	Strong recommendation based on moderate quality studies
	Tests other than CT (diagnostic imaging) A qualified clinician should evaluate patients with TIA or minor stroke symptoms and initiate risk factor assessment and counseling, and blood work including complete blood count, electrolytes, urea nitrogen, creatinine, International Normalized Ratio, activated partial thromboplastin time, fasting lipids, fasting glucose, HbA1c, troponins. (pg. 24)	Strong recommendation based on moderate quality studies

CI=confidence interval; CT= computed tomography; DWI= diagnostic accuracy of diffusion-weighted magnetic resonance imaging; TIA= transient ischemic attack