CHAPTER 3
Hyperacute Stroke Care
(UPDATE May 2013)

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on Behalf of the Acute Stroke
Best Practices Writing Group 2013
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CANADIAN BEST PRACTICE RECOMMENDATIONS FOR STROKE CARE

The Canadian Best Practice Recommendations for Stroke Care are intended to provide up-to-date evidence-based guidelines for the prevention and management of stroke. The goal of disseminating and implementing these recommendations is to reduce practice variations in the care of stroke patients across Canada, and to reduce the gap between knowledge and practice. Recommendations are updated on a rotating cycle every two years to ensure they continue to reflect contemporary stroke research evidence and leading expert opinion. Each update involves critical review of the current medical literature, which informs decisions regarding modification of the recommendations and the performance measures used to assess their impact. Every attempt is made to coordinate with other Canadian groups who are developing guidelines that relate to stroke, such as hypertension, atrial fibrillation and diabetes. As well, if significant new evidence becomes available in between update cycles, a process is in place to conduct a modified Delphi process to rigorously review the new evidence and gain consensus on the impact of that evidence on current recommendations. Modifications that are required through the consensus process will be made as soon as they are available, which is readily enabled through the web-based format of the Canadian stroke best practices.

This is the fourth edition of the Canadian Best Practice Recommendations for Stroke Care, which was first released in 2006. The theme of the 2012 – 2013 update is TAKING ACTION, and stresses the critical role and responsibility of healthcare providers at every stage of the continuum of care to ensure that best practice recommendations are implemented and adhered to. TAKING ACTION will lead to optimal outcomes for each stroke patient by providing the best care within the most appropriate setting. This includes rapid and efficient access to diagnostic services, stroke expertise and medical and surgical interventions, rehabilitation and support for ongoing recovery and community reintegration.

TAKING ACTION requires a committed team approach and strong coordination of care across regions and networks, with pre-hospital, acute care, rehabilitation and community-based healthcare providers working together to ensure optimal outcomes for patients and their families, regardless of geographic location.

TAKING ACTION also applies to patients who have experienced a stroke, their families and informal caregivers. Stroke patients and their families need to actively participate in their recovery and openly communicate with their healthcare team. Patients and families must participate in setting the goals they want to achieve during recovery from a stroke, and share concerns, as well as physical, mood and cognitive issues with their team, which will lead to the care required for optimal recovery in all aspects of health.

ALL CANADIAN BEST PRACTICE RECOMMENDATIONS FOR STROKE CARE, AS WELL AS SUPPORTING DOCUMENTS AND IMPLEMENTATION TOOLS CAN BE ACCESSED THROUGH OUR STROKE BEST PRACTICES WEBSITE AT: WWW.STROKEBESTPRACTICES.CA
SECTION 3.0 HYPERACUTE STROKE CARE OVERVIEW

TAKING ACTION IN HYPERACUTE STROKE CARE

TAKING ACTION is an imperative across stroke systems of care, healthcare providers, patients, families, and the broader community. The primary underpinnings of ‘hyperacute stroke care’ are to RECOGNIZE and MOBILIZE. This starts with recognition of stroke symptoms by patients, families and bystanders. Mobilization has to occur without delay, from emergency medical services response to a new stroke patient, transport to hospitals with specialized stroke services, rapid access to neuroimaging, stroke specialists and time-sensitive treatments, such as acute thrombolysis. A coordinated and seamless system taking all these components into account will minimize the time from stroke symptom onset (time last known well) to arrival at a hospital providing specialized stroke diagnostic and intervention services and lead to better outcomes.

TAKING ACTION for hyperacute care requires all healthcare professionals involved in this phase to have specialized stroke training, develop knowledge and skills for competent and efficient care delivery, and function as an integrated and seamless team. The hyperacute stroke team involves a range of providers from both the community and several hospital departments. Key team members during the hyperacute phase include primary care when patients with symptoms initially present to a community physician or nurse practitioner, emergency medical service professionals, emergency department physicians and nurses, stroke neurologists, diagnostic imaging, laboratory services, pharmacists, intensive care specialists, neuroradiologists, neurosurgeons and social workers. Several other specialists may be required in the hyperacute phase to meet the needs of individual patients and their unique clinical presentations. Communication among these professionals and departments are paramount to coordinated hyperacute care, and protocols and agreements should be in place for high priority rapid access to all specialists, departments and services required for each stroke patient to optimize outcomes and meet patient and family needs in the immediate post stroke time frame.

The Quality of Stroke Care in Canada (2011), which reported current levels of performance on key quality stroke indicators, found that more than one-third of stroke patients do not contact emergency medical services for transport to hospital, and only just over 30% of stroke patients arrived at hospital within the 3.5 hour time frame to be eligible for acute thrombolysis. Time to brain imaging was prolonged, and on average the time from arrival at hospital to tPA administration was greater than 60 minutes; exceeding the current one hour target for door-to-needle time. TAKING ACTION in hyperacute stroke care going forward aims to improve performance in these areas and thereby improve outcomes and reduces morbidity and long-term disability for all stroke patients.
HIGHLIGHTS OF THE HYPERACUTE STROKE CARE UPDATE 2013

The 2013 update of the Hyperacute Stroke Care Chapter of the Canadian Best Practice Recommendations for Stroke Care reinforces the growing and changing body of research evidence available to guide assessment, diagnosis and management in the first hours following a stroke.

Key messages for 2013 and significant changes to previous recommendations include:

✓ strong emphasis on educating the public to call 911 or local emergency number to access emergency services for on-site assessment, management and transport to appropriate facilities providing advanced stroke services;
✓ clarity on the critical role emergency medical services personnel play in all aspects of pre-hospital stroke care and communication with receiving hospital during transport;
✓ need for essential coordination among all hospital departments and services involved in hyperacute care to reduce process delays to acute thrombolysis;
✓ integration of the findings from the International Stroke Trial 3 (IST3) into thrombolysis recommendations and eligibility criteria;
✓ new recommendations on the management of seizures in the hyperacute phase of care;
✓ moderate updates to management of subarachnoid hemorrhage and Intracerebral hemorrhage patients in the first hours after onset, with stronger emphasis on the need for communication and coordination between the emergency department, stroke experts and neurosurgery services;
✓ update on the management of blood pressure in the hyperacute phase of care for ischemic stroke, subarachnoid hemorrhage and Intracerebral hemorrhage;
✓ new recommendations on the identification and evaluation of patients who may be candidates for hemicraniectomy;
✓ new guidance on addressing palliative care issues in patients with severe stroke;
✓ development of a Taking Action Towards Optimal Stroke Care resource kit including stroke care information, educational modules, summary tables and resource links.

HYPERACUTE STROKE CARE UPDATE 2013 RESOURCE PACKAGE INCLUDES:

i. Stroke Best Practice Recommendations for Hyperacute Stroke Care
ii. Taking Action Towards Optimal Stroke Care resource kit, with implementation materials and educational slide decks for all topic areas
iii. Hyperacute Stroke Care Assessment Tools Summary Tables
iv. Links to implementation tools for all topic areas
**Hyperacute and Acute Inpatient Stroke Care Definitions**

Hyperacute and Acute Stroke care involves all direct care, service delivery and interactions from first contact with the healthcare system after the onset of an acute stroke to discharge from an emergency department or acute inpatient care, and moving on to the next stage of care or return to the community.

**Hyperacute Stroke Care**

Hyperacute care refers to the key interventions involved in the assessment, stabilization and treatment in the first hours after stroke onset. This represents all pre-hospital and initial emergency care for TIA, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage and acute venous sinus thrombosis. This includes thrombolysis or endovascular interventions for acute ischemic stroke, emergency neurosurgical procedures, and same-day TIA diagnostic and risk stratification evaluation.

The principal aim of this phase of care is to diagnose the stroke type, and to coordinate and execute the treatment plan as rapidly as possible.

Hyperacute care is time-sensitive by nature, minutes for disabling stroke and hours for TIA, but specific interventions are associated with their own individual treatment windows. Broadly speaking “hyperacute” refers to care offered in the first 24 hours after stroke (ischemic and hemorrhagic) and the first 48 hours after TIA.

**Acute Stroke Care**

Acute care refers to the key interventions involved in the assessment, treatment or management, and early recovery in the first days after stroke onset. This will represent all of the initial diagnostic procedures undertaken to identify the nature and mechanism of stroke, interprofessional care to prevent complications and promote early recovery, institution of an individualized secondary prevention plan, and engagement with the stroke survivor and family to assess and plan for transition to the next level of care (including a comprehensive assessment of rehabilitation needs). New models of acute ambulatory care such as rapid assessment TIA and minor stroke clinics or day-units are also starting to emerge.

The principal aims of this phase of care are to identify the nature and mechanism of stroke, prevent further stroke complications, promote early recovery, and (in the case of severest strokes) provide palliation or end-of-life care.

Broadly speaking “acute care” refers to the first days to weeks of inpatient treatment with stroke survivors transitioning from this level of care to either inpatient rehabilitation, community based rehabilitation services, home (with or without support services), continuing care, or palliative care. This acute phase of care is usually considered to have ended either at the time of acute unit discharge or by 30 days of hospital admission.
CANADIAN STROKE BEST PRACTICES FRAMEWORK FOR OPTIMAL STROKE SERVICES DELIVERY

There are variations in the levels of stroke care service provided within the Canadian healthcare system. These services can be arranged along a continuum from minimal, non-specialized services provided in facilities that offer general medical and surgical care, to more advanced and comprehensive stroke care centres (See Figure 1). The goal for each organization involved in the delivery of stroke care services is to continue to develop the expertise and processes needed to provide optimal patient care, taking into consideration that organization’s geographic location, patient population, structural resources, and relationship to other centres within their healthcare region or system. Once a level of stroke services has been achieved, the organization should strive to develop and incorporate components of the next higher level for ongoing growth of stroke services where appropriate, as well as continuous quality improvement within the level of service currently provided.

Figure 1: CANADIAN STROKE BEST PRACTICES FRAMEWORK FOR OPTIMAL STROKE SERVICES DELIVERY

FOR ADDITIONAL INFORMATION AND DETAILS ABOUT THE STROKE SERVICES FRAMEWORK, PLEASE REFER TO THE “TAKING ACTION TOWARDS OPTIMAL STROKE CARE” RESOURCE AVAILABLE AT WWW.STROKEBESTPRACTICES.CA
DEVELOPMENT OF THE CANADIAN BEST PRACTICE RECOMMENDATIONS FOR STROKE CARE

For detailed methodology on the development and dissemination of the Canadian Best Practice Recommendations for Stroke Care please refer to the stroke best practices website at http://www.strokebestpractices.ca/index.php/methods/.

Acknowledgements

The Canadian Stroke Best Practices Team, Heart and Stroke Foundation and the Canadian Stroke Network gratefully acknowledge the writing group leaders and members, the external reviewers, all of who have volunteered their time and expertise to this update. We thank the Canadian Stroke Quality and Performance Advisory Group for their work in updating and confirming the performance measures that accompany each recommendation. We acknowledge Norine Foley and Katherine Salter for their work on implementation tool development. We are grateful to Dr. Robert Teasell, Andrew McClure and their team for work on the systematic reviews of the literature and evidence tables; and, we thank Marie-France Saint-Cyr and Jan Carbon for their work on the French translations. All participants complete a Conflict of Interest form and these are reviewed by the CSN privacy officer for risk assessment.

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Citing the Hyperacute Stroke Care Update 2013


Comments

We invite comments, suggestions, and inquiries on the development and application of the Canadian Best Practice Recommendations for Stroke Care and ongoing updates.

Please forward comments to the Heart and Stroke Foundation Stroke Best Practices and Performance team at strokebestpractices@hsf.ca
## Canadian Best Practice Recommendations for Stroke Care

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UPDATE: May 23rd, 2013
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Best Practice Recommendation 3.1
Outpatient Management of Transient Ischemic Attack and Non-Disabling Ischemic Stroke


3.1.1 Timing of Initial Assessment
i. Highest Risk for Stroke Recurrence: Patients who present to a family physician’s office, nurse practitioner, other community primary care setting, or other ambulatory care setting within 48 hours of a suspected transient ischemic attack or non-disabling ischemic stroke and with persistent or fluctuating motor or speech symptoms or other clinically localizable symptoms are considered at highest risk of recurrent stroke, and should have an immediate clinical evaluation and investigations to establish the diagnosis, rule out stroke mimics, and develop a stroke management plan [Evidence Level B].

a. These high risk patients should be immediately transferred to the closest emergency department that has access to neurovascular imaging facilities and stroke expertise [Evidence Level B].

ii. Patients who present to a family physician’s office, nurse practitioner, other community primary care setting, or other ambulatory care setting between 48 hours and 2 weeks from time last known well, and without persistent or fluctuating motor or speech symptoms or other clinically localizable symptoms, are considered at increased risk for recurrent stroke, and should receive a comprehensive clinical evaluation and investigations within 24 hours of first contact with the healthcare system [Evidence Level B].

a. Patients identified as at increased risk who cannot be evaluated as an outpatient within 24 hours from clinical presentation should be reviewed by a stroke expert either through physician to physician telephone consultation, telestroke consult using 2-way video conferencing with the patient and a stroke expert, or through an in person consultation; or, the patient should be transported to an emergency department that has access to neurovascular imaging facilities and stroke expertise [Evidence Level B].

iii. Patients presenting to a family physician’s office, nurse practitioner, or other community primary care setting more than two weeks following a suspected transient ischemic attack or non-disabling ischemic stroke, and/or those patients experiencing isolated sensory symptoms (such as tingling) may be considered as less urgent, and should be seen by a stroke specialist for evaluation, generally within one month of presentation [Evidence Level B].

3.1.2 Evaluation
i. All patients with suspected transient ischemic attack or non-disabling ischemic stroke
should undergo an initial assessment that includes: brain imaging, non-invasive vascular imaging (for carotid territory transient ischemic attacks or non-disabling strokes), such as carotid dopplers, CT angiography or magnetic resonance angiography, and an electrocardiogram, within the time frames recommended in 3.1.1, based on level of urgency [Evidence Level B]. Refer to Recommendation 3.3 for additional information.

ii. The following laboratory investigations should be undertaken routinely for patients with suspected transient ischemic attack or non-disabling ischemic stroke as part of the initial evaluation: haematology (CBC), electrolytes, coagulation (aPTT, INR), renal function (creatinine, glomerular filtration rate), troponin, fasting lipid profile, fasting glucose level and HbA1c, and thyroid-stimulating hormone (TSH) [Evidence Level C].

   a. Additional blood work is recommended in the following patients: patients with a prothrombotic state such as cerebral venous thrombosis, deep vein thrombosis and stroke owing to paradoxical embolism; young patients with ischemic stroke or TIA; and/or where a vasculitic cause is suspected [Evidence Level C]. Refer to Table 3.3B for additional information on recommended laboratory investigations.

iii. Echocardiogram should be performed in cases where stroke mechanism has not been identified, especially in children and younger adults with stroke or TIA [Evidence Level C].

iv. Holter monitoring should be performed in cases where cardioembolic mechanism is suspected, and where another stroke mechanism has not been identified [Evidence Level C].

v. Patients with non-disabling ischemic stroke who are not admitted to hospital should be assessed for the need to have a comprehensive outpatient assessment of functional impairment, which should include a cognitive evaluation, screening for depression, screening of fitness to drive, and functional assessments for potential rehabilitation treatment [Evidence Level B].

   a. Referral should be made to an appropriate rehabilitation program, and assessment should take place ideally within one week of first presentation to the healthcare system [Evidence Level C]. Refer to Recommendations 5.1 and 5.6 for additional information.

3.1.3 Management (Also refer to Chapter 2: Prevention of Stroke for additional guidance)

i. All patients with transient ischemic attack or non-disabling ischemic stroke who are not on an antiplatelet agent at time of presentation should be started on antiplatelet therapy immediately after brain imaging has excluded intracranial hemorrhage [Evidence Level A].

   a. A loading dose of ASA should be at least 160 mg. [Evidence Level A].

   b. If clopidogrel is used, a loading dose of 300 mg should be given then maintenance therapy should be started according to parameters set out in recommendation 2.5 for antiplatelet therapy for secondary stroke prevention [Evidence Level A]. Refer to Recommendation 2.5 for additional information.

ii. Patients with transient ischemic attack or non-disabling stroke and ipsilateral 50 to 99 percent internal carotid artery stenosis (measured by two concordant non-invasive imaging modalities such as dopplers, CTA, or MRA) should be evaluated by an individual with stroke expertise (neurosurgeon/vascular surgeon) and selected patients should be offered carotid endarterectomy as soon as possible, with the goal of operating within fourteen days of the incident event once the patient is clinically stable [Evidence Level
A]. Refer to Recommendation 2.7 for additional information.

iii. Patients with transient ischemic attack or non-disabling ischemic stroke with atrial fibrillation should receive oral anticoagulation therapy with apixaban, dabigatran, or rivaroxiban [Evidence Level A], or warfarin [Evidence Level A]. Therapy should be started as soon as it is thought to be safe for the patient. Refer to Recommendation 2.6 for additional information.
   a. For patients on warfarin, the target therapeutic International Normalized Ratio (INR) is 2.5 with a range of 2.0 to 3.0 [Evidence Level A]. Refer to Recommendation 2.6 for additional information.
   b. For patients with acute ischemic stroke and atrial fibrillation, routine use of bridging with heparin or heparinoid anticoagulation is not recommended [Evidence Level A]. Most physicians would use ASA 81 mg daily until the patient is anticoagulated [Evidence Level C]. Refer to Recommendation 2.6 for additional information.

iv. All risk factors for cerebrovascular disease must be aggressively managed through pharmacological and non-pharmacological means to achieve optimal control [Evidence Level A]. While there is a lack of conclusive evidence supporting acute-phase modification of individual risk factors, there is evidence of benefit from a comprehensive approach, which includes initiating or modifying antihypertensive therapy and statin medication [Evidence Level C]. Refer to Chapter 2. Stroke Prevention recommendations for additional information.

v. Patients with transient ischemic attack or non-disabling ischemic stroke who smoke should be strongly advised to quit immediately, and be provided with the pharmacological and non-pharmacological means to do so [Evidence Level B]. Refer to Recommendation 2.9 for additional information.

Rationale
The goal of outpatient management of transient ischemic attack and non-disabling ischemic stroke is rapid assessment and management to reduce the risk of a recurrent, possibly more serious, event.

There is clear evidence that transient ischemic attacks or minor strokes are unstable conditions that warn of high future risk of stroke, other vascular events, or death. The risk of recurrent stroke after a transient ischemic attack is 10 to 20 percent within 90 days, and the risk is “front-loaded”, with half of the strokes occurring in the first two days following initial symptom onset. The seven-day risk of stroke following a transient ischemic attack can be as high as 36 percent in patients with multiple risk factors. Timely initiation of secondary prevention medical therapy and carotid endarterectomy has been shown to significantly reduce the risk of major stroke after an initial transient ischemic attack or non-disabling stroke.

System Implications
- Education for the public and healthcare providers about the urgency of assessment and management of transient ischemic attack or non-disabling ischemic stroke is critical to reduce the risk of recurrent, potentially more serious events. Patients and families will also require ongoing education and support related to prevention and management of stroke.
- Physicians who work in primary, secondary, and tertiary care settings who have education, training, and knowledge to manage patients with transient ischemic attack or non-disabling ischemic stroke.
- Processes and protocols in community healthcare settings and acute healthcare facilities to
enable rapid access to diagnostic tests and expertise for patients with transient ischemic attack or minor stroke.

- Established and accessible stroke prevention clinics, or broader vascular prevention programs in all communities, and healthcare practitioners who are aware of these programs. These resources should be listed, easily accessible to primary care physicians and healthcare providers, and updated annually.
- Any suspicion of ischemic stroke warrants an emergent consult or assessment in a pediatric emergency department. All hospitals should have a referral process established with the closest specialized pediatric facility.

Performance Measures

1. Proportion of acute stroke and TIA patients who are discharged alive from an emergency department or after an inpatient stay and then readmitted to hospital with a new stroke diagnosis within 90 days of index acute care discharge (core).

2. Time from first encounter with medical care (primary care or emergency department) to assessment by a stroke expert (in clinic or other setting).

3. Time from first encounter with medical care to brain imaging (CT/MRI) and vascular imaging (Doppler of cervical arteries, CT or MR angiography) and electrocardiogram.

Measurement Notes

- Data access and quality with respect to timing of first encounter and referral dates and times.
- Primary care data from physician billing. This should rely on International Classification of Diseases (ICD) codes and not on physician descriptions of diagnoses, as these may be less accurate.
- Measures from other prevention recommendations in this document also apply applicable to this recommendation but are not repeated here.

Implementation Resources and Knowledge Transfer Tools

- Taking Action Towards Stroke Prevention Pocket Cards 2012

- Taking Action Towards Stroke Prevention Posters 2012

- Canadian Stroke Best Practices Table 3.3A: Screening and Assessment Tools for Acute Stroke

- Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2012
  http://download.journals.elsevierhealth.com/pdfs/journals/0828-282X/PIIS0828282X12000463.pdf

- American College of Chest Physicians (ACCP) Guidelines for Diagnosis & Management of DVT / PE, 9th Ed.

- Canadian Association of Radiologists 2012 guidelines

- HSF Stroke Nurses Assessment Pocket Cards
  http://www.heartandstroke.on.ca/site/c.pv13teNWJwE/b.5852913/k.AC4B/Order_Resourc
Summary of the Evidence

The highest risk of recurrent stroke for patients presenting with TIA or minor stroke is within the first week of symptom onset (Giles & Rothwell, 2007). A systematic review by Giles et al. assessing risk of recurrent stroke found a pooled risk of 3.1% at day 2 and 5.2% at day 7 (Giles & Rothwell, 2007). Rates of recurrence are quite variable in the literature; however a general trend of decreasing recurrence rates after the first month has been found (Thacker et al., 2010). Thacker et al. identified an OR of 30.4 (95% CI 10.4 to 89.4) within the first month, OR of 18.9 (95% CI 8.58 to 41.6) from one to three months, and continual decreasing odds of recurrent stroke thereafter (Thacker et al., 2010). These findings highlight the value of assessing patients who present with suspected stroke or TIA according to time since onset of symptoms.

It is particularly important for healthcare personnel at non-emergent health centers, such as a family physician’s offices to refer a suspected stroke or TIA to appropriate assessment and diagnostic services. A study by Chandratheva et al. found that 72.1% of patients with minor stroke and 77.3% of patients with TIA accessed a general practitioner as their first contact with the healthcare system following a suspected stroke or TIA (Chandratheva et al., 2010). Recognizing symptoms are further complicated when a patient waits to access care. Delays in seeking care are particularly evident for patients who fail to recognize their symptoms, experience no motor or speech deficits and have a TIA of short duration (Chandratheva et al., 2010).

Several screening tools are available for use to assess the likelihood of recurrent stroke in patients presenting with TIA. Purroy et al. found that the ABCD scoring tool with vascular imaging offers the greatest ability to predict recurrent stroke in the short term and long term in the population of patients included in their study (Purroy et al., 2012). Patients who have immediate access to services that offer diagnostic testing such as imaging achieve better outcomes. Rothwell et al. found that immediate access to a stroke unit and timely initiation of prophylactic medication resulted in fewer recurrent strokes and fewer adverse events for patients compared to patients who had a lengthier delay in receiving this care (Rothwell et al., 2007).

For patients with TIA or minor stroke, a CT/CTA performed within 24 hours has been found to be predictive of recurrent stroke at 90 days (Coutts et al., 2012). A positive CT/CTA was the only clinical and imaging parameter that remained a significant predictor of recurrent stroke in the multivariable analysis performed in this study (Coutts et al., 2012). An electrocardiogram (ECG) can help to further identify patients at risk of recurrent stroke. A prospective cohort study that evaluated the effectiveness of serial ECGs and Holter monitoring for the identification of atrial fibrillation in patients post stroke found that both were equally effective in identifying cases that were not present on a baseline assessment (Douen et al., 2008). The two diagnostics together (serial ECGs and a Holter monitor) offer the greatest ability to detect possible causes of stroke (Douen et al., 2008). For patients whose stroke etiology is unknown, an echocardiogram may be beneficial. deBruijn et al found that it was useful for patients of all ages in the population included in their study to identify possible sources of cardiac embolism (de Bruijn et al., 2006).

Laboratory investigations and assessment of physiological variables as part of a patient’s initial assessment after minor stroke or TIA can be considered if the patient’s medical history includes factors that increase their risk of recurrent stroke.
evaluation provides important information for patient management. A small preliminary case control study found that maintenance of normal physiological variables within the first three days of stroke has a beneficial effect on outcomes post stroke (Langhorne et al., 2000). Furthermore, blood biomarkers have been found to correlate with cerebral lesion size and stroke severity (Kisialiou et al., 2012). Ferrari et al. found that hypertension, diabetes, possible etiology, acute infection and cardiac abnormalities were predictors of deterioration for patients presenting with TIA or minor stroke (Ferrari et al., 2010). The researchers recommend immediate diagnostic testing to identify these risk factors in patients post TIA or minor stroke (Ferrari et al., 2010). Together, these findings suggest a complete evaluation of patients presenting with suspected stroke or TIA is beneficial for predicting risk of recurrent stroke and guiding patient management.

Link to Evidence Table 3.1 and References available on website at www.strokebestpractices.ca
Best Practice Recommendation 3.2
Emergency Medical Services Management of Acute Stroke Patients

NOTES on this recommendation

Only about half of all patients who seek acute care for stroke arrive at the emergency department by ambulance, while a significant proportion of the rest will seek help from their primary care physician. This section addresses management of patients with stroke and transient ischemic attack in these two care settings.

Following extensive consultation, two timelines have been established to provide emergency medical services in Canada within the 4.5 hour-window from symptom onset to administration of thrombolytic therapy. These are:

(1) The pre-hospital phase that starts with symptom onset and includes on-scene management and transport time, which should be 3.5 hours or less; and

(2) The emergency department phase that includes the diagnostic evaluation and consideration of treatment options, which should be 60 minutes or less.

♦ This recommendation covers management of potential stroke patients between the time of first contact with the local emergency medical services to transfer of care to the hospital, as well as care of suspected or confirmed stroke patients who are being transferred between healthcare facilities by emergency medical services.

♦ This recommendation is directed to paramedics and those individuals who support emergency medical services, including communications officers and dispatchers. It also applies to other first responders such as emergency medical responders and primary care paramedics who have been trained to screen for stroke and manage potential stroke patients during transfer.

♦ These guidelines are intended to be translated into practice by the entire breadth of out-of-hospital healthcare providers within the defined scope of practice of each. This includes EMS professionals such as paramedics and emergency medical dispatchers, but also allied EMS providers such as medical first responders and emergency medical responders.

* Local variations need to be taken into consideration for pre-hospital time.

3.2 Out-of-hospital patient management should be optimized to meet the needs of suspected acute stroke patients, including recognition, management and transport, usually done concurrently [Evidence Level A].

3.2.1 ACCESS to Emergency Medical Services (EMS)
   i. Immediate contact with emergency medical services (e.g., 911) by patients or other members of the public is strongly recommended; it reduces time to treatment for acute stroke [Evidence Level B]. Refer to Recommendation 1.1 for additional information on Signs and Symptoms of Stroke
   ii. EMS Communications Centre: All regions should implement a dispatch process through the emergency medical services (EMS) communications centre to recognize the probable stroke symptoms, urgency, potential diagnosis, and need for priority response to the scene and transport to a hospital capable of providing
services for the rapid diagnosis and treatment of stroke [Evidence Level C].

iii. After dispatching the ambulance, the personnel at the EMS communications centre should provide pre-arrival instructions (such as unlock door, move pets, determine stroke symptom onset time, determine current medications) to the patient or person reporting the stroke, in order to expedite and optimize pre-hospital care [Evidence Level C].

iv. The personnel at the EMS communications centre should convey relevant information (such as symptom-onset time or time last known well, and availability of alternate decision-maker) to the responding paramedics while they are on route [Evidence Level C].

3.2.2 EMS On Scene Management

On-scene goal is to ‘recognize and mobilize’ – it is of the utmost importance proceed rapidly and safely to transport these patients as on-scene management for stroke patients is limited.

i. EMS personnel should be aware that stroke can affect individuals of any age, including children, adolescents and young adults as well as older adults [Evidence Level C].

ii. EMS personnel should use a standardized acute stroke out-of-hospital diagnostic screening tool as part of on scene assessment [Evidence Level B]. Refer to Table 3.2 Canadian Stroke Best Practices Table of Standardized Acute Stroke Out-of-Hospital Diagnostic Screening Tools.

iii. EMS personnel should obtain information from patient and/or family members about the suspected stroke event (presenting symptoms, time of onset or time of symptom recognition or time last known well, and sequence of events), co-morbid conditions, and any formal or informal advance directives that may influence care by EMS and in the emergency department [Evidence Level C].

iv. On-scene time with suspected stroke patients should be as short as possible; ideally less than 15 minutes for patients who present within the 4.5-hour time window [Evidence level C].

v. Initial care provided by paramedics on-scene must include blood glucose measurement [Evidence Level B].

vi. Prior to transport, EMS personnel should provide education and instructions to family, including recommend the family/decision-maker accompany patient to hospital or be accessible by phone for decision-making, confirming time last known well, and be able to provide required information about existing health conditions, current medications and other information as needed [Evidence Level C].

Note: Screening for potential stroke should be done early in the on-scene assessment. If the stroke screen is positive and the patient is eligible for reperfusion, all actions on scene from that point should be directed at moving to the ambulance and beginning transport. All treatments not immediately required (IV’s, etc.) should wait until the patient is en route to the hospital. Scene time is an important variable that EMS professionals can control and needs to be monitored very closely. Time lost due to inefficient scene care cannot be made up during subsequent transport to hospital (e.g., through use of lights and sirens).
3.2.3 Transport of Suspected Stroke Patients

i. **Direct Transport Protocols** must be in place to facilitate the transfer of suspected hyperacute stroke patients who are potentially eligible for thrombolytic therapy to the closest and most appropriate acute care facility capable of providing services for the diagnosis and hyperacute treatment of stroke [Evidence Level C].

ii. Direct Transport Protocol criteria must be based on:
   a. the medical stability of the patient;
   b. the advanced acute stroke care emergency department performance which is recommended as being 60 minutes or less from arrival to treatment time (door-to-needle time);
   c. the pre-hospital phase, including symptom duration and anticipated transport time, being 3.5 hours or less; and
   d. other acute care needs of the patient [Evidence Level B].

iii. The emergency medical services system must be set up to categorize patients exhibiting signs and symptoms of a hyperacute stroke as a high priority for evaluation, response and transport [Evidence Level C].

iv. Patients with suspected stroke should be triaged by EMS personnel as Canadian Triage Acuity Scale (CTAS) Level 2 in most cases, and as a CTAS Level 1 for patients presenting with severe symptoms or compromised airway, breathing or cardiovascular function [Evidence Level B].
   a. For pediatric stroke cases, patients with suspected stroke should be triaged by EMS personnel as Pediatric Canadian Triage Acuity Scale (P-CTAS) Level 2 in most cases, and as a P-CTAS Level 1 for patients presenting with severe symptoms or compromised airway, breathing or cardiovascular function [Evidence Level C].

v. While en route to the receiving hospital, paramedics should notify the emergency department of the incoming suspected hyperacute stroke patient; a “Code Stroke” may be activated at this time in hospitals where acute stroke protocols are in place [Evidence Level B].

vi. Patients who are considered ineligible for time-sensitive thrombolytic therapy should be transported urgently (either directly or indirectly) to the closest hospital capable of providing services for the rapid diagnosis and treatment of stroke (emergency department, access to neuroimaging, and stroke expertise on site or through telestroke) [Evidence Level C].

3.2.4 Hospital Arrival and EMS Handover to Emergency Department Staff

i. Transfer of care from paramedics to receiving facility personnel should occur with minimal delay; patients with suspected hyperacute stroke who are potentially eligible for thrombolytic therapy should receive the highest priority in the ED triage queue [Evidence Level B]. Refer to Recommendation 3.3 for more information.

ii. Paramedics should provide the receiving hospital with the following information during patient transport or on hospital arrival: time of stroke onset or time of symptom recognition or time when last known well (as accurate as possible), total symptom duration time at anticipated time of arrival in the ED, Glasgow Coma Scale score (GCS), CTAS triage score (or P-CTAS), patient age, and expected time of arrival at
the receiving hospital [Evidence Level C].

a. Paramedics should ensure all information noted in ‘i’ is documented on the patient’s EMS record and provided to the receiving hospital during transport with prenotification and upon arrival to the hospital [Evidence Level B].

Clinical Considerations:
- The term ‘eligible’ is usually defined within regional jurisdictions. Generally it refers to acute stroke patients within the 4.5 hour time window, however local definitions should be clarified during implementation of these guidelines.
- In some institutions the TPA time frame may extend beyond 4.5 hours under the directive of a research protocol. These factors should be taken into consideration during transport and prior agreements should be in place between the EMS dispatch and the receiving hospitals.
- In regions with a specialized paediatric hospital every attempt should be made to transport children with symptoms of stroke to that specialized paediatric hospital.

Rationale
Hyperacute stroke is a medical emergency and optimizing out-of-hospital care improves patient outcomes. Emergency medical services play a critical role in out-of-hospital (pre-hospital) assessment and management of suspected stroke patients. Acute interventions such as thrombolytic therapy are time-sensitive and therefore strategies such as re-directing ambulances to stroke centres facilitate earlier assessment, diagnosis, and treatment, and may result in better outcomes.

System Implications
- Programs to train all emergency medical services personnel regarding stroke assessment, management, and transport requirements in the pre-hospital phase of care.
- Paramedic education that includes the recognition of the signs and symptoms of acute stroke and the need to provide appropriate out-of-hospital treatment.
- Ongoing paramedic education on the use of validated and rapid pre-hospital stroke screening protocols and tools and the ability to incorporate such protocols and tools into all pre-hospital assessments of suspected stroke patients. The Canadian Stroke Best Practices group has developed assessment tools in collaboration with emergency medical service leaders for implementation across Canada.
- Direct transport agreements (bypass or redirect) between emergency medical service providers and regional health authorities and/or receiving facilities.
- Emergency medical service providers who are able to provide coordinated seamless transport (land, water, and air) and care for acute stroke patients.
- Communication systems such as telemedicine to support access to specialized stroke services.
- Each region that has adult and paediatric acute services should develop criteria for transporting children with suspected stroke – based on symptoms and age – to paediatric versus adult stroke centres. These criteria should be agreed upon by both centres and EMS.

Performance Measures
1. Time from initial call received by emergency dispatch centre to patient arrival at an emergency department that provides stroke services.
2. Percentage of (suspected) stroke patients arriving in the emergency department who
were transported by emergency medical services.

3. Proportion of acute stroke patients transported by EMS to the correct (i.e. designated hyperacute treatment enabled facility) centre as first hospital destination. Target greater or equal than 90%.

4. Proportion of acute stroke patients presenting to the emergency department as a result of EMS transport versus “walk in”. Target greater or equal than 90%.

5. Time from initial call received by emergency dispatch centre to emergency medical services arrival on scene.

6. Time from emergency medical services arrival on scene to arrival at the receiving emergency department (ideally at a stroke centre providing required services for patient).

7. Percent of EMS transports of ischemic stroke patients with symptoms less than 4.5 hours for which the receiving hospital received notification en route (pre-notification) of an incoming acute stroke patient.

8. Percentage of EMS calls where out-of-hospital time is less than 3.5 hours from time last known well to arrival at the emergency department (performance target is ≥ 75 percent).

9. Percentage of potential stroke patients transported by emergency medical services who received a final diagnosis of stroke or transient ischemic attack in the emergency department or at hospital discharge.

10. For paediatric stroke patients, the time from initial presentation to any entry point in the healthcare system with symptoms of stroke to a confirmed diagnosis of stroke is received.

**Measurement Notes**

- Emergency department records and administrative databases track stroke patients who arrive by ambulance (land, air, or water) as a standard data element.
- "Appropriate" emergency department refers to an emergency department that has access to a CT scanner in the facility, provides access to acute thrombolysis, and has medical personnel with stroke expertise available for emergent consult.
- An appropriate/acceptable ‘over-triage’ rate should be less than 15%.
- Refer to the Canadian Stroke Performance Measurement Manual for additional measures related to hospital bypass and pre-notification.

**Implementation Resources and Knowledge Transfer Tools**

- Table 3.2: Canadian Stroke Best Practices Table of Standardized Acute Stroke Out-of-Hospital Diagnostic Screening Tools.
- Canadian Triage Acuity Scale for adults (CTAS) and Pediatric Scale (P-CTAS) http://caep.ca/resources/ctas

**Summary of the Evidence**

Patients arriving to hospital by EMS (emergency medical services) experience fewer delays in receiving appropriate diagnostic tests (e.g. brain imaging) and are more likely to receive tPA if eligible (Patel et al., 2011). Delays may also be reduced by identifying urgent cases through the use of an EMS dispatch process. For example, Berglund et al. found that a population of patients assigned a higher priority level by
dispatching personnel experienced fewer delays along the chain of stroke care from symptom onset to arrival at a stroke unit and had greater access to tPA (Berglund et al., 2012).

To further expedite the transport of patients to hospital, the use of screening tools for on-scene diagnosis of stroke is recommended. Common pre-hospital screening tools for which validation studies have been identified include the CPSS (Kothari, Pancioli, Liu, Brott, & Broderick, 1999), LAPSS (Kidwell et al., 2000), MASS (Bray et al., 2005), Ontario Prehospital screening tool (Chenkin et al., 2009), and the ROISER scale (Mingfeng et al., 2012). The CPSS is a 3-item tool that is intended to identify suspected stroke patients and potential candidates for thrombolysis on the basis of three physical symptoms: facial drooping, arm drift, and speech as abnormal or normal. The presence of one abnormal finding is a positive screen and indicates that the patient may be a candidate for thrombolysis (Kothari et al., 1999). The LAPSS includes two of the three physical assessment criteria that are included in the CPSS (facial droop and arm drift) but also includes criteria associated with patient history, including age, history of seizure, pre-morbid independence, blood glucose measure, and time of symptom onset. A patient is identified as having a suspected stroke when all history criteria responses are “Yes” and there is at least one abnormal physical symptom (Kothari et al., 1999). The MASS, Ontario Prehospital stroke screen and the ROISER contain items that reflect those included in the CPSS and LAPSS but use a different scoring system. Although the LAPSS is reported to have the highest specificity (up to 99%) (Kidwell et al., 2000) among the tools listed above, evaluation of psychometric properties does not provide a clear indication for the use of any particular tool.

Blood glucose measurement is an important component of paramedic protocols; however, there is limited evidence to support the initiation of blood glucose control in the pre-hospital setting. Nurmi and colleagues evaluated the effect of IV and subcutaneous insulin therapy in the pre-hospital setting as compared to a parallel non-randomized control group (n=61, with 23 in the intervention group) (Nurmi et al., 2011). Nurmi et al. reported that blood glucose was effectively lowered upon arrival to hospital (with IV insulin administration) but extended the time EMS personnel spent on scene (Nurmi et al., 2011).

In general, the available literature examining interventions for EMS processes in the pre-hospital phase of stroke care is limited. However, a systematic review that included studies published from 2000 to 2010 found that rates of thrombolysis were highest in settings that had a stroke code system in place (Dalloz et al., 2012). A stroke code system may include efforts to improve the identification, transport and presentation of suspected stroke patients to the emergency department. For example, McKinney and colleagues reported that an EMS pre-notification system to the hospital was effective in reducing in-hospital delays for diagnostic tests (McKinney et al., 2013).

Link to Evidence Table 3.2 and References available on website at www.strokebestporactices.ca
### Table 3.2  Canadian Stroke Best Practices Table of Standardized Acute Stroke Out-of-Hospital Diagnostic Screening Tools.

<table>
<thead>
<tr>
<th>Assessment Tool</th>
<th>Number and description of Items</th>
<th>Time to Administer</th>
<th>Reliability/validity</th>
<th>Interpretation of Scores</th>
<th>Training Required</th>
<th>Assessment Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cincinnati Pre-Hospital Stroke Scale (CPSS)(1)</td>
<td>3 items: presence/absence of facial palsy, unilateral arm weakness and speech impairment. Items simplified versions from the NIHSS.</td>
<td>Rapid, not reported.</td>
<td>Inter-observer reliability: ICC in pre-hospital care providers (paramedics and EMTs) = 0.89 for total score, 0.91, 0.84, 0.75 for arm weakness, speech and facial droop respectively. Between pre-hospital providers and physicians, ICC=0.92 (total) and 0.91, 0.87 and 0.78 each of the items as listed above (1)</td>
<td>Abnormality demonstrated on one or more items is considered indicative of suspected stroke.</td>
<td>The scale developers reported that using discharge diagnosis with stroke as the gold standard, physician assessment of abnormality on any one CPSS item was associated with a sensitivity of 66% and specificity of 87%. For paramedics/EMTs, sensitivity = 59%, specificity = 89%, (1) Other studies have mostly confirmed (or exceeded) the high level of sensitivity associated with use of the CPSS (ranging from 71%(2) to 95%(3, 4). A single study reported a very low sensitivity of 44%(5). However, most studies have demonstrated low levels of specificity associated with the use of the CPSS ranging from 24%(6) - 56%(4).</td>
<td>No* See note below.</td>
</tr>
<tr>
<td>Face Arm Speech Test (FAST)(7, 8)</td>
<td>3 items derived from the CPSS: facial palsy, arm weakness, speech disturbance. Assessment of speech is not dependent on the repetition of</td>
<td>Rapid.</td>
<td>Inter-observer reliability: Agreement between paramedic and physician examiners was moderate to good, k=0.49 (facial palsy), k=0.77 (arm weakness), k=0.69 (speech)</td>
<td>As above.</td>
<td>Scale developers demonstrated diagnostic sensitivity of FAST associated with paramedic use to be 79%, (8) Other studies have demonstrated higher levels of sensitivity ranging from 81%(10) to 95%(3). However, like the CPSS, specificity tends to be far lower ranging from 33%(3) to 39%, (10)</td>
<td>Yes.(8)</td>
</tr>
</tbody>
</table>
# Section 3: Hyperacute Stroke Care Recommendations

## Los Angeles Prehospital Stroke Screen (LAPSS)\(^{(11)}\)

<table>
<thead>
<tr>
<th>a stock phrase.</th>
<th>disturbance(^{(9)})</th>
<th>If the patient has positive criteria, a blood glucose level within the specified range and unilateral weakness on the clinical exam items, they are considered to be a positive screen for stroke.</th>
<th>In the original validation study, the scale developers reported a sensitivity 92% (total stroke) and 93% (ischemic stroke) when compared against discharge diagnosis.(^{(11)}) Note: The original criteria for symptom duration were 12 hours and have since been changed to 24.(^{(11, 12)}) In a follow-up field validation study conducted by the scale developers reported sensitivity = 91% and sensitivity = 97%.(^{(11, 12)}) Subsequent evaluations of the sensitivity and specificity of the LAPSS have demonstrated sensitivity ranging from 74%(^{(3)}) - 78%(^{(4)}) and specificity ranging from 83%(^{(3)}) - 85%(^{(4)}) when assessed against discharge diagnosis.</th>
<th>All studies reported provision of training to pre-hospital care providers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 items: 4 screening/history items (age&gt;45 years, no history of seizures, symptom duration &lt;24 hours, ambulation status at baseline not bedridden or wheelchair bound), blood glucose (between 60 and 400) level, a clinical assessment (of 3 items to identify obvious asymmetry: facial palsy, grip, arm strength).</td>
<td>Less than 3 minutes.</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

## Ontario Prehospital Stroke Screen\(^{(13)}\)

| 3 inclusion criteria (unilateral weakness, slurred speech or muteness, facial droop), a 2-hour time limit from symptom onset and 6 exclusion criteria (to rule out stroke mimics, patients in need of emergent intervention and patients not | Not reported. | Patients are considered appropriate candidates for transport to an acute stroke centre if they have at least one inclusion criteria, are within 2 hours of symptom onset and none of the exclusion criteria. | Neither sensitivity nor specificity is reported for the Ontario Prehospital Stroke Screen. Instead, scale authors reported only a positive predictive value, which is dependent upon condition prevalence. PPV was reported to be 89.5% for patients with at least one inclusion criteria identified on the screening tool (using discharge diagnosis of stroke as the gold standard for comparison).\(^{(13)}\) | Yes |

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\(^{(9)}\) Disturbance.

\(^{(11)}\) Los Angeles Prehospital Stroke Screen (LAPSS) was developed to identify patients with potential stroke who warrant rapid transfer to a tertiary hospital. It is a simple, quick, and effective tool that can be easily performed by pre-hospital care providers.

\(^{(12)}\) In a follow-up field validation study conducted by the scale developers, the sensitivity of the LAPSS was reported as 91% and specificity as 97%.

\(^{(13)}\) The Ontario Prehospital Stroke Screen is another tool designed to identify patients with potential stroke who warrant rapid transfer to a tertiary hospital. It is a quick and effective tool that can be easily performed by pre-hospital care providers.
<table>
<thead>
<tr>
<th>Additional Assessment Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glasgow Coma Scale (GCS)</strong> (14, 15)</td>
</tr>
<tr>
<td>Approximatel y 1 minute.</td>
</tr>
</tbody>
</table>
on GCS. GCS scores significantly associated with length of coma (p<0.0001).

(20)

**Predictive Validity:**

GCS score is a significant predictor of death following stroke (21, 22) or traumatic brain injury (modified by age and mechanism of injury) (23), though eye-opening may be less strongly associated than either the motor or verbal score components (24). GCS scores are also predictive of survival (AUC=0.89), though eye-opening may not add to predictive accuracy (25). GCS scores have been demonstrated to be predictive of Glasgow Outcome scores at 6 months to 1 year post injury (20, 26-29), Disability Rating Scale scores at discharge (30) and at 6 months (31), FIM scores at discharge (30, 32) and employment status at one-year (33).
<table>
<thead>
<tr>
<th>Recognition of Stroke in the Emergency Room Scale (ROSIER)[35]** *</th>
<th>Not reported</th>
<th>Not reported.</th>
<th>A -1 is awarded for each clinical history item present and a +1 for each neurological sign. Total scores range from -2 to +5. A score &gt;0 is associated with possible stroke.</th>
<th>In their initial, prospective validation study, scale authors reported sensitivity = 93%, specificity = 83% compared against clinical diagnosis of stroke.[35] Byrne et al. demonstrated that nurses, using the ROSIER scale identified patients with stroke with approximately the same accuracy as physicians relying on standard neurological assessment (98% vs. 94% accuracy).[36] Whitely and colleagues compared in-hospital use of the ROSIER to the FAST and reported 83% sensitivity, 44% specificity associated with use of the ROSIER and 81% sensitivity, 39% specificity associated with the FAST (no significant difference between the FAST and the more complex ROSIER).[10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-items: 2 clinical history items (loss of consciousness, convulsive fits/syncope) and 5 neurological signs of stroke (facial palsy/weakness, arm weakness, leg weakness, speech disturbance and visual field defect).</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Note: Although in the majority of studies in which the pre-hospital care provider (paramedic or EMT) administered the CPSS, they were provided with some form of training, several studies also examined the impact of training and the need for medical training in order to administer the test. Frendl and colleagues demonstrated that providing training to paramedics made no significant difference in the rates of scale use or in the accuracy of identification of possible stroke.[2] In addition, two studies evaluated the possibility of directed administration of the CPSS by non-medical laypersons (e.g. an individual guided by a 9-1-1 dispatcher, for instance). In each of these studies, a volunteer layperson was guided through the administration both in-person[37] and via a telephone call[38] using a standardized set of instructions. In each case, the sensitivity and specificity reported was high (sens = 91%(37) & 94.3%(38) and spec. = 88%(37) and 82.9%(38)) using ratings made by a medically-trained observer as the gold-standard for comparison. ***Please note that the ROSIER scale was not developed for prehospital assessment, but rather was designed for use in the identification of probable stroke by ER physicians. It has been evaluated for use in a pre-hospital setting only once in a limited setting in China where sensitivity was reported to be 90% and specificity 83%(39)***

Useful links:
2) [http://www.strokeassociation.org/idc/groups/stroke-public/@wcm/@private/@hcm/@gwtg/documents/downloadable/ucm_428607.pdf](http://www.strokeassociation.org/idc/groups/stroke-public/@wcm/@private/@hcm/@gwtg/documents/downloadable/ucm_428607.pdf) This is an American Stroke Association
References


**Best Practice Recommendation 3.3**

**Emergency Department Evaluation and Management of Patients with Transient Ischemic Attack and Acute Stroke.**

### NOTES on this recommendation

- **Time is Brain!** The goal of emergency department management is rapid assessment of all patients with a suspected acute stroke. For patients who may be eligible for intravenous tissue plasminogen activator, the target is to complete rapid assessment and initiate treatment within 90 minutes of stroke symptom onset.
- Section 3.3.1 identifies the aspects of assessment and interventions that are recommended for all patients, and further identifies recommended evaluations which can wait until thrombolysis decisions are made and acted upon for eligible patients, in order to optimize time from stroke onset to acute treatment where possible.

### 3.3 All patients presenting to an emergency department with suspected stroke or transient ischemic attack must have an immediate clinical evaluation and investigations to establish the diagnosis, rule out stroke and TIA mimics, determine eligibility for thrombolytic therapy, and develop a plan for further management [Evidence Level B].

Patients presenting with stroke or transient ischemic attack should not be discharged from the ED without diagnostic evaluations, consideration of functional impairments, initiation or modification of secondary prevention therapy, and a plan for ongoing management [Evidence Level B].

### 3.3.1 Initial Evaluation

#### i. Patients with suspected acute stroke should have a rapid initial evaluation for airway, breathing and circulation [Evidence Level B].

#### ii. A neurological examination should be conducted to determine focal neurological deficits and assess stroke severity [Evidence Level B]. A standardized stroke scale should be used (such as the National Institute of Health Stroke Scale or the Canadian Neurological Scale). Refer to Table 3.3A Screening and Assessment Tools for Acute Stroke for more detailed information.

#### iii. Monitoring in the acute phase should include heart rate and rhythm, blood pressure, temperature, oxygen saturation, hydration, swallowing ability, and presence of seizure activity [Evidence Level B].

#### iv. Acute blood work should be conducted as part of the initial evaluation [Evidence Level B]. Initial blood work should include: electrolytes, glucose, hematology (CBC), coagulation (INR, aPTT), creatinine, glomerular filtration rate (GFR), BUN, lipid profile, liver panel, and troponin.

   a. Additional blood work may be required if a prothrombotic or vasculitic cause is suspected [Evidence Level C]. Refer to Table 3.3B Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack for additional detailed information on laboratory tests.

   v. Electrocardiogram and chest X-ray should be completed, especially where the patient has a clinical history or evidence of heart disease or pulmonary disease [Evidence Level B].
a. However, for patients without cardiac or pulmonary symptoms, chest x-ray should not delay assessment for thrombolysis and can be deferred until after a decision regarding thrombolysis therapy is made. [Evidence Level C].

vi. Patient swallowing screen should be completed as early as possible as part of initial assessment, but should not delay decision-making regarding eligibility for thrombolysis. [Evidence level A].

a. Patients should remain NPO (no oral intake) until swallowing screen completed for patient safety [Evidence Level B];

b. Oral medications should not be administered until swallowing screen has been completed [Evidence Level B]; alternate routes such as intravenous and rectal should be considered until swallowing ability verified;

c. A patient’s clinical status can change in the first hours following a stroke or TIA, therefore patients should be closely monitored for changes in swallowing ability following initial screening [Evidence level C];

d. Patients found to have abnormal swallowing ability on screening should be referred to a speech-language pathologist or other qualified professionals for an in-depth dysphagia assessment [Evidence Level B].

Refer to Recommendations 4.2 and 5.7 for additional information on screening for swallowing ability and dysphagia management.

vii. Seizure Assessment: New-onset seizures at the time of an acute stroke, occurring either immediately before or within 24 hours of the stroke onset, should be treated using appropriate short-acting medications (e.g., lorazepam IV) if they are not self-limiting [Evidence Level C]. Treatment may be required before completing hyperacute investigations for stroke, including brain and vascular imaging.

a. A single, self-limiting seizure occurring at the onset, or within 24 hours after an acute stroke (considered an “immediate” post-stroke seizure) should not be treated with long-term anticonvulsant medications [Evidence Level C].

b. Patients that have an immediate post-stroke seizure should be monitored for recurrent seizure activity during routine monitoring of vital signs and neurological status. Recurrent seizures in patients with ischemic stroke should be treated as per treatment recommendations for seizures in other neurological conditions [Evidence Level C].

   ➢ Seizures are a common presentation with stroke in neonates and children. Consider enhanced or increased seizure monitoring in at-risk populations such as neonates, children with stroke and adults with otherwise unexplained reduced level of consciousness [Evidence Level C];

   ➢ Electroencephalogram monitoring may be appropriate in patients at high risk of seizures, such as neonates and children [Evidence Level C].

c. Patients with one or more seizures in the early (defined as occurring up to four weeks post index stroke) or late (occurring beyond four weeks) post-stroke period should be treated as per treatment recommendations for seizures in other neurological conditions [Evidence Level C]. Other investigations may include electroencephalogram (EEG) and tests to rule out other precipitating factors of seizures (e.g., infections) may be warranted in these patients [Evidence Level C].

d. Prophylactic use of anticonvulsant medications in patients with acute stroke is not recommended [Evidence Level C]. There is no evidence to support
the prophylactic use of anticonvulsant medications in patients with acute stroke and there is some evidence to suggest possible harm with negative effects on neural recovery.

### 3.3.2 Neurovascular Imaging

All patients with suspected acute stroke should undergo brain and vascular imaging of the brain and neck arteries immediately (CT/CTA, or MRI/MRA if urgently available) [Evidence Level A].

All patients with suspected transient ischemic attack should undergo brain imaging immediately (CT, or MRI if urgently available) [Evidence Level A], and vascular imaging of the brain and neck arteries within 24 hours [Evidence Level B].

**Note:** It is important to optimize time from patient arrival to tPA decision and administration initiation. Advanced imaging should not result in delays to tPA administration.

1. A non-contrast CT scan of the brain should be performed as a first step with or without CT angiography [Evidence Level B].
2. If MRI is performed emergently, it should include diffusion-weighted (DWI) sequences with apparent diffusion co-efficient (ADC) map to detect recent infarction, gradient echo (GRE) for diagnosis of hemorrhage, and fluid-attenuated inversion recovery (FLAIR) sequences to determine extent of infarct [Evidence Level B].
3. Non-invasive vascular imaging of the carotid and vertebral arteries by duplex ultrasonography, CT angiography (CTA), or magnetic resonance angiography (MRA) should be performed at the time of brain imaging or as soon as possible for an ischemic stroke, and within 24 hours of a transient ischemic attack unless the patient is clearly not a candidate for revascularization [Evidence Level B].
   - a. Ideally CTA or MRA is performed at the time of the initial CT or MRI;
   - b. By contrast to Duplex ultrasonography, CTA or MRA are preferred as they advantageously show the anatomy of intracranial arteries and of the posterior circulation. [Evidence Level C].
4. Non-invasive imaging of the extracranial and intracranial vessels is preferable. However, in some circumstances catheter angiography of the extracranial and intracranial vessels may be considered [Evidence Level B].

### 3.3.3 Cardiovascular Investigations

1. An initial electrocardiogram (ECG) should be completed on all stroke and TIA patients on arrival to the ED [Evidence Level B].
2. If the initial ECG does not identify an arrhythmia, serial ECGs (i.e., daily) should be done over the first 72 hours post-stroke to detect atrial fibrillation and other acute arrhythmias [Evidence Level B].
3. Perform an echocardiogram in patients where a cardiac cause of stroke is suspected, including in young adults and children who present with stroke, and when infectious endocarditis is suspected [Evidence Level B].
   
Refer to Recommendation 4.2.1 for additional information.

### 3.3.4 Acute Blood Pressure Management

There is a lack of clear evidence from randomized controlled trials to guide the treatment of elevated blood pressure within the first few hours after an acute ischemic or hemorrhagic stroke. Pharmacological agents and routes of administration should be chosen to avoid
precipitous falls in blood pressure [Evidence Level C]. The following recommendations reflect the paucity of evidence in this area and indicate the need for further research.

i. **Ischemic stroke eligible for thrombolytic therapy:** Very high BP (>185/110mmHg) should be treated concurrently in patients receiving thrombolytic therapy for acute ischemic stroke as this may reduce the risk of secondary intracranial hemorrhage [Evidence Level B].

ii. **Ischemic stroke patients not eligible for thrombolytic therapy:** Treatment of hypertension in the setting of acute ischemic stroke should not be routinely undertaken [Evidence Level C].
   a. Extreme blood pressure elevation (e.g. systolic > 220 or diastolic > 120mmHg) may be treated to reduce the blood pressure by ~15 percent, and not more than 25%, over the first 24h with gradual reduction thereafter [Evidence Level C];
   b. Avoid excessive lowering of blood pressure as this may exacerbate existing ischemia or may induce ischemia, particularly in the setting of intracranial arterial occlusion or extracranial carotid or vertebral artery occlusion [Evidence Level C].

Note: New information regarding acute blood pressure management for stroke patients is forthcoming at the 2013 European Stroke Conference, with release of the INTERACT2 trial results on May 30th, 2013. This new information will be considered and incorporated into these recommendations as appropriate when it becomes publicly available.

### 3.3.5 Blood Glucose Abnormalities

i. All patients with suspected acute stroke should have their blood glucose concentration checked immediately [Evidence Level B].

ii. Blood glucose measurement should be repeated if the first random glucose value is elevated greater than 11.0 mmol/L. The repeat measures should include a fasting glucose and an HbA1c [Evidence Level C].

iii. Hypoglycemia should be corrected immediately [Evidence Level B].

iv. If the repeat glucose levels and the HbA1c are elevated (fasting glucose greater than 7 mmol/L; HbA1c greater than or equal to 6.5 percent) (CDA 2013), the use of anti-hyperglycemic agents should be considered [Evidence Level C in the setting of acute stroke], and in the longer term, education on lifestyle changes and diabetes [Evidence Level A]. Refer to Recommendation 2.4 for additional information.

### 3.3.6 Additional Management Considerations in the Emergency Department

i. For some patients, based on clinical presentation and medical history, additional investigations should be considered [Evidence level B]. Refer to Table 3.3B for additional detailed information.

ii. The use of indwelling urethral catheters should be avoided due to the risk of urinary tract infections [Evidence Level A]. Refer to Recommendation 4.2.5 for additional detailed information.
   a. If used, indwelling catheters should be assessed daily and removed as soon as possible [Evidence Level A].
   b. Fluid status and urinary retention should be assessed as part of vital sign assessments [Evidence Level C].
   c. Excellent pericare and infection prevention strategies should be implemented to
minimize risk of infections [Evidence Level C].

**Rationale:**

Patients who present to hospital with suspected stroke often also have significant physiological abnormalities and comorbidities. These can complicate management of stroke. Signs and symptoms that may explain the cause of the stroke or predict later complications (such as space-occupying infarction, bleeding, or recurrent stroke), and medical conditions such as hypertension or the presence of a coagulopathy, will have an impact on treatment decisions. An efficient and focused assessment is required to understand the needs of each patient.

It is impossible to differentiate infarct from hemorrhage by clinical examination alone. Brain imaging is required to guide management, including the selection of time-sensitive interventions. A CT scan or MRI is important since clinicians may disagree on the clinical diagnosis of stroke (versus not stroke) in about 20 percent of patients.

Initial management of elevated blood pressure in acute stroke patients remains controversial due to the lack of evidence to clearly guide practice. At the same time, this is an area where clinicians often seek guidance from stroke specialists. The recommendations for this area emphasize caution and diligence in monitoring and treating extremely high blood pressure in the first hours after stroke onset.

Diabetes is a major modifiable risk factor for vascular disease that may be first diagnosed at the time of a stroke. Severe hyperglycemia (blood glucose greater than 22 mmol/L) is a relative contraindication to the administration of intravenous tPA. Hyperglycemia at the time acute stroke increases size of the damaged area in experimental animals and is associated with poor clinical outcomes in epidemiological studies.

**System Implications**

- Protocols and standing orders to guide initial blood work and other clinical investigations.
- Local protocols for prioritizing stroke patients for rapid access to appropriate diagnostics such as CT scans and duplex ultrasound, communicated to all relevant personnel such as emergency department, imaging, and stroke teams.
- Agreements to ensure patients initially managed in rural hospitals without neurovascular imaging capability have timely access to CT scan within 24 hours at partnering facilities.
- Local protocols, especially in rural and remote locations, for rapid access to clinicians experienced in interpretation of diagnostic images, including access through telemedicine technology.

**Performance Measures**

1. Proportion of stroke patients who receive a brain CT/MRI within 24 hours of hospital arrival (core).
2. Proportion of patients with carotid territory TIA or minor stroke that do not undergo carotid imaging in the emergency department but have arrangements made before discharge for carotid imaging as an outpatient.
3. Median time from time INR drawn to results available.
4. Proportion of patients with blood glucose levels documented during assessment in the emergency department.
5. Proportion of stroke patients who receive a CT scan in less than 25 minutes from hospital
arrival in patients arriving <3.5 hrs from last known well time, and without contraindications to thrombolysis.

6. Median time from stroke symptom onset to carotid imaging.

7. Proportion of patients with known diabetes who have blood glucose levels in therapeutic range for that patient.

**Measurement Notes**

- Data may be obtained from laboratory reports or patient chart.
- Stratify analysis for patients who arrive within 3.5 hours of stroke symptom onset and those who arrive beyond 3.5 hours.
- Performance measure 1: apply to patients who may be candidates for acute thrombolysis (i.e. who arrive at hospital within 3.5 hours of stroke onset) and for patients who may be eligible for other time-sensitive interventions.
- Performance measures 1 and 2: Time interval measurements for CT and MRI should be calculated from the time the patient is enters the emergency department until the time noted on the actual brain imaging scan. In some hospitals triage time may not be the best point at which to start the clock.
- Performance measure 3: For outPATient carotid imaging, a notation should appear in the discharge summary, or in nursing notes, with an indication that the test has actually been requested or requisitioned prior to the patient leaving the hospital.
- Performance measure 5: Use medical history to determine whether patient was known to have diabetes prior to the stroke event.

**Implementation Resources and Knowledge Transfer Tools**

- Canadian Stroke Best Practices Patient Order Set of Initial Emergency Department Evaluation of a Suspected Stroke Patient
- Canadian Stroke Best Practices Patient Order Set for Admission to Inpatient Stroke Care
- Canadian Stroke Best Practices Table 3.3A Screening and Assessment Tools for Acute Stroke
- Canadian Stroke Best Practices Table 3.3B Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack
- HSF Stroke Nurses Assessment Pocket Cards http://www.heartandstroke.on.ca/site/c.pvl3ieNWJwE/b.5852913/k.AC4B/Order_Resources/apps/k a/ct/contactcustom.asp
- RNAO Stroke Assessment Across the Continuum of Care (2005) http://rnao.ca/sites/rnao-ca/files/Stroke_Assessment_Across_the_Continuum_of_Care
Summary of the Evidence

Initial Assessment

Patients require immediate evaluation when presenting to the emergency department with suspected stroke or transient ischemic attack (TIA). Urgent evaluation is essential because the administration of thrombolysis is time dependent. For patients presenting to the emergency department with TIA, an appropriate evaluation should be complete before discharge. This is important because the risk of recurrent stroke in patients with TIA is highest within 7 days of the index event (Purroy et al., 2012). A review of common clinical prediction tools used in emergency department evaluation of TIA found that the available tools (e.g. ABCD score and the California risk score), were useful in predicting risk of recurrent stroke after a TIA diagnosis (Purroy et al., 2012; Giles & Rothwell, 2010). Each scale is comprised of a combination of criterion which may include age, presence of diabetes, hypertension, coronary heart disease, cardiac failure, peripheral arterial disease, history of stroke or TIA, symptom duration, motor and speech disturbances and imaging results (Purroy et al., 2012). These scoring algorithms have also been found to be useful in ruling out stroke mimics (Giles & Rothwell, 2010), an important component of emergency department evaluation.

Standard assessments for patients with suspected acute stroke include a neurological examination, monitoring of vitals, blood work, imaging and cardiovascular investigations, dysphagia screens and seizure assessment. Monitoring of patient vitals, such as heart rate and rhythm, blood pressure and temperature are important in the early stages of stroke. A preliminary case-control study by Langhorne et al. (Langhorne et al., 2000) found that patients with normal physiological variables within three days post-stroke had significantly greater scores on the Scandinavian stroke scale (SSS) and Barthel Index (BI), greater neurological improvement, and were more likely to be independent one week after stroke (Langhorne et al., 2000). Additional evidence for the control of physiological variables post stroke can be derived from studies assessing outcomes for patients receiving care in an acute stroke unit. For example, Sulter et al. (Sulter et al., 2003) found that continuous monitoring of physiological variables such as temperature, blood pressure and oxygen saturation in a stroke care monitoring unit for the first 48 hours after stroke resulted in a significant reduction in mortality at 3 months, and a lower, but not statistically significant, odds of poor outcome (Sulter et al., 2003).

Blood work is also indicated for initial patient assessment. In a population of patients with ischemic stroke, a selection of blood biomarkers were assessed for their association with cerebral lesion size, location of lesion, and stroke severity measures (Kisialiou et al., 2012). Blood markers significantly associated with lesion size included albumin, triglycerides, fibrinogen, erythrocyte sedimentation rate (ESR) and platelets (Kisialiou et al., 2012). Additionally, higher values for coagulation measures (INR and PTT) were found to be associated with worse outcomes, while lower values of albumin were found to be associated with better outcomes, as measured by the NIHSS (Kisialiou et al., 2012).

Dysphagia screens and seizure management are other important components of initial evaluation of patients in the emergency department. Dysphagia screening is particularly relevant for identifying patients at high risk of aspiration and pneumonia (Lakshminarayan et al., 2010). Further information regarding the evaluation, assessment and management of dysphagia can be found in Section 5.0: Stroke Rehabilitation. Evidence regarding the management of post-stroke seizures is limited. Nonetheless, it is also important to address during initial evaluation because treatment may be required prior to completing necessary diagnostic assessments. A recent Cochrane review with a protocol to assess the effectiveness of antiepileptic drugs compared to placebo did not identify any studies for inclusion (Kwan & Wood, 2010). Prophylactic use of antiepileptic medications suffers from similar limitations. There is no evidence to support the use of antiepileptic medications to prevent seizure post-stroke in a population of patients included in a study by Van Tuilj et al. (van Tuilj et al., 2011). Further information regarding seizure management can be found in Section 4.0: Acute Stroke Management.

Neurovascular Imaging

Immediate access to brain and vascular imaging is required for all patients arriving to hospital with suspected acute stroke or TIA. Wardlaw et al found that a computed tomography (CT) scan for all patients
with suspected stroke on admission to hospital was the best scanning strategy (Wardlaw et al., 2004). Although a cost-effectiveness study, it demonstrated that scanning all patients early increased quality of life based on functional status at 6, 12 and 24 months, and decreased inpatient length of stay. Imaging is equally relevant for patients with suspected TIA. A CT scan has been found to be a useful predictor of functional status at 90 days for these patients (Coutts et al., 2009). The presence of a new infarct on the CT scan has also been found to be a significant predictor of future stroke at 90 days for patients presenting to the emergency department with TIA (Douglas et al., 2003).

A non-contrast CT scan is considered the imaging standard for patients with suspected stroke or TIA; it is known to be the most accessible diagnostic imaging tool. There is, however, evidence that magnetic resonance imaging (MRI) may offer higher sensitivity compared to a CT scan for the diagnosis of ischemic stroke (Brazzelli et al., 2009). Notably, the authors caution against the interpretation of these findings as the population of patients included in the study may have artificially inflated the results (Brazzelli et al., 2009). Their findings also revealed limited evidence for the comparability of diagnostic tools for diagnosing hemorrhagic strokes, which is a contraindication for the administration of tPA (Brazzelli et al., 2009). If an MRI is available and performed in place of CT, enhanced imaging in the form of DWI, GRE and FLAIR is indicated. These diagnostics allow for a more thorough diagnostic test and have been reported to be equally sensitive and specific for identifying intracerebral hemorrhage in a preliminary study by Oppenheim et al. (Oppenheim et al., 2005). Urgency is the primary concern for diagnostic imaging tool selection.

Early imaging is particularly important for deriving a patient management plan, which may include the administration of tPA (tissue plasminogen activator). Thrombolysis is a time-sensitive intervention that requires brain imaging to identify candidate patients. In a systematic review and meta-analysis by Wardlaw et al. assessing the impact of tPA on patients with ischemic stroke compared to control groups, the methods stipulated that patients with hemorrhagic stroke or other brain disorders must be identified and excluded using imaging findings (Wardlaw et al., 2012). Vascular imaging of intracranial and extracranial vessels is also suggested as an immediate diagnostic test when available. De Silva et al. found that magnetic resonance angiography (MRA) results may be useful in further defining patients who may experience the greatest benefits from the administration of tPA (De Silva et al., 2011). In this study, patients who experienced cranial artery occlusion achieved the greatest benefit from the administration of tPA as indicated by lower infarct growth compared to patients who did not have arterial occlusion (P<0.001) (De Silva et al., 2011).

### Cardiovascular Investigations

An electrocardiogram (ECG) should be performed immediately for all patients with stroke and TIA presenting to the emergency department for the potential to identify arrhythmias. Atrial fibrillation (AF) is commonly diagnosed post-stroke, and is of particular concern due to its role in forming emboli. Immediate testing is important; Suissa et al. (Suissa et al., 2012) found that the greatest odds of AF detection were within the first 24 hours after stroke [OR 9.82; 95% CI 3.01 to 32.07]. It is important to note, however, that an initial ECG is often not enough to detect all cases of AF. In the same study, it was found that ECG monitoring beyond the baseline assessment resulted in the identification of additional cases of AF in 2.3%-14.9% of the population (Suissa et al., 2012). The greatest number of new cases was identified with continual monitoring in an intensive stroke unit (Suissa et al., 2012). For sites not equipped with continuous monitoring equipment, the use of serial ECG assessments is an effective means of diagnosing AF (Douen et al., 2008). There was a statistically significantly greater percentage of patients diagnosed with AF as a result of serial ECG assessments within 72 hours of stroke compared to the percentage of patients diagnosed with AF at baseline (P=0.001) in this study (Douen et al., 2008). A Holter monitor may offer additional sensitivity to identify cases of AF (Douen et al., 2008). 2007 systematic review found that the use of a Holter monitor for variable durations of time following acute stroke identified AF in approximately 5% of patients (Liao et al., 2007). The use of a Holter monitor as an adjunct to serial ECGs offers the greatest ability to detect AF (Douen et al., 2008).

The use of a transesophageal echocardiography (TEE) is indicated when there is suspected cardiac embolism involvement. For patients with an unknown cause of stroke following baseline diagnostic assessments, and no contraindications to anticoagulation therapy, TEE was found to identify possible sources of cardiac embolism (de Bruijn et al., 2006). In this study, TEE was found to perform better than transthoracic echocardiography in identifying possible sources of cardiac embolism, and was appropriate for all ages in the population of patients assessed (>45 years and ≤45 years) (de Bruijn et al., 2006).
Acute Blood Pressure Management
There is no evidence to suggest that managing blood pressure after stroke in patients who are not eligible for thrombolysis offers any beneficial effects. The majority of vasoactive drugs do have blood pressure lowering effects; however, the association between these decreases and outcomes could not be assessed in two Cochrane reviews (Geeganage & Bath, 2008; Geeganage & Bath, 2010). No conclusions could be drawn because of the heterogeneity between studies (Geeganage & Bath, 2008; Geeganage & Bath, 2010). A metaregression by Geeganage et al. offers some interpretation of the effects of changes in blood pressure on outcomes (Geeganage & Bath, 2009). Extreme changes in blood pressure, both increases and decreases, are associated with worse outcomes in terms of death and dependency immediately after stroke and during follow up periods (Geeganage & Bath, 2009). In this study, a decrease in blood pressure between 8mmHg and 14.6mmHg was associated with the lowest odds of poor outcome (death, dependency and intracerebral hemorrhage) (Geeganage & Bath, 2009). These findings are supported by an RCT assessing the effects of the ACE inhibitor, candesartan (Sandset et al., 2012). It found that patients who experience a large decrease in blood pressure in the first two days of stroke have greater odds of experiencing an adverse event such as a recurrent stroke, hypotension or further neurologic decline (Sandset et al., 2012).

A different management strategy is indicated for patients who are eligible for thrombolysis. These patients must have met blood pressure standards before the initiation of therapy. Furthermore, it has been found that patients who receive thrombolysis benefit from blood pressure control if elevated within 2 to 24 hours of treatment (Ahmed et al., 2009). Blood pressure readings greater than 170mmHg are associated with greater odds of death, dependency and subsequent hemorrhage compared to blood pressures between 141 and 150mmHg in patients during the post-thrombolytic stage (Ahmed et al., 2009).

Glucose Management
A patient’s blood glucose reading and diabetic status are important for predicting outcomes post-stroke (Yong & Kaste, 2008). A study based on the population of patients enrolled in the ECASS II trial had outcomes assessed at 7 days, 30 and 90 days according to pre-stroke diabetes status and type of hyperglycemia experienced during the first 24 hours of admission to hospital (Yong & Kaste, 2008). Significantly poorer outcomes were experienced by nondiabetic patients with persistent hyperglycemia compared to the persistent normoglycemia reference group (Yong & Kaste, 2008). Several observational studies have found an association between blood glucose level following stroke and patient outcomes (death and dependency). Despite this consensus, no statistically significant differences in death, dependency and neurological deficits were found in a Cochrane review assessing the outcomes associated with insulin interventions initiated within the first 24 hours of stroke (Bellolio et al., 2011). Mean blood glucose levels were lower in the intervention groups; however hypoglycemia events were significantly greater (Bellolio et al., 2011). Monitoring of hypoglycemia is therefore important if insulin therapy is administered. The threshold for insulin administration in these trials was >6.1mmol/L measured within 24 hours (Bellolio et al., 2011). The largest trial included in this review, with 899 patients randomized, found no differences in death or dependency between control (intravenous saline solution) and intervention groups (intravenous glucose-potassium insulin) and also found hypoglycemic episodes to be of concern (Gray et al., 2007). A more recent study of glucose management within 6 hours of stroke found a similar increase in hypoglycemic events among intravenously (IV) administered insulin compared to subcutaneously administered insulin (Rosso et al., 2012). Infarct size was also increased for the IV group compared to the subcutaneous group (Rosso et al., 2012). These findings reinforce the importance of repeat blood-glucose testing and careful monitoring to avoid risk of hypoglycemia.
# Canadian Stroke Best Practices Table 3.3A Screening and Assessment Tools for Acute Stroke

<table>
<thead>
<tr>
<th>Assessment Tool</th>
<th>Number and description of Items</th>
<th>Time to Administer</th>
<th>Reliability/validity</th>
<th>Interpretation of Scores</th>
<th>Training Required</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological Status/Stroke Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Canadian Neurological Scale (CNS)</strong>(1)</td>
<td>Items assess mentation (level of consciousness, orientation and speech) and motor function (face, arm and leg). Motor function evaluations are separated into sections A1 (and A2. A1 is administered if the patient is able to understand and follow instructions (5 items). A2 is administered in the presence of comprehension deficits (3 items)(1, 2)</td>
<td>5-10 minutes(1, 2)</td>
<td><strong>Interobserver reliability</strong>: k ranged from 0.535(facial weakness) to 1.000 and there was no significant difference in agreement between physician and nurse raters(1); agreement between assessments by 2 nurses, r=0.924 - at the item level k ranged from 0.535 (level of consciousness) to 1.00 (motor response- face)(2)</td>
<td>Motor items are rated in terms of severity. Ratings are weighted and summed to provide a total score out of 11.5.(2) Higher scores represent decreasing levels of stroke severity or improved neurological status.</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>National Institutes of Health Stroke Scale (NIHSS)</strong>(9)</td>
<td>15 items: impairment in LOC, ability to respond to questions/ obey simple commands, papillary response, gaze deviation, hemianopsia, facial</td>
<td>Approximately 6-7 minutes(9)</td>
<td><strong>Test-retest</strong>: ranging from 0.66 (emergency department nurse clinician) to 0.77 (neurologist)(9); ICC = 0.93 (3 month test interval-assessment of videotaped patient)(10)</td>
<td>Total scale score = 0-42. Higher scores reflect greater severity. Stroke severity may be stratified as follows: &gt;25 = very severe, 15 – 24 = severe, 5 –</td>
<td>Yes(11, 23, 24)</td>
</tr>
</tbody>
</table>
palsy, resistance to gravity (weaker limb), plantar reflexes, limb ataxia, sensory loss, visual neglect, dysarthria and aphasia. Each item is graded on an ordinal scale from 0-3 or 0-4 where 0=no impairment.

<table>
<thead>
<tr>
<th><strong>Pediatric National Institutes of Health Stroke Scale (PedNIHSS)</strong>(25)</th>
<th>This is a variation of the adult form NIHSS designed for use in individuals aged 2 – 18. All items from the original version have been retained; however, age appropriate adaptations have been applied to language items, pictures and commands.</th>
<th>Not reported.</th>
<th>Interobserver reliability:*** For prospective administration, reported ICC = 0.99 (95% CI 0.97, 0.99) between study neurologists. Item level agreement ranged from $K_w = 0.40$ (sensory) to 1.00 (LOC-commands) (25); When used for retrospective derivation of PedNIHSS scores, ICC=0.95 and item level agreement ranged from $K_w = 0.47$ (visual) to 0.93 (motor left and right arm items). (26)</th>
<th><strong>Construct validity (known groups):</strong> NIHSS scores were significantly different ($p&lt;0.001$) for patients grouped as “alive at home”, “alive in care” and “dead” at 3 months(4); baseline NIHSS scores correlated strongly with TOAST classification(19)</th>
<th>Predictive validity: NIHSS scores have been demonstrated to be predictive of function/impairment status(9, 19-21) and of discharge destination or place or residence(9, 22)</th>
<th>Yes. The scale authors provide a guide for administration in children aged 2-18.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glasgow Coma Scale (GCS)</strong>(27, 28)</td>
<td>15 items in 3 categories: motor response (6 items), verbal response (5 items)</td>
<td>Approximately 1 minute.</td>
<td>Interobserver reliability: Scale authors reported low rates of disagreement, but noted variations in motor responses based on stimulus used(28). Reported agreements ranged 0.48 (verbal) to 0.72 (eye open).</td>
<td>GCS scores range from 3 – 15, where 3 represents total unresponsiveness</td>
<td>Yes.</td>
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</tbody>
</table>
items), and eye opening (4 items). Points are awarded for the best response in each category. Categories are summed to provide a total score.

Percentage agreements have been reported as 90% overall, and as ranging from 83.8% (eye opening, right) to 98.7% (best motor response – left). In addition, similar rates of between observer agreement have been reported in groups of experienced nurses (98.6% - 100%), newly graduated nurses (94.3%-96.2%) and student nurses (77.3% - 100%).

**Construct validity:** In review of GCS, evidence supports association between extent of brain damage and depth of coma as assessed on GCS. GCS scores significantly associated with length of coma (p<0.0001).

**Predictive validity:** GCS score is a significant predictor of death following stroke (34, 35) or traumatic brain injury (modified by age and mechanism of injury) (36), though eye-opening may be less strongly associated than either the motor or verbal score components(37). GCS scores are also predictive of survival (AUC=0.89), though eye-opening may not add to predictive accuracy(38).

GCS scores have been demonstrated to be predictive of Glasgow Outcome scores at 6 months to 1 year post injury (33, 39-42), Disability Rating Scale scores at discharge (43) and at 6 months (44), FIM scores at discharge (43, 45) and employment status at one-year (46).

**Grading of Subarachnoid Hemorrhage**

**Hunt and Hess Scale (HH) (48, 49)**

Based on clinical signs on 3 axes: 1) intensity of meningeal inflammatory reaction, 2) severity of neurodeficit and 3) level of arousal. Subjective assignment of grade. (50)

**Interobserver reliability:** Reports have varied substantially ranging from k=0.41 (51), k=0.42(50) to k=1.0(52) for total scale scores.

**Predictive validity:** Studies have demonstrated significant associations between HH Grades and clinical outcomes, GOS scores, mortality and LOS(50, 53). However, it should be noted that there has been little difference demonstrated in clinical outcomes for individuals with grades <3 and only Grade 3 may be significantly different than Grade 0, in terms of risk for poor outcome.(50, 53) Studies that have dichotomized Grades (0-3 vs 4,5) have demonstrated clearer association with clinical outcome(53)

Grades correspond to neurological deficit originally ranged from 1 (none) through 5 (deep coma or moribund). A Grade of ’0’ was added later to represent “unruptured”; however, there is no method to

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**Notes:**
- GCS scores may be divided into categories by severity: 13-15 = mild; 9-12=moderate and ≤8 represents severe injury.
- Grades correspond to neurological deficit originally ranged from 1 (none) through 5 (deep coma or moribund). A Grade of ’0’ was added later to represent “unruptured”; however, there is no method to
<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
<th>Interobserver reliability</th>
<th>Predictive validity</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher Scale (FS) (54)</td>
<td>4-level grade based on the pattern of blood viewed on CT. The FS is not regarded as a primary grading system for SAH.</td>
<td>Not reported.</td>
<td></td>
<td>Grades range from 1 [no blood] through 4 [diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots].</td>
</tr>
<tr>
<td>World Federation of Neurological Surgeons Scale (WFNS) (55)</td>
<td>5-level grade system based on compression of GCS scores into 5 grades with the addition of a focal motor deficit axis that is graded separately.</td>
<td>Not reported.</td>
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<tr>
<td>Assessment of Function</td>
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<tr>
<td>Modified Rankin Scale (mRS) (56)</td>
<td>A global outcomes rating scale in which individuals are assigned a subjective grade or rank ranging from 0-5 based on level of independence with reference to pre-stroke activities rather than observation of task-based performance. Modifications to the 15 minutes [via structured interview] (59, 60)</td>
<td>Interobserver reliability: In a systematic review, there was substantial variability demonstrated with reported weighted kappa agreements ranging from 0.25 to 0.95. The authors note, however, that reliability was often low, particularly in studies with larger sample sizes (61); Overall reported agreement was ICC=0.675, between the experienced and inexperienced raters $k_w=0.686$, agreement between experienced and inexperienced raters using a decision making tool $k_w=0.568$, and agreement between inexperienced raters without a tool and inexperienced raters with a decision tool was $k_w=0.736$ (62)</td>
<td>Test-retest reliability: $k_w=0.95$ (63); $k_w=0.94$ for rater 1</td>
<td>mRS scores range from 0-5 such that '0' is indicative of no symptoms, while a rank of 5 is indicative of the most severe disability (described as bedridden, incontinent, requiring constant nursing care). No. However, training and/or the use of structured interview tools has been associated with improved reliability.</td>
</tr>
</tbody>
</table>

*References: 50, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62*
<table>
<thead>
<tr>
<th>Functional Independence Measure (FIM) (71)</th>
<th>18 items to evaluate 6 areas of function (self-care, sphincter control, mobility, locomotion, communication and social cognition). These may be placed into 2 domains: 1) motor (13 items: motor-FIM) and cognitive (5 items: cognitive-FIM).</th>
<th>Approx. 30 minutes to administer and score; however, it is recommended that ratings be derived by multidisciplinary team consensus following a period of observation. (72)</th>
<th>Interobserver reliability: In a review and meta-analysis (n=11 studies), interobserver reliability ranged from 0.89 to 1.0. When converted to a common metric and pooled, median agreement was reported to be 0.95(73). Test-retest reliability: In a review and meta-analysis (n=11 studies), median test-retest reliability was reported to be 0.95(73). Internal consistency reliability: Reported values for a range from 0.88(74) to 0.95(75, 76); reported item-to-total correlations range from 0.53 to 0.87(76). Construct validity: The 2-factor structure (motor + cognitive) of the FIM has been confirmed on factor analysis(77, 78), although a possible 3-factor model has also been reported (self-care, cognition, elimination)(79). Concurrent validity: Strong associations have been demonstrated between motor-FIM scores and scores from the Barthel Index(67, 74), the mRS(67), the Disability Rating Scale (DRS)(80), the Action Research Arm Test (81), The Fugl-Meyer Assessment(81), the Wolf Motor Items are scored on a 7-pt. Likert scale according to the amount of assistance required in the performance of each one (1=total assistance, 7 = total independence). Item scores are summed to provide a total out of 126. Motor and cognitive subscale scores may be calculated separately an may yield more useful information specific to each domain.(77)</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>Yes.</td>
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<tr>
<td>Function Test (time and functional assessment scores) [81] as well as between the cognitive-FIM and the DRS [80]</td>
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<tr>
<td><strong>Construct validity (known groups):</strong> FIM scores discriminated between groups right vs left-sided involvement in individuals with stroke at admission (p&lt;0.005) and discharge (p&lt;0.05) [75]; at admission and discharge, FIM scores were significantly different for individuals with and without neglect (p&lt;0.001 and p&lt;0.02, respectively) and with or without aphasia (p&lt;0.01; p&lt;0.09) [82].</td>
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<tr>
<td><strong>Predictive validity:</strong> admission (rehab) FIM has been reported to be associated with discharge FIM scores (total FIM, motor-FIM, cognitive-FIM) [83], length of inpatient rehabilitation stay [83, 84], functional gain [82], discharge assessments of balance and mobility [84], discharge walking speed [85] as well as discharge destination [75, 86]. FIM scores have been reported to predict burden of care in terms of minutes of help/day required [87]; motor-FIM scores have been associated with amount of direct assistance required, cognitive-FIM scores with direct supervision required [88]; FIM scores at one month post stroke have been reported to be associated with depression at 3 months post stroke [89].</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Alpha-FIM(90)</th>
<th>A shortened version of the Functional Independence Measure. 6 items: 4 motor (eating, grooming, bowel management and toilet transfers) and 2 cognition items (expression and memory). If the individual with stroke is able to ambulate ≥150 feet then walking and bed-to-chair transfers may be</th>
<th>Approx. 5 minutes [92]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interobserver reliability:</strong> ICC=0.92 [92]</td>
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<tr>
<td><strong>Internal consistency reliability:</strong> α=0.87, item-to-total correlations ranged from 0.27 (toilet transfer) to 0.75 (memory) [90]; α=0.90 [92]</td>
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<tr>
<td><strong>Construct validity:</strong> A single factor/component has been identified on factor analyses, accounting for the majority of the variance in functional status [90, 92]</td>
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<tr>
<td><strong>Concurrent validity:</strong> Alpha-FIM scores were significantly associated with total-FIM scores (r=0.75), and there was no significant difference reported between projected and actual FIM scores [90]; correlated with Barthel Index scores (r=0.68) [92]</td>
<td></td>
<td></td>
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<tr>
<td><strong>Predictive validity:</strong> Alpha-FIM scores obtained in acute care were predictive of FIM scores on admission to and discharge from rehabilitation [90, 91], length of stay [90, 91], FIM gain [91] and discharge to the community [90].</td>
<td></td>
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</tr>
<tr>
<td>Items on the Alpha-FIM are scored as per the original FIM scale. Scale scores range from 6 – 42. Alpha-FIM scores may be transformed to projected FIM scores using a proprietary algorithm ranging from 18-100. [90]</td>
<td>Yes.</td>
<td></td>
</tr>
</tbody>
</table>
A number of studies have examined the reliability of retrospective calculation of CNS scores based on documentation provided in medical records. In general, these studies have demonstrated consistently high (excellent) levels of interobserver (93-95) and internal consistency (93) reliability. **As for the CNS, investigators have studied the use of the NIHSS for performing retrospective, chart-based evaluations. (94, 96, 97) In general, the reported reliability of these assessments is lower than that associated with the CNS and should be based upon neurologist reports where possible (94, 98). ***The PedNIHSS appears to maintain a high level of reliability when used for retrospective derivation of an NIHSS score. In addition, there was no significant difference demonstrated between scores derived prospectively vs. retrospectively (p=0.49) (26)

Useful Links:
1. Additional information regarding the CNS, NIHSS, mRS, and FIM is available at [www.ebrsr.com](http://www.ebrsr.com) and at [www.strokengine.ca](http://www.strokengine.ca)
2. There is a site for international users of the NIHSS scale – it may be found here: [http://www.nihstrokescale.org/](http://www.nihstrokescale.org/) It provides links to the scale in English, as well as lots of good training information – but it also provides links to the scale in quite a number of other languages as well.
3. Here is a link to the NIHSS booklet in PDF form: [http://www.mdcalc.com/clinical_images/NIH_Stroke_Scale_Booklet.pdf](http://www.mdcalc.com/clinical_images/NIH_Stroke_Scale_Booklet.pdf)
5. Here is a link to the Hunt and Hess Scale itself:
   - or [http://radiopaedia.org/articles/hunt-and-hess-grading-system](http://radiopaedia.org/articles/hunt-and-hess-grading-system) (this page also supplies links to the Fisher scale and to the WFNS scale)
8. The Rankin scale has its own website: [http://www.rankinscale.org/](http://www.rankinscale.org/)
10. The official site for the Alpha-FIM: [http://www.udsmr.org/WebModules/Alpha/Alp_About.aspx](http://www.udsmr.org/WebModules/Alpha/Alp_About.aspx)
**Table 3.3B: Recommended Laboratory Investigations for Patients with Acute Stroke or Transient Ischemic Attack**

<table>
<thead>
<tr>
<th>Initial Laboratory Investigations on arrival to the emergency department</th>
<th>Additional Laboratory Investigations (following initial blood work, and based on clinical presentation).</th>
<th>Coagulopathy Screen</th>
<th>Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>complete blood count (CBC)</td>
<td>calcium, Magnesium, Phosphate</td>
<td>antiparcardiolipin (Antiphospholipid) antibody</td>
<td>erythrocyte sedimentation rate (ESR)</td>
</tr>
<tr>
<td>international normalized ratio (INR)</td>
<td>fasting lipid profile</td>
<td>lupus anticoagulant</td>
<td>C-reactive protein (CRP)</td>
</tr>
<tr>
<td>partial thromboplastin time (PTT)</td>
<td>blood cultures x 3 (per individual institutional protocol)</td>
<td>Sickle cell screen</td>
<td>antinuclear antibody (ANA)</td>
</tr>
<tr>
<td>troponin test</td>
<td></td>
<td>anti-beta2-glycoprotein type 1</td>
<td>C3/C4</td>
</tr>
<tr>
<td>electrolytes</td>
<td></td>
<td>protein C</td>
<td></td>
</tr>
<tr>
<td>glucose (routine)</td>
<td></td>
<td>Antithrombin III</td>
<td></td>
</tr>
<tr>
<td>creatinine</td>
<td></td>
<td>prothrombin gene mutation</td>
<td></td>
</tr>
<tr>
<td>thyroid-stimulating hormone (TSH)</td>
<td></td>
<td>homocysteine</td>
<td></td>
</tr>
<tr>
<td>AST, ALP, ALT, Bilirubin, serum protein</td>
<td></td>
<td>PNH screen (Paroxysmal Nocturnal Hemoglobinuria)</td>
<td></td>
</tr>
<tr>
<td>Cross and Type may be considered</td>
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<td></td>
<td></td>
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<tr>
<td>If female less than 50 years of age, serum β HCG</td>
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</tr>
</tbody>
</table>

**Special considerations especially in young adults and children with stroke in absence of identified etiology:**

- Consider LP for CSF analysis (cell count and differential, protein, glucose, bacterial and viral cultures; possibly cytology/flow cytometry if CNS lymphoma is a consideration)
- Further genetic tests – CADASIL, Fabry’s, MELAS
- Further blood tests – Lipoprotein (a), Homocysteine
- Catheter cerebral angiography
- Brain biopsy (if vasculitis of the central nervous system or angiocentric lymphoma is a consideration)

Refer to Canadian Stroke Patient Order Sets 1, 2, 3 and 4 for additional information

*This table provides a comprehensive list of first line laboratory investigations for consideration by clinicians. Patient presentation and clinical judgment are important factors to also consider in selecting appropriate investigations for individual patients.*
**Best Practice Recommendation 3.4**

**Acute Thrombolytic Therapy**

All patients with **disabling** acute ischemic stroke who can be treated within 4.5 hours of symptom onset should be evaluated **without delay** by a physician with stroke expertise (either on-site or by telemedicine/telestroke consultation) to determine their eligibility for treatment with intravenous tissue plasminogen activator (tPA) (Alteplase) [Evidence Level A].

### 3.4.1: Intravenous Thrombolysis

i. Eligible patients are those who can receive intravenous tPA within 4.5 hours of the onset of stroke symptoms in accordance with criteria adapted from National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study and the European Cooperative Acute Stroke Study (ECASS III) [Evidence Level A]. (Refer to Box 3.4 for inclusion and exclusion criteria for tPA eligibility.)

ii. All eligible patients should receive intravenous tPA as soon as possible after hospital arrival, with a target door-to-needle time of less than 60 minutes [Evidence Level C].

iii. Administration of tPA should follow the American Stroke Association guidelines using a dose of 0.9 mg/kg to a maximum of 90 mg total dose, with 10 percent (0.09 mg/kg) given as intravenous bolus over one minute and the remaining 90 percent (0.81 mg/kg) given as an intravenous infusion over 60 minutes [Evidence Level A].

**Caution:** the dosing of tPA for stroke is **not** the same as the dosing protocol for administration of tPA for myocardial infarction.

iv. Features of early ischemia on the initial brain CT scan in an acute ischemic stroke patient may predict responsiveness to tPA and risk of post-tPA intracerebral hemorrhage, and should be assessed using the Alberta Stroke Program Early CT Score (ASPECTS).

   a. In patients with brain CT scans showing early signs of more extensive infarction, represented by an ASPECTS of less than five, the decision to treat or not treat with tPA should be made based on the clinical judgment of the treating physician [Evidence Level B].

   b. Where the technology and expertise are available, advanced imaging studies such as CTA should be completed with the initial brain CT [Evidence Level C].

   c. When it is unclear whether or not a patient should be treated with tPA, urgently consult with a stroke specialist within the institution or through telestroke services [Evidence Level C].

v. There remain situations in which clinical trial data to support the use of intravenous thrombolytic therapy is more limited. In these situations urgent consultation with a stroke expert is recommended alongside the clinical judgement of the treating physician and discussion with the patient [Evidence Level B]. This applies to:

   a. pediatric stroke (newborn to age 18 years);

   b. pregnant women with stroke;

   c. adults who present within the first few hours of onset of an acute ischemic stroke but do not initially meet criteria for treatment with intravenous tPA.

vi. Hospital inpatients that present with a sudden onset of new stroke symptoms should be rapidly evaluated by a specialist team and provided with access to appropriate hyperacute interventions (including thrombolysis) [Evidence Level B].
vii. Management of Complications from tPA Administration:
   a. use of fresh frozen plasma, prothrombin complex concentrates, or platelet transfusions is not recommended for tPA-associated bleeding [Evidence Level C];
   b. for tPA-induced angioedema, discontinue the tPA infusion if it is still running, obtain assistance for airway management if required, and give intravenous hydrocortisone 100 mg, diphenhydramine 50 mg, and ranitidine 50 mg. The use of epinephrine should be weighed against the risk of sudden hypertension and the risk of intracranial hemorrhage [Evidence Level C].

3.4.2: Endovascular Therapies for Acute Ischemic Stroke Treatment

i. Endovascular therapies for acute ischemic stroke treatment, including intra-arterial delivery of thrombolytic drug and/or endovascular mechanical thrombectomy by device or by aspiration, are being investigated as additions to acute stroke thrombolysis. **However, IV thrombolysis remains the standard of care for hyperacute ischemic stroke treatment for appropriate patients** [Evidence Level A].
   a. Endovascular therapies for acute ischemic stroke should ideally be reserved for investigational use in the context of randomized controlled trials [Evidence Level C].
   b. Endovascular therapy is a possible therapeutic addition to intravenous thrombolysis in highly selected circumstances. Emergency consultation with stroke experts and interventional radiology experts is relevant for this kind of decision-making [Evidence Level C].

ii. Endovascular mechanical thrombectomy alone, without intravenous or intra-arterial tPA, is a possible therapeutic option for patients who do not qualify for tPA thrombolysis due to increased systemic bleeding risks [Evidence Level C].

**Clinical Considerations:**

- **tPA is still the standard of care, and currently the only approved agent for acute ischemic stroke treatment.** There are other drugs being investigated; however, at this time are not approved for use in stroke patients.
- **The IST3 trial (2012) suggests that in some patients it is safe to administer tPA up to 6 hours from time last known well.** At this time, the evidence is not strong enough to extend recommended treatment times for tPA out to six hours for intravenous therapy.
- **tPA administration for patients on novel oral anticoagulants (NOACs):** until such time when there is a commercially available and validated assessment tool for NOAC levels, and until such time as it is reliably known what these levels mean clinically, tPA should not routinely be administered to patients on NOACs presenting with acute ischemic stroke.

**Note on Alteplase approval status in Canada:**

In Canada, Alteplase is approved by Health Canada for use in adults with acute ischemic stroke within three hours after the onset of stroke symptoms; the manufacturer has not yet applied to extend the time window.
Box 3.4: Criteria for Acute Thrombolytic Therapy

These criteria are designed to guide clinical decision-making; however, the decision to use tPA in these situations should be based on the clinical judgment of the treating physician.

Criteria adapted in accordance with the criteria identified in National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study and the European Cooperative Acute Stroke Study (ECASS III, IST3).

Treatment Inclusion Criteria

- Diagnosis of ischemic stroke causing measurable neurologic deficit in a patient who is 18 years of age or older.
- For adolescents, decision to administer tPA should be based on clinical judgment, presenting symptoms, and patient age; and, if possible, consultation with a pediatric stroke specialist.
- Time from last known well (onset of stroke symptoms) less than 4.5 hours before tPA administration.

Exclusion Criteria

Historical
- History of intracranial hemorrhage in previous six months.
- Stroke or serious head or spinal trauma in the preceding three months.
- Recent major surgery, such as cardiac, thoracic, abdominal, or orthopedic.
- Arterial puncture at a non-compressible site in the previous seven days.
- Any other condition that could increase the risk of hemorrhage after tPA administration.

Clinical
- Symptoms suggestive of subarachnoid hemorrhage.
- Stroke symptoms due to another non-ischemic acute neurological condition such as seizure with post-ictal Todd's paralysis or focal neurological signs due to severe hypo- or hyperglycemia.
- Hypertension refractory to antihypertensives such that target blood pressure <185/110 cannot be achieved.

Laboratory
- Blood glucose concentration below 2.7 mmol/L or above 22.2 mmol/L.
- Elevated activated partial-thromboplastin time.
- International Normalized Ratio greater than 1.7.
- Platelet count below 100,000 per cubic millimetre.

CT or MRI Findings
- Any hemorrhage on brain CT or MRI.
- CT showing early signs of extensive infarction, represented by a score of less than five on the Alberta Stroke Program Early CT Score (ASPECTS), or MRI showing an infarct volume greater than 150 cc on diffusion-weighted imaging.

Rationale:

Meta-analyses of the randomized controlled trials of intravenous Alteplase for acute ischemic stroke have shown that thrombolytic treatment can reduce the risk of disability and death, despite the risk of serious bleeding. The latest time for tPA administration after stroke onset remains imprecisely defined, but currently available data show clear evidence of benefit when given up to 4.5 hours after the onset of symptoms. The available evidence demonstrates a strong inverse relationship between treatment delay and clinical outcome; eligible patients should be treated without delay, regardless of when they present within the treatment window.

System Implications

- Local protocols for prioritizing stroke patients for rapid access to appropriate diagnostics such as CT scans and duplex ultrasound, communicated to all relevant personnel such as emergency department, imaging, and stroke teams.
• A system for rapid access to physicians experienced in administration of acute thrombolysis, including through telemedicine, which includes protocols for contacting physicians and for administration of tissue plasminogen activator.

• Access to specialized stroke units where staff are experienced in managing patients who have received tissue plasminogen activator for stroke.

### Performance Measures

1. Proportion of all ischemic stroke patients who receive treatment with intravenous tPA (Alteplase) (core).
2. Proportion of ischemic stroke patients presenting to medical attention within 3.5 hours of symptom onset who receive treatment with intravenous tPA (Alteplase).
3. Proportion of all thrombolyzed stroke patients who receive tPA (Alteplase) within one hour of hospital arrival (core).
4. Median time (in minutes) from patient arrival in the emergency department to administration of tPA (Alteplase).
5. Proportion of patients with symptomatic intracerebral hemorrhage following tPA (Alteplase) treatment.
6. Proportion of patients in rural or remote communities who receive tPA (Alteplase) through the use of telestroke technology (as a proportion of all ischemic stroke cases in that community and as a proportion of all telestroke consults for ischemic stroke cases).

### Measurement Notes

- Data may be obtained from patient charts, through chart audit or review.
- Time interval measurements should be taken from the time the patient is triaged or registered at the hospital (whichever time comes first) until the time of medication administration noted in the patient chart (nursing notes, emergency department record, or medication record).
- When recording if tPA is given, the route of administration should also be recorded, as there are different times to administration benchmarks for intravenous versus intra-arterial routes.

### Implementation Resources and Knowledge Transfer Tools

- Canadian Stroke Best Practices Patient Order Set of Initial Emergency Department Evaluation of a Suspected Stroke Patient
- Canadian Stroke Best Practices Patient Order Set for tPA (Alteplase) administration.
- Canadian Stroke Best Practices Table 3.3A Screening and Assessment Tools for Acute Stroke
- HSF Stroke Nurses Assessment Pocket Cards
  http://www.heartandstroke.on.ca/site/c.pvI3i3eNWJwE/b.5852913/k.AC4B/Order_Resources/apps/ka/ct/contactcustom.asp
- American College of Chest Physicians (ACCP) Anticoagulation Guidelines
Summary of the Evidence

The weight of evidence from many large, international trials over a time frame of 20 years suggests that treatment with intravenous Alteplase can reduce the risk of death or disability following ischemic stroke, 3 to 6 months post treatment. The NINDS trial (1995) was one of the earliest, large trials, which was conducted in the USA. Patients were randomized to receive Alteplase or placebo within 3 hours of symptom onset. At 3 months, significantly more patients in the tPA group had experienced a good outcome (using any one of the study’s 4 metrics), with no difference in 90-day mortality between groups. In contrast, patients who received Alteplase within 3 to 5 hours in the ATLANTIS trial (1999) were no more likely to have a good neurological or functional outcome at 90 days than patients in the placebo group.

In the first ECASS trial (1995) 620 patients received Alteplase or placebo within 6 hours of event. Using intention-to-treat analysis and including the data from 109 patients with major protocol violations, the authors did not report a significant benefit of treatment. The median Barthel Index and modified Rankin scores at 90 days did not differ between groups. In an analysis restricted to patients in the target population, there were differences favouring patients in the Alteplase group. In the ECASS II trial (1998), there was again no significant difference on any of the primary outcomes. The percentages of patients with a good outcome at day 90 (mRS<2) treated with Alteplase and placebo were 40.3% vs. 36.6%, respectively, absolute difference =3.7%, p=0.277. In subgroup analysis of patients treated < 3 hours and 3-6 hours, there were no between-group differences on any of the outcomes. The authors suggested that the reason for the null result may have been that the study was underpowered, since it was powered to detect a 10% difference in the primary outcome, but the observed difference between groups in previous trials was only 8.3%. Finally, in the ECASS III trial (2008) 821 patients were randomized within 3 and 4.5 hours of symptom onset. In this trial, a higher percentage of patients in the Alteplase group experienced a favourable outcome, defined as mRS scores <2 (52.4% vs. 45.2%, adjusted OR=1.34, 95% CI 1.02 to 1.76, p=0.04). A higher percentage of patients in the Alteplase group also had NIHSS scores of 0 or 1, (50.2% vs. 43.2%, adjusted OR=1.33, 95% CI 1.01 to 1.75, p=0.04). Secondary outcomes of the ECASS III trial were reported by Bluhmki et al. (2009). At 90 days, there were no between-group differences in the percentages of patients with mRS score of 0-2 (59% vs. 53%, p=0.097) or BI score≥85 (60% vs. 56%, p=0.249, but a significantly greater percentage of patients had improved NIHSS scores of ≥8 points (58% vs. 51%, p=0.031).

In all of the trials described above there was an increased risk of symptomatic ICH associated with treatment with Alteplase and in some cases, increased short-term mortality; however, there were no differences between treatment and placebo groups in 90-day mortality.

The Third International Stroke Trial (2012), is the largest (n=3,035) and most recent trial of Alteplase, in which patients were randomized to receive a standard dose of Alteplase (0.9 mg/kg) or placebo. Investigators aimed to assess the risks and benefits of treatment among a broader group of patients, and to determine if particular subgroups of patients might benefit preferentially from treatment. In this trial, 95% of patients did not meet the strict licensing criteria, due to advance age or time to treatment. Unlike all previous, large trials, which excluded them, IST-3 included patients >80 years. In fact, the majority of patients (53%) were >80 years. Approximately one-third of all patients were treated within 0-3 hours, 3.0-4.5 hours and 4.5-6.0 hours of onset of symptoms. Overall, there was an increase in the risk of death within 7 days in patients who had received Alteplase, although there was no difference in 6-month mortality in both crude and adjusted analyses. There was no significant difference in the percentage of patients who were treated with Alteplase who were alive and independent (defined as an Oxford Handicap Score of 0-1) at 6 months (37% vs. 35%, adjusted OR=1.13, 95% CI 0.95 to 1.35, p=0.181, although a secondary ordinal analysis suggested a significant, favourable shift in the distribution of OHS scores at 6 months. Significantly improved odds of a good outcome at 6 months were associated with the sub groups of older patients (≥80 years), higher NIHSS scores, higher baseline probability of good outcome and treatment within 3 hours. Fatal or non-fatal symptomatic intracranial hemorrhage within 7 days occurred more frequently in patients in the tPA group (7% vs. 1%, adjusted OR=6.94, 95% CI 4.07 to 11.8, p<0.0001).

Although it is known that the optimal timing of administration of intravenous Alteplase is <3 hours, debate continues as to the safety and efficacy of treatment provided between 3 and 6 hours post stroke. The results from a few studies suggest that treatment is still beneficial if provided beyond the 3-hour window. The Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) includes patients who were treated with intravenous Alteplase under strict licensing criteria and also those who were thought to be good candidates based on clinical/imaging assessment of the treating facility. Wahlgren et
al. (2008) used data from a cohort of patients collected from 2002-2007 to compare the outcomes of patients who had been treated with Alteplase within 3 hour of symptom onset (n=11,865) and those treated from 3-4.5 hours (n=644). The primary focus of this analysis was to assess treatment safety beyond the 3-hour treatment window. Patients in the <3 hour group had significantly lower initial median NIHSS scores (11 vs. 12, p<0.0001). There were no significant between group differences on any of the outcomes (symptomatic ICH within 24-36 hours, mortality within 3 months, or percentage of patients who were independent at 3 months); however, there was a trend towards increased number of patients treated from 3 to 4.5 hours who died (12.7% vs. 12.2%, adjusted OR=1.15, 95% CI 1.00-1.33, p=0.053) and who experienced symptomatic ICH (2.2% vs. 1.6%, adjusted OR=1.32, 95% CI 1.00-1.75, p=0.052). Additional analysis from the SITS-ISTR cohort was conducted to further explore the timing of Alteplase treatment (Ahmed et al. 2010). In this study, patients treated within 3 hours (n=21,566) and 3-4.5 hours (n=2,376) of symptom onset between 2007 and 2010, were again compared. Significantly more patients treated from 3-4.5 hours experienced a symptomatic ICH (2.2% vs. 1.7%, adjusted OR=1.44, 95% CI 1.05-1.97, p=0.02), and were dead at 3 months (12.0% vs. 12.3%, adjusted OR=1.26, 95% CI 1.07-1.49, p=0.005). Significantly fewer patients treated from 3-4.5 hours were independent at 3 months: (57.5% vs. 60.3%, adjusted OR=0.84, 95% CI 0.75-0.95, p=0.005). A meta-analysis restricted to RCTs patients from the ECASS I, II and III and ATLANTIS trials (n=1,622) who had received Alteplase or placebo 3 to 4.5 hours following stroke suggested a benefit of treatment (Lansberg et al. 2009). Patients who had received Alteplase had a significantly greater likelihood of a favourable outcome (OR=1.31, 95% CI 1.1-1.56, p=0.002) and were no more likely to be dead at 90 days. OR=1.01, 95% CI 0.75-1.43, p=0.83). Outcome data for ICH were not reported.

An updated systematic review and meta-analysis of intravenous thrombolysis (Wardlaw et al. 2013) that included the results from 12 RCTs (7,012 patients) of tPA, published from 1992-2012 strengthen the evidence that treatment with tPAs is safe and effective. The authors concluded that for every 1,000 patients treated up to 6 hours following stroke, 42 more patients were alive and independent (mRS<2) at the end of follow-up, despite an increase in early ICH and mortality. The authors also suggested that patients who did not meet strict licensing criteria due to age and timing of treatment (i.e., patients from the IST-3 trial were just as likely to benefit; however, early treatment, within 3 hours of stroke onset, was more effective.

The use of thrombolytic therapy in patients who are younger than 18 years and in women at any stage of pregnancy has not been evaluated empirically. Twelve case reports of women who received thrombolysis treatment constitute the evidence base for this group. The results from 11 cases have been summarized by Li et al. (2012) and the 12th case report was published recently (Tassi et al. 2013). In 4 cases, tPA was administered using the intra-arterial route. The neurological outcomes of these women were described as being similar to (non-pregnant) patients who met the eligibility criteria. The evidence in terms of thrombolytic treatment for patients <18 years comes primarily from the International Pediatric Stroke Study, (IPSS) an observational study (n=687) in which the outcomes of 15 children, aged 2 months to 18 years who received thrombolytic therapy (9 with intravenous Alteplase, 6 with intra-arterial Alteplase). Overall, at the time of hospital discharge, 7 patients were reported having no or mild neurological deficits, 2 had died and the remainder had moderate or severe neurological deficits. The thrombolysis in Pediatric Stroke (TIPS) study (Amelie-Lefond et al. 2009) is currently recruiting subjects for 5-year, prospective cohort, open-label, dose-finding trial of the safety and feasibility of intravenous and intra-arteral tPA to treat acute childhood stroke (within 4.5 hours of symptoms). The TIPS investigators are aiming to include 48 subjects.

Re-vascularization can also be achieved through intra-arterial administration of thrombolytic agents or mechanical dislodgement with specialized devices. The body of evidence for these procedures is not as well developed as it is for intravenous thrombolysis. A meta-analysis (Nam et al. 2013) included 6 RCTs examining the treatment contrasts of intraarterial thrombolysis (IAT) and either standard treatment (n=4) or intravenous thrombolysis (n=2) following acute ischemic stroke. Treatment with IAT was associated with the reduction of poor functional outcome at end of follow-up (RR=0.83, 95% CI 0.73 to 0.94, p=0.004), compared with standard treatment. Although the risk of ICH was increased (RR=3.90, 95% CI 1.41 to 10.76, p=0.009), mortality was not (RR=0.82, 95% CI 0.56 to 1.21, p=0.32). In the two studies that compared IAT with i.v. tPA, there was a trend towards the reduction in poor outcome associated with IAT (RR = 0.68, 95% CI 0.46 to 1.00, p=0.05). The rates of ICH and mortality between groups were similar. In the SYNTHESIS trial, Ciccone et al. (2013) randomized 362 patients to receive either pharmacological or mechanical thrombolysis, or a combination of these approaches or ii) intravenous IPA within 4.5 hours of symptom onset. Patients in both groups received a IPA dose of 0.9 mg/kg (max dose 90 mg). At 90 days, the percentages of patients alive without disability was similar between groups (30.4% vs. 34.8%, adjusted...
OR=0.71, 95% CI 0.44 to 1.14, p=0.16). There were no differences in adverse events between groups (death or ICH).

Link to Evidence Table 3.4 and References available on website at www.strokebestpractices.ca
Best Practice Recommendation 3.5
Acute Aspirin Therapy

All acute stroke patients not already on an antiplatelet agent should be given at least 160 mg of acetylsalicylic acid (ASA) immediately as a one-time loading dose after brain imaging has excluded intracranial hemorrhage [Evidence Level A].

i. In patients treated with tissue plasminogen activator (tPA), acetylsalicylic acid (ASA) should be delayed until after the 24-hour post-thrombolysis scan has excluded intracranial hemorrhage [Evidence Level B].

ii. Acetylsalicylic acid (80 to 325 mg daily) should then be continued indefinitely or until an alternative antithrombotic regime is started [Evidence Level A].

   Refer to Recommendations 2.5 and 2.6 for additional information.

iii. In dysphagic patients, acetylsalicylic acid may be given by enteral tube or by rectal suppository [Evidence Level A].

iv. In pediatric patients, initial treatment with anticoagulation (heparin) or aspirin at established pediatric dosing should be considered and continued until cervical artery dissection and intracardiac thrombus is excluded. If neither is present, switch to acute aspirin therapy at dose of 1-5 mg/kg [Evidence Level B]. (Roach et al 2008)

v. In patients already on acetylsalicylic acid prior to ischemic stroke or transient ischemic attack, clopidigrel may be considered as an alternative [Evidence Level B]. If rapid action is required then a loading dose of 300 mg of clopidigrel could be considered, followed by a maintenance dose of 75 mg once a day [Evidence Level B].

Rationale

Acute-phase aspirin therapy reduces the risk of early recurrent ischemic stroke. Long-term aspirin therapy reduces the risk of ischemic stroke, myocardial infarction, and vascular death. There is a paucity of data from randomized controlled trials to support the use of other antiplatelet regimes in acute stroke patients. In clinical trials for tPA, antithrombotic drugs (including aspirin) were avoided until after the 24-hour post-thrombolysis scan had excluded intracranial hemorrhage.

System Implications

- Protocols and standing order sets should be developed and available to guide initial management of ischemic stroke and transient ischemic attack patients
- Pediatric awareness campaigns and education to healthcare professionals to optimize recognition of stroke and management.

Performance Measures

1. Proportion of ischemic stroke or TIA patients who receive acute aspirin therapy within the first 48 hours following symptom onset (core).
2. Median time from stroke onset to administration of first dose of aspirin in hospital.

Measurement Notes

- Time interval measurements should be taken from the time the patient is triaged or registered at the hospital (whichever time comes first) until the time the first dose is administered.
- This indicator focuses on aspirin. Some centres may include other antiplatelet medications, such as clopidogrel or ASA combined with extended release dipyridamole. In cases where
another agent is used instead of aspirin in the first 48 hours, this should be noted in the indicator definition.

- Possible data sources include history and physical, physician’s admission notes, nurses’ admission notes, medication record.

**Implementation Resources and Knowledge Transfer Tools**

- Canadian Stroke Best Practices Patient Order Set of Initial Emergency Department Evaluation of a Suspected Stroke Patient
- Canadian Stroke Patient Order Set - Prevention of Stroke
- Stroke Best Practices Stroke Prevention Pocket Cards 2012
- Stroke Best Practices Stroke Prevention Posters 2012
- CCS Atrial Fibrillation Guidelines 2012
  - http://download.journals.elsevierhealth.com/pdfs/journals/0828-282X/PIIS0828282X12000463.pdf
- American College of Chest Physicians (ACCP) Anticoagulation Guidelines

**Summary of the Evidence**

In an updated Cochrane review, Sandercock and colleagues identified 12 RCTs (n=43,041) comparing placebo/no treatment to antiplatelet therapy initiated within 14-days of the onset of ischemic stroke (Sandercock, Counsell, Gubitz, & Tseng, 2009). Two large trials investigating aspirin therapy (160-300 mg/day) initiated within 48-hours of stroke onset contributed 94% of the data. Treatment with aspirin was associated with a significant decrease in death or dependency at follow up (at least one-month post-stroke; OR=0.95, 95% CI 0.91 to 0.99). Moreover, the authors reported that for every 1,000 patients treated with aspirin, 13 will avoid death or dependency (number needed to treat to benefit = 79). Although antiplatelet therapy was associated with a significant increase in the odds of intercerebral hemorrhage (OR=1.33, 95% CI 1.10 to 1.62), a net reduction was reported in terms of the odds of any stroke recurrence (i.e., ischemic or hemorrhagic; OR=0.88, 95% CI 0.80 to 0.97). Sandercock et al. concluded that aspirin therapy initiated within 48-hours of ischemic stroke improves long-term outcomes without producing a major risk of early hemorrhagic complication (Sandercock et al., 2009).

Current evidence suggests that patients should not receive antiplatelet therapy within 24-hours of treatment with tPA due to increased risk of symptomatic intercrainal hemorrhage (Zinkstok & Roos, 2012). Evidence also suggests that long-term antiplatelet therapy reduces the risk of subsequent serious vascular events by about one quarter (Sandercock et al., 2009). In-hospital initiation of secondary prevention therapy after an ischemic stroke or transient ischemic attack is associated with greater adherence rates three-months following discharge (Ovbiagele et al., 2004).
Due to a lack of high-quality, randomized controlled trials in the literature, controversy exists regarding the use of antiplatelets in the hyperacute management of paediatric stroke patients. The Royal College of Physicians and the American Heart Association paediatric stroke guidelines both recommend the use of aspirin unless there is a known dissection or cardiac clot, in which case low molecular weight heparin is recommend (Paediatric Stroke Working Group, 2004; Roach et al., 2008). Conversely, the American College of Chest Physicians guidelines recommend that low molecular weight heparin should be used until the absence of dissection or cardiac clot is established (Guyatt, Cook, Jaeschke, Pauker, & Schunemann, 2008). Although the current paediatric literature base is limited, it is clear that the rate of transient ischemic attack / stroke recurrence in children with arterial ischemic stroke is nearly 50% without antithrombotic treatment, demonstrating the need for prompt diagnosis and treatment within paediatric stroke patients (Antithrombotic Trialists’ Collaboration, 2002). Results from the Warfarin-Aspirin Recurrent Stroke Study Trial, in a sub-group analysis of adults who are somewhat similar to children with stroke (i.e. non-hypertensive, non-atherosclerotic), reveal a benefit of anticoagulation over aspirin in preventing stroke recurrence (Fullerton, Wu, Sidney, & Johnston, 2007).

Link to Evidence Table 3.5 and References available on website at www.strokebestpractices.ca
Best Practice Recommendation 3.6
Early Management of Acute Subarachnoid Hemorrhage

NOTES on this recommendation

- This recommendation is for patients with subarachnoid hemorrhage (SAH). It applies to the initial assessment in the emergency department within the first few hours of patient arrival.
- Detailed treatment and management of subarachnoid hemorrhage patients is outside the scope of these recommendations.
- Symptoms of subarachnoid hemorrhage may include sudden onset of severe headache (sometimes described as "thunderclap headache") that patients will often characterize as the worst of their life. The headache of SAH is usually associated with nausea, vomiting, meningismus and photophobia and can also be associated with altered level of consciousness. Signs on physical examination vary depending on the location of the aneurysm and the extent of the hemorrhage as well as whether there is intraventricular or intracerebral extension of the subarachnoid hemorrhage. Physical signs can include diminished level of consciousness, cranial nerve palsy, hemiparesis and subhyaloid hemorrhage on fundoscopic exam, but it is important to note that patients with acute SAH often have a NORMAL neurological examination, so the absence of physical findings should not alter the index of suspicion raised by the clinical presentation.

3.6 Patients with aneurysmal subarachnoid hemorrhage should be treated as a medical emergency and evaluated immediately by physicians with expertise in stroke management [Evidence Level B]. There is a high early risk for rebleeding in SAH patients; therefore they should be assessed without delay [Evidence Level B].

3.6.1 Initial Clinical Assessment of a Patient with SAH

i. Patients with suspected subarachnoid hemorrhage should have a non-contrast CT scan as soon as possible after hospital arrival to confirm the diagnosis [Evidence Level B].

ii. Patients with a strongly suggestive clinical history of subarachnoid hemorrhage, but negative non-contrast CT scan as reported by a radiologist, should undergo lumbar puncture for cerebrospinal fluid analysis [Evidence Level B].
   a. Xanthochromia evaluation may be more sensitive after a minimum delay of 4 hours from onset of headache but such a delay may not be practical or clinically appropriate [Evidence Level B].
   b. Cerebrospinal fluid analysis for xanthochromia by spectrophotometry is preferable to visual inspection, but is not routinely available in Canada [Evidence Level B].

iii. Patients with subarachnoid hemorrhage should undergo vascular imaging of the brain. High-quality CT angiography may be preferable to catheter angiography as an initial investigation [Evidence Level B], but catheter angiography should still be considered as the "gold standard" when initial CTA is negative.
   Note: Highly suspicious SAH undergoing CTA requires visualization of the vasculature starting from the aortic arch, including cervical and intracranial arteries, to identify all possible hemorrhage sites.

iv. The severity of subarachnoid hemorrhage patients should be determined using a validated scale (strong predictors of patient outcomes after an SAH) [Evidence Level B].
   a. Recommended assessment tools may include: World Federation of Neurological Surgeons (WFNS), Glasgow Coma Scale (GCS), Hunt and Hess scale (H&H), National Institute of Medicine Stroke Scale (NIHSS), and the Fisher Scale. Other tools may be considered as appropriate to individual patients.
3.6.2 Consultation with Neurosurgery for Patients with Subarachnoid Hemorrhage

i. Patients with subarachnoid hemorrhage should have an urgent consultation with a neurosurgeon [Evidence Level B].

3.6.3 Interventions for Patients with Subarachnoid Hemorrhage

i. Once a subarachnoid hemorrhage is confirmed, patients initially seen in non-comprehensive stroke centres should be transferred to a tertiary centre for ongoing management [Evidence Level C].

ii. Patients with subarachnoid hemorrhage and negative non-invasive vascular imaging should be considered for further imaging with catheter angiography [Evidence Level C].

iii. Patients who present within 96 hours of a subarachnoid hemorrhage and have an adequate blood pressure should immediately be started on nimodipine 60 mg every four hours by mouth for 14 to 21 days [Evidence Level A].

iv. Patients with an aneurysmal subarachnoid hemorrhage should have the aneurysm secured urgently by endovascular coiling or microsurgical clipping, ideally within 24 to 48 hours [Evidence Level B].

v. Patients with aneurysmal subarachnoid hemorrhage and CT evidence of hydrocephalus that is clinically symptomatic should undergo urgent placement of an external ventricular drain (EVD) or other cerebrospinal fluid diversion technique [Evidence Level B].

vi. For subarachnoid hemorrhage patients with intraparenchymal extension at the time the aneurysm is secured, urgent evacuation of the hematoma should be considered [Evidence Level C].

vii. For most patients with subarachnoid hemorrhage who are technically eligible for endovascular or microsurgery treatment, an endovascular approach is preferred [ISAT trial] [Evidence Level A].

a. Decisions regarding modality of treatment should be based on patient-specific characteristics, which include consideration of patient age, clinical grade, size, location and morphology of the aneurysm, medical co-morbidity and institutional experience and resources [Evidence Level B].

viii. In the absence of seizures, routine use of prophylactic anti-convulsants is not recommended [Evidence Level B].

3.6.4 Blood Pressure Management

i. Patients with an unsecured aneurysm in a subarachnoid hemorrhage should have their blood pressure closely monitored and maintained as normotensive [Evidence Level B].

ii. Treatment for high blood pressure should be initiated while the aneurysm is unsecured to reduce the risk of hypertension-induced rebleeding and maintain cerebral perfusion pressure (ASA 2012) [Evidence Level B].
3.6.5 Additional Aspects of Clinical Management

i. Neurological assessment should be conducted as part of regular vital signs, using standardized assessment tools throughout the course of stay to monitor changes, and ideally every two to four hours until patient is stable [Evidence Level C].
   a. Frequency of neurological assessment should be adjusted according to patients condition (e.g., frequency may increase during episodes of vasospasm);
   b. Recommended assessment tools may include: Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS). Other tools may be considered as appropriate to individual patients.

ii. Patients with SAH should have the head of their bed elevated 30 degrees for at least first 24 to 48 hours [Evidence Level B].

iii. Elevated temperature should be treated to achieve normothermia in SAH patients [Evidence Level B]. Refer to Recommendation 4.2 for additional information.

iv. Patients with subarachnoid hemorrhage should receive venous thromboembolism prophylaxis [Evidence Level A].
   a. Sequential compression devices may be preferred in the early stages prior to having the aneurysm secured. Refer to recommendation 4.2 for additional information.

v. For patients with poor prognosis for neurological recovery, an initial course of supportive non-surgical management may be appropriate [Evidence Level B].
   a. Goals of care should be established early after patient arrival at hospital, with patient and/or designated substitute decision-maker (Evidence Level B);
   b. “Do not resuscitate” (DNR) discussion should not occur with the patient’s family until such a time as there is no significant response to medical treatment or worsening despite medical care;
   c. Patients who are given DNR status at any point should receive all other appropriate medical and surgical interventions unless otherwise explicitly indicated. Pre-existing DNR orders should be considered where appropriate.

Rationale

Subarachnoid hemorrhage is a catastrophic neurosurgical emergency that is prevalent in approximately seven percent of adults with stroke, and also in children, and accounts for prolonged hospital lengths of stay. Recent mortality rates in Canada for patients with subarachnoid hemorrhage are just over 40 percent within 30 days of the event. Over the past decade, several advances have been made in early treatment of subarachnoid hemorrhage, including endovascular techniques. Prompt recognition and access to expert medical professionals may reduce mortality and morbidity and improve long-term outcomes.

System Implications

- Awareness and education for physicians and nursing staff to recognize subarachnoid hemorrhage as a medical emergency and usually has different distinct presentation, even in those patients with other headache disorders.
- Protocols for acute SAH management, including rapid access to neurosurgical specialists for hemorrhagic patient management, including rapid referral process if neurosurgical services
not available within the initial treating hospital.

Performance Measures

1. **Risk-adjusted mortality rates for subarachnoid hemorrhage in-hospital, 30-day and one year (core).**
2. Percentage of subarachnoid hemorrhage patients who receive a consult to a neurosurgeon within 24 hours of hospital arrival.
3. Percentage of subarachnoid hemorrhage patients who receive a CT scan or MRI within 24 hours of hospital arrival.
4. Rebleeding rate for subarachnoid hemorrhage patients (stratified by whether patient underwent surgical or endovascular intervention) within 7 days and 30 days of hospital presentation.

Measurement Notes
- Risk adjustment should include age, gender, and initial stroke severity scores, as well as co-morbidities.

Implementation Resources and Knowledge Transfer Tools
- American Stroke Association Guidelines for Management of Subarachnoid Hemorrhage 2012
- Canadian Stroke Best Practices Table 3.3A Screening and Assessment Tools for Acute Stroke
- Canadian Stroke Best Practices Table 3.3B Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack
- HSF Stroke Nurses Assessment Pocket Cards

Summary of the Evidence

Subarachnoid hemorrhage (SAH) is a medical emergency with potentially devastating effects of early mortality or significant morbidity. Lovelock et al. (2010) examined trends in case-fatality with SAH in a systematic review and by comparing results from the Oxford Community Stroke Project (1981 to 1986) and the Oxford Vascular Study (2002 to 2008). The analysis did not show reductions in incidence of SAH (RR = 0.79, 95% CI: 0.48 to 1.29, p = 0.34) or in 30-day case-fatality (RR = 0.67, 95% CI: 0.39–1.13, p = 0.14) in the Oxford Vascular Study vs. Oxford Community Stroke Project, but there was a decrease in overall mortality (RR = 0.47, 95% CI: 0.23 to 0.97, p = 0.04). Following adjustment for age and baseline SAH severity, patients surviving to hospital had reduced risk of death or dependency (modified Rankin score > 3) at 12 months in the Oxford Vascular Study vs. Oxford Community Stroke Project. In a meta-analysis of data from all studies, unadjusted case-fatality fell by 0.9% per annum (0.3 to 1.5, p = 0.007) and by 0.9% per annum (0.2 to 1.6, p = 0.01) within the seven population studies.

The HUNT study of risk factors for SAH found that systolic and diastolic blood pressure were strong predictors of aneurysmal SAH and there was a substantially increased risk associated with smoking (Sandvei et al. 2009). Systolic blood pressure was positively associated with risk (p for trend=0.001). Compared with the reference (<130 mm Hg), the adjusted hazard ratio (HR) in people with systolic blood pressure of 130 to 139 mm Hg was 2.3 (95% CI, 1.4 to 3.8) and for systolic blood pressure >170 mm Hg, the HR was 3.3 (95% CI, 1.7 to 6.3) with similar positive association seen in the diastolic pressure. Adequate blood pressure control has been found as an independent risk factor in reducing the severity of SAH. Uncontrolled hypertension has been found to be a predictor of poorer outcomes, thus blood pressure management is of utmost importance.
Recent studies have reported the sensitivity of the modern CT scanners as a diagnostic tool for SAH. In a retrospective study consisted of 499 patients referred to neurosurgical center on suspicion of SAH or with verified SAH, CT scanning was found to have a sensitivity of 100% from day 1-5 on symptom onset (Cortnum et al. 2010). Overall, CT scanning had a sensitivity of 99.7 % (95% CI: 98.1 to 99.99%). Data from 11 tertiary-care emergency departments across Canada on 3,132 patients who presented with non-traumatic acute headache showed that CT imaging had an overall sensitivity of 92.9% (95% CI: 89.0 to 95.5%) for the identification of patients with SAH (Perry et al. 2011). Moreover, for the 953 patients who were scanned within 6 h of headache onset, the sensitivity increased to 100% (95% CI: 97 to 100%).

A number of pharmacological treatments have been evaluated in the management of SAH. Results from a Cochrane Review (Dorhout et al. 2007) support the use of calcium antagonist particularly nimodipine for aneurysmal SAH. The review included 16 RCTs trials, involving 3361 patients; three of the studies were of magnesium sulphate in addition to nimodipine. Overall, calcium antagonists reduced the risk of poor outcome with relative risk (RR) of 0.81 (95 %CI: 0.72 to 0.92); the corresponding number of patients needed to treat was 19 (95% CI 11 to 51). For oral nimodipine alone the RR was 0.67 (95% CI: 0.55 to 0.81), for other calcium antagonists or intravenous administration of nimodipine the results were not statistically significant. For magnesium in addition to standard treatment with nimodipine, the RR was 0.75 (95% CI 0.57 to 1.00) for a poor outcome and 0.66 (95% CI 0.45 to 0.96) for clinical signs of secondary ischemia. Given the potential benefits, oral nimodipine is currently indicated in patients with aneurysmal SAH. A systematic review and meta-analysis on the use of prophylactic magnesium showed that the drug did not improve neurologic outcome or decrease cerebral infarction, radiographic vasospasm or mortality in aneurysmal SAH (Golan et al. 2007). A Cochrane Review (Zhang et al. 2010) of 5 RCTs on the use of tirilazad, a neuroprotective agent concluded that there is no evidence that tirilazad, in addition to nimodipine, reduces mortality or improves poor outcome in patients with aneurysmal SAH. There have been recent interest in the use of endothelin receptor antagonist (ETRA) to prevent endothelin -mediated cerebral vasospasm after SAH. The CONSCIOUS-2 trial, a randomised, double-blind, placebo-controlled phase 3 trial showed that Clazosentan has no significant effect on mortality and vasospasm related morbidity or functional outcome (Macdonald et al. 2011). A meta-analysis of 5 RCTs showed that there is evidence that ETRAs could benefit clinical outcome in patients with SAH (Junpeng et al. 2012).

With regards to prophylactic use of anticonvulsants, a study of 3,552 patients participating in 4 prospective double-blind, placebo controlled RCT suggested that outcome was worse in those who received prophylactic anticonvulsants (Rosengart et al. 2007). Patients treated with anticonvulsants had an increased risk for poor outcome (adjusted OR=1.56, 95% CI: 1.16 to 2.10; p = 0.003) based on the Glasgow Outcome Scale; and increased risk for cerebral vasospasm, neurological deterioration, cerebral infarction and for elevated temperature during hospitalization. In the absence of seizures, routine use of anticonvulsants is not recommended.

A systematic review conducted on the timing of aneurysm surgery showed that in a single RCT, the RR of poor outcome was 0.42 (95% CI: 0.17 to 1.04) for patients planned for early surgery and 1.07 (95% CI: 0.56 to 2.05) for intermediate surgery (deGans et al. 2002). The analysis of the observational study data found the RR of poor outcome for patients in good clinical condition at admission was 0.41 (95% CI: 0.34 to 0.51) for early surgery and 0.47 (95% CI: 0.32 to 0.69) for intermediate surgery. For patients in poor clinical condition at admission, the RR of poor outcome was 0.84 (95% CI: 0.67 to 1.05) for early surgery and 0.54 (95% CI: 0.24 to 1.22) for intermediate surgery.

Endovascular treatment is used with increasing frequency as alternative to neurosurgical clipping for SAH; however, questions remain as to its safety and effectiveness. The International Subarachnoid Aneurysm Trial (ISAT) was a large, multi-site RCT which included 2,143 patients from 42 institutions with definitive SAH occurring within the previous 28 days (Molyneux et al. 2005). Patients were randomly assigned to receive neurosurgical clipping or endovascular treatment. Clinical outcomes were assessed at two months and at one year with interim ascertainment of rebleeds and death. Recruitment was stopped following planned interim analysis, but follow-up of patients enrolled continues. At one year, 23.5% (250/1063) patients allocated to endovascular treatment were dead or dependent, compared with 30.9% (326/1055) patients allocated to neurosurgery, an absolute risk reduction of 7.4% (95% CI: 3.6 to 11.2, p=0.0001) which is equivalent to 74 patients avoiding death or dependency at one year for every 1,000 patients treated.
early survival advantage was maintained for up to seven years and was significant (log rank p=0.03). The authors concluded that endovascular coiling, compared with surgical clipping, for ruptured intracranial aneurysms that were anatomically suitable for either procedure leads to a significant reduction in the relative risk of death or dependency of 23.9 percent (12.4 to 33.9). The ISAT has been criticized for its selection bias and threats to external validity, since only 22% of patients screened were recruited. The Barrow Ruptured Aneurysm Trial (BRAT) (McDougall et al. 2012) was designed to be more inclusive and included 65% of patients screened. In this trial there were many protocol violations. Sixty-five patients who had been randomized to receive treatment with coil, in fact received clipping. More patients in the surgical group had a poor outcome (33.7% vs. 23.2%, RR=1.68, 95 CI% 1.08-2.61, p=0.02) (ITT analysis).

A Cochrane Review (van der Schaaf et al. 2005) comparing endovascular coiling vs. clipping showed that after one year of follow up, the risk of poor outcome was reduced for patients who had received the coiling procedure (RR=0.76, 95%CI: 0.67 to 0.88). The absolute risk reduction was 7% (95% CI: 4 to 11). In the worst-case scenario analysis for poor overall outcome, the RR for coiling versus clipping was 0.81 (95% CI: 0.70 to 0.92) and the absolute risk reduction was 6% (95% CI: 2% to 10%). For patients with anterior circulation aneurysm the RR of poor outcome was 0.78 (95% CI: 0.68 to 0.90) and the absolute risk decrease was 7% (95% CI: 3 to 10). For those with a posterior circulation aneurysm the RR was 0.41 (95% CI: 0.19 to 0.92) and the absolute decrease in risk 27% (95% CI: 6 to 48). The author concluded that for patients in good clinical condition with ruptured aneurysms of either the anterior or posterior circulation and considered suitable for surgery, endovascular coiling is preferred as it is associated with better outcome compared to clipping.

A recent systematic review and meta-analysis examining clipping versus coiling for SAH included the results from 27 studies (Li et al. 2013). When only the results from the 4 RCTs were included, coiling was associated with better odds of avoiding an unfavorable outcome (mRS 3-6) (OR= 1.48; 95% CI: 1.24 to 1.76). When only the results from observational studies were included, the benefit was lost. (OR= 1.11; 95% CI: 0.96 to 1.28). Subgroup analysis revealed coiling yielded better outcomes for patients with good preoperative grade (OR= 1.51; 95% CI: 1.24 to 1.84) than for patients with poor prognosis (OR= 0.88; 95% CI: 0.56 to 1.38). Overall, there was no difference in 1-year mortality between groups (OR=1.07, 95% CI 0.88-1.30, p=0.51). Rebleeding rate was lower in patients who had received clipping. (OR=0.43, 95% CI 0.28-0.67, p=0.001). Vasospasm was more common after clipping, whereas ischemic infarct, shunt-dependent hydrocephalus and procedural complication rates did not differ significantly between techniques. The authors concluded that coiling yields a better clinical outcome, with greater benefit in those with a good preoperative prognosis, although there is greater risk of rebleeding with coiling.

Link to Evidence Table 3.6 and References available on website at www.strokebestpractices.ca
## Best Practice Recommendation 3.7
**Early Management of Intracerebral Hemorrhage**

### NOTES on this recommendation
- This recommendation is for patients with primary spontaneous intracerebral hemorrhage, not hemorrhagic conversion of an ischemic infarction. It applies to the initial assessment in the emergency department within the first few hours of patient arrival.
- Ongoing treatment and management of hemorrhagic stroke patients is outside the scope of these recommendations.
- These recommendations are intended to follow all appropriate initial assessments and imaging, and be used once a confirmed or highly suspected diagnosis of ICH is obtained.

### 3.7 Patients with intracerebral hemorrhage must be treated as a medical emergency. Intracerebral hemorrhage should be promptly recognized and patients evaluated immediately by physicians with expertise in hyperacute stroke management [Evidence Level A].

#### 3.7.1 Initial Clinical Assessment of an ICH Patient
   i. An NIHSS should be conducted on awake or drowsy patients, or a GCS on patients who are obtunded, semi or fully comatose, as part of initial assessment to determine baseline severity of neurological impairments [Evidence Level B]. This has been found to be a strong predictor of outcomes following ICH.
   
   ii. Patients with suspected intracerebral hemorrhage should undergo a CT or MRI immediately to confirm diagnosis, location and extent of hemorrhage [Evidence Level A].
   
   iii. In patients with confirmed acute intracerebral hemorrhage, CT angiography, MR angiography, or catheter angiography is recommended to exclude an underlying lesion such as an aneurysm, arteriovenous malformation, or tumor [Evidence Level B].
   
   iv. Evaluation of patients with acute intracerebral hemorrhage should include questions about anticoagulant therapy, measurement of platelet count, partial thromboplastin time (PTT) and International Normalized Ratio (INR) [Evidence Level A].
   
   v. Patients should be assessed for clinical signs of increased intracranial pressure [Evidence Level B].
   
   vi. A Canadian Neurological Scale (CNS) score should be conducted (usually by nurses) on baseline and repeated every 30 to 60 minutes, depending on stability of patient. Stability will be determined based on size of bleed, location of bleed, and patient’s clinical status [Evidence Level C].

#### 3.7.2 Blood Pressure Management
   i. Blood pressure should be assessed on initial arrival to the emergency department and every 15 minutes thereafter until blood pressure has stabilized [Evidence Level C].
      a. The target for stabilized blood pressure is either a blood pressure that can spontaneously remain less than 180 mmHg, or can be adequately controlled through the use of antihypertensive medications [Evidence Level C].
      b. Close blood pressure monitoring (e.g. every 30 to 60 minutes, or more frequently if above target) should continue for at least the first 24 to 48 hours [Evidence Level C].
ii. Patients with elevated blood pressure should be treated to maintain systolic blood pressure less than 180 mmHg, and there is evidence demonstrating it is safe to target systolic blood pressure to less than 160 mmHg [Evidence Level B]. There is presently no evidence that lower targets are associated with better clinical outcomes, and research is ongoing in this area.

   a. Labetalol is an acceptable choice for treatment for acute blood pressure management if there are no contraindications [Evidence Level B].

   b. Blood pressure targets in ICH patients may be challenging to achieve and require careful monitoring, and in some cases aggressive repeated dosing or intravenous infusion of antihypertensive medications [Evidence Level C].

iii. Patients with suspected or confirmed raised global intracranial pressure (ICP), including those with larger ICH volumes and/or decreased levels of consciousness (LOC), may be more vulnerable to acute blood pressure reductions. Therefore blood pressure parameters should be established on an individual basis to ensure adequate cerebral perfusion [Evidence Level C].

iv. After the first 24 to 48 hours following the onset of an ICH, further blood pressure lowering should be continued with the intiation of parenteral or oral antihypertensive medications (depending on swallowing ability), to achieve individualized blood pressure targets that will optimize secondary stroke prevention [Evidence Level B].

3.7.3 Management of Anticoagulation

i. Patients with acute intracerebral hemorrhage and an established coagulopathy or a history of anticoagulation medications should be promptly assessed with laboratory tests (INR/PTT) and have a medical treatment plan to control bleeding [Evidence Level B].

ii. Warfarin use should be treated appropriately to reverse the coagulopathy with prothrombin complex concentrate (PCC) and Vitamin K 10 mg IV. Fresh-frozen plasma and Vitamin K could be used as alternative if PCC is not available [Evidence Level B].

iii. ASA should be stopped immediately in patients who present who are routinely on ASA and/or have taken ASA to manage headache symptoms [Evidence Level C].

iv. Novel oral anticoagulants (NOAC) use requires urgent consultation with a hematologist in the absence of direct reversal agents [Evidence Level C].

v. If there is a persisting strong indication for anticoagulation (e.g. mechanical heart valve), the decision about when to restart anticoagulant therapy should be made on a case-by-case basis [Evidence Level C]. The evidence is unclear regarding timing to restart anticoagulation. Consultation with a cardiologist, hematologist/thrombosis expert may be considered to optimize individual patient care.

3.7.4 Consultation with Neurosurgery

i. Patients with cerebellar hemorrhage should be referred for urgent neurosurgical consultation and consideration of evacuation of intracerebral hemorrhage particularly in the setting of altered level of consciousness or new cranial neuropathy [Evidence Level A].

ii. Patients with new onset of acute hydrocephalus requiring placement of external ventricular drain (EVD) should be referred for urgent neurosurgical consultation [Evidence Level A]

iii. Select patients with acute supratentorial intracerebral hemorrhage may be considered for surgical intervention with craniotomy for evacuation of superficial lobar intracerebral
iv. Early consultation with a neurosurgeon is recommended in cases where decompressive craniectomy is considered [Evidence Level C]. Refer to Recommendation 3.8 on Hemicraniectomy for additional information.

3.7.5 Initial Interventions for ICH Patients

i. Medically stable patients with an acute intracerebral hemorrhage should be admitted to a Stroke Unit or neuro-intensive care unit [Evidence Level B], and undergo interprofessional stroke team assessment to determine their rehabilitation and other care needs. Refer to Recommendation 5.1 on Rehabilitation Assessment for additional information.

ii. Administration of recombinant Factor VIIIa (NiaStase®) prevents hematoma growth, but increases the risk of arterial thromboembolic phenomena and does not provide a clinical benefit for survival or outcome. It is not recommended for use outside of clinical trials at this time, and clinical trials are currently ongoing to address this issue [Evidence Level A].

iii. Statin therapy is not indicated for prevention of intracerebral hemorrhage. For intracerebral hemorrhage patients who have a clear concomitant indication for cholesterol lowering treatment, statin therapy should be individualized and should take into account the patient’s overall thrombotic risk as well as the possibility of increased risk of intracerebral hemorrhage on statin therapy [Evidence Level B]. Refer to Recommendation 2.4 on Lipid Management for additional information.

iv. Beyond the acutely symptomatic period, patients with intracerebral hemorrhage should be managed similarly to those with ischemic stroke, except for avoidance of antithrombotic medications [Evidence Level B].

   a. Goals of care should be established early after patient arrival at hospital, with patient and/or designated substitute decision-maker [Evidence Level B].

   b. Discussion with most patients and their families regarding “do not resuscitate” (DNR) status should not occur until 24 to 48 hours following stroke onset, and if there is no significant response to medical treatment, or if there the patient’s condition is worsening despite optimal medical care [Evidence Level C].

   c. Patients who are given DNR status at any point should receive all other appropriate medical and surgical interventions unless otherwise explicitly indicated. Pre-existing DNR orders should also be re-assessed after 24 to 48 hours [Evidence Level C].

   d. Currently there is no role for prophylactic anti-convulsant treatment [Evidence Level C]. If a patient were to present with or proceed to have a seizure, anti-convulsants should be initiated. Refer to Recommendations 3.3 and 4.2 for additional information.

Box 3.7: Symptoms of Intracerebral Hemorrhage: (updated 2012)
Clinical assessment cannot reliably distinguish intracerebral hemorrhage from ischemic stroke; brain imaging is required.

- Alteration in level of consciousness (approximately 50%)
- Nausea and vomiting (approximately 40-50%)
- Headache (approximately 40%)
- Seizures (approximately 6-7%)
- Focal neurological deficits
- Sudden tingling, weakness, numbness, or paralysis of the face, arm or leg, particularly
The classic presentation of ICH is sudden onset of a focal neurological deficit that progresses over minutes to hours with accompanying headache, nausea, vomiting, decreased consciousness, and elevated blood pressure. Rarely patients present with symptoms upon awakening from sleep. Neurologic deficits are related to the site of parenchymal hemorrhage. Thus, ataxia is the initial deficit noted in cerebellar hemorrhage, whereas weakness may be the initial symptom with a basal ganglia hemorrhage. Early progression of neurologic deficits and decreased level of consciousness can be expected in 50% of patients with ICH. (Ramandeep Sahni and Jesse Weinberger; Vasc Health Risk Manag. 2007 October; 3(5): 701–709.)

**Rationale**

Intracerebral hemorrhage is a life-threatening emergency and requires prompt recognition and action. Intracerebral hemorrhage commonly occurs in about 12 to 15 percent of all stroke patients admitted to Canadian hospitals, and is associated with high rates of early mortality – 25 to 50 percent in the first 30 days. Patients who survive an intracerebral hemorrhage are often left with moderate to severe persistent functional deficits which place a significant burden on families and the healthcare system.

**System Implications**

- Timely access to diagnostic services such as neuro-imaging, with protocols for prioritizing potential stroke patients.
- Timely access to specialized stroke care (i.e. a neuro-intensive care unit) and neurosurgical specialists for hemorrhagic patient management, including rapid referral process if neurosurgical services not available within the initial treating hospital.
- Access to organized stroke care, ideally stroke units with a critical mass of trained staff and an interprofessional team.
- Education for pre-hospital, emergency department, and hospital staff on the characteristics and urgency for management of intracerebral hemorrhage patients.

**Performance Measures**

1. Risk-adjusted mortality rates for intracerebral hemorrhage in-hospital, 30-day and one year (core).
2. Percentage of intracerebral hemorrhage patients who receive a CT or MRI within 25 minutes and one hour of hospital arrival.
3. Percentage of intracerebral hemorrhage patients who require surgical intervention.
4. Percentage of intracerebral hemorrhage patients who experience intraoperative complications and mortality during surgery for intracerebral hemorrhage.
5. Distribution of functional ability measured by standardized functional outcome tools at time of discharge from hospital.

**Measurement Notes:**

- Mortality rates should be risk-adjusted for age, gender, stroke severity and comorbidities.
- Time interval measurements should start from symptom onset of known or from triage time in the
emergency department as appropriate.

**Implementation Resources and Knowledge Transfer Tools**

- American Stroke Association Guideline for the Management of Intracerebral Hemorrhage 2010  
  [http://stroke.ahajournals.org/content/41/9/2108.full.pdf+html](http://stroke.ahajournals.org/content/41/9/2108.full.pdf+html)

- Canadian Stroke Best Practices Table 3.3A Screening and Assessment Tools for Acute Stroke

- Canadian Stroke Best Practices Table 3.3B Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack

- HSF Stroke Nurses Assessment Pocket Cards  

**Summary of the Evidence**

Intracerebral hemorrhage (ICH) is the most fatal form of stroke and carries the poorest prognosis for survival and functional recovery. Baseline hematoma volume is a strong predictor of outcome, but cannot be reversed. In addition, 30-40% of patients will continue to bleed and experience hematoma expansion, which is also a predictor of poor outcome. Risk factors for hematoma expansion may include the presence of “spot sign” (contrast extravasation), early presentation, anticoagulation use and initial hematoma volume. The presence of the spot sign appears to be a strong predictor of hematoma expansion. In the PREDICT study, (Demchuck et al. 2012) CT scans were conducted on 268 patients to estimate the volume of ICH at baseline and follow-up and then to determine if hematoma expansion had occurred (defined as an absolute growth greater than 6 mL or relative growth of ≥33%). CT angiography (CTA) was used to determine presence/absence of the spot sign using standardized, accepted criteria. Hematoma expansion occurred more frequently in the spot-sign positive patients (60.7% vs. 21.6%, p<0.001). After adjusting for baseline factors, positive spot sign on CTA remained an independent predictor of hematoma expansion (RR=2.3, 95% CI 1.6 to 3.1). Delgado Almandoz et al. (2009) also reported that the spot sign (+/-) was an independent predictor of hematoma expansion in a cohort of 367 patients. Cucchiara et al. (2008) examined 303 patients enrolled in the placebo arm of the CHANT study to determine the effect of previous and current use of oral anticoagulant (OAT) use. Hemorrhage expansion (>33% increase in ICH volume from baseline to 72 hours) occurred more frequently in ICH determined to be of OAT etiology (56% vs. 26%, p=0.006) and mortality was significantly increased in OAT ICH (62% vs. 17%, p<0.001); however, only 21 OAT ICH patients were included. Baseline ICH volume and time to neuroimaging were also independent predictors of absolute change in ICH volume. Elevated blood glucose levels, lower body mass index, increased serum creatinine and decreasing cholesterol levels have also been identified as additional independent predictors of changes in hemorrhage volume (Broderick et al. 2007).

One of the few pharmacological treatments available that may help to minimize hematoma expansion is recombinant activated factor VII. Unfortunately, while the results from the two largest trials suggested that treatment decreases hematoma expansion, it remains uncertain whether treatment is associated with improved odds of a favourable outcome at 3 months, or a greater likelihood of being alive. In the phase II trial (Mayer et al. 2005) including 399 patients, those who had received the drug, particularly at higher doses, had smaller percentage increases in ICH volume from baseline to 24 hours on CT scans. The percentage increase for patients who received placebo, 40, 80, and 160 μg/kg were 29%, 16%, 14% and 11%, respectively. When results from all treatment groups were combined, the percentage of
patients who were dead was lower compared with patients in the placebo group (18% vs. 29%, p=0.02), and there were fewer patients with a poor outcome in the treatment group (mRS 3-6) (53% vs. 69%, p=0.004). There were a total of 21 serious thromboembolic events in the combined treatment groups and 2 in the placebo group (p=0.12). There were more serious arterial thromboembolic events among patients in the treatment groups (16 vs. 0, p=0.01). In the phase III, FAST trial (Mayer et al. 2008), patients were randomized to receive placebo, or rFVIIa at a dose of 20 or 80 μg/kg. Compared with placebo there was a smaller mean increase in volume of ICH at 24 hours in patients in the 80μg group (11% vs. 26%, p<0.001), but no significant difference in the mean increase in volume of ICH at 24 hours in patients in the 20 μg group (18% vs. 26%, p=0.08). At 90 days there were no significant differences between groups (20μg vs. 80μg vs. placebo) on any of the clinical outcomes (death, dependency or the combined outcome of death or dependency). Once again, arterial events occurred more frequently in patients in the treatment group (80μg group 8% vs. placebo 4%, p=0.04). A meta-analysis including the results from 5 RCTs, which recruited patients with both spontaneous ICH (sICH) and traumatic ICH reported no benefit of treatment (Yuan et al. 2010). There was no significant overall reduction in mortality associated with treatment. The overall was OR=0.86, 95% CI 0.65 to 1.15, p=0.31. In the subset of patients restricted to sICH, the results were also not significant (OR=0.85, 95% CI 0.64 to 1.15, p=0.29). There was a significant increase in the odds of arterial thromboembolic events in the treatment group (OR=2.18, 95% CI 1.13 to 4.19, p=0.02) but not venous events (OR=0.73, 95% CI 0.36 to 1.47, p=0.38). It has been suggested that one of the reasons that treatment did not appear to be beneficial is because of the inclusion of patients who were less likely to suffer hematoma expansion. If so, then better selection criteria are required to identify more appropriate treatment candidates. Since the spot sign has been found to be an independent predictor of hematoma expansion, it is being used as a selection tool in two RCTs, currently recruiting subjects in trials of rFVIIa, STOP-IT and SPOT-LIGHT.

Blood pressure management is another potential method of reducing hematoma expansion. There is some evidence from the INTERACT I study (Anderson et al. 2008) and ATACH I (Quershi et al. 2010) pilot studies that aggressive BP management can attenuate hematoma expansion: however, results from the ICH ADAPT trial (Butcher et al. 2013) suggest that BP management did not minimize ICH expansion or favorably impact clinical outcomes. The secondary phases of the INTERACT II and ATACH II are currently recruiting subjects.

There are few reports of the outcomes of patients undergoing neurosurgical procedures following supratentorial intracerebral hemorrhage and uncertainty as to whether invasive treatment is beneficial. In the Surgical Trial in Intracerebral Hemorrhage (STICH) conducted in 2005, 1,033 patients with CT evidence of a spontaneous ICH that had occurred within 72 hours were randomized to early (within 24 hours) surgery for evacuation of the hematoma combined with appropriate and best medical treatment or to initial conservative treatment (Mendelow et al. 2005). Later evacuation was allowed if necessary due to neurological deterioration. Even though the primary outcome was defined differently for patients with good and poor prognosis at baseline, there was no difference in the percentage of patients with a favourable outcome. 26% of patient in the early surgical group vs. 24% of patients in the medical management group, OR=0.89, 95% CI 0.66-1.19, p=0.414, absolute benefit=2.3, 95% CI -3.2 to 7.7. In the Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II) trial (Mendelow et al. 2011) patients were randomized to early craniotomy (within 12 hours) to evacuate haematoma or treated conservatively, following spontaneous superficial intracerebral haemorrhage affecting the lobar region, within 1 cm of the cortex and without ventricular extension. This subgroup of patients who may benefit from surgery was identified based on the results from the STICH I trial. The study, which recruited 601 patients is now complete and the results are expected to be published in 2013. (Gregson et al. 2012). In a Cochrane review (Prasad et al. 2008) included the results from 10 RCTs wherein 2,059 patients with primary supratentorial intracerebral hematoma, confirmed
by CT scanning were studied. Patients were treated with surgery (craniotomy, stereotactic endoscopic evacuation or stereotactic aspiration) plus medical management vs. medical management only. Overall, surgery was associated with a reduction in the odds of death or dependency at the end of follow-up (OR=0.71, 95% CI 0.58-0.88, p<0.001) and death (OR=0.74, 95% CI 0.61-0.90, p=0.0026. Steiner et al. (2011) reported on the outcomes of a subset of patients who were recruited for the Factor Seven for Acute Hemorrhagic Stroke Trial (FAST). The main purpose of this trial was to evaluate the effectiveness of recombinant factor VIIa as a treatment for reducing or stopping bleeding following ICH. Despite the fact that patients who were anticipated to require surgery within 24 hours were excluded, 55/851 patients (6.7%) did require surgery for symptoms of neurological deterioration. The authors examined whether surgery improved the odds of a good outcome controlling for a variety of factors, including demographic, comorbid conditions and prognostic variables. Separate analyses were conducted for patients who had received surgery for hematoma evacuation or who had surgery to place an external ventricular drain (EVD). The odds of unfavourable outcome (NIHSS ≥16) at day 90 were significantly elevated for patients in the EVD group (OR=4.77, 95% CI 1.24 to18.30, p=0.02) with a non-significant increase for patients who had hematoma removal (OR=2.68, 95% CI 0.54 to 13.34, p=0.23).

Although non-contrast CT imaging is the method used most commonly to distinguish ICH from ischemic stroke, it has been suggested that MRI, including diffusion-weighted and gradient-echo sequences, could detect haemorrhage in the first hours after stroke. MRI scans may also provide important clues about the etiology. In a Cochrane review, which included the findings from 8 Studies, two of which recruited patients with ICH, Brazzelli et al. (2009) concluded that there was insufficient evidence of the accuracy of MRI for detection of haemorrhagic stroke in routine practice. In both included studies the reference standard was a hospital discharge diagnosis based on all available clinical and imaging data (including acute imaging data) but in many cases, CT was not performed and the sample sizes were small.

While it is now well-accepted that patients admitted to a stroke unit featuring dedicated beds and staff have better outcomes compared with patients admitted to general or less-specialized units, there is also evidence that the subset of patients who have experienced ICH realize the same benefits. Diringer & Edwards (2001) reviewed the charts of 1,038 patients who had been admitted to either a neuro-ICU (n=2) or a medical and/or surgical ICU (n=40) following ICH and reported that after adjusting for demographics, severity of ICH, and ICU and institutional characteristics, admission to a general ICU was associated with an increase in hospital mortality (OR=3.4; 95% CI 1.65–7.6). Additional independent predictors of higher mortality were advancing age, lower GCS scores, fewer ICH patients treated and smaller ICU size. In contrast, having a full time intensivist was associated with lower mortality rate. Ronning et al. (2001) also reported improved survival during the first 30 days and one year associated with acute stroke unit care. At 30 days, fewer patients in the stroke unit group were dead (39% vs. 63%, adjusted OR=0.40, 95% CI 0.17-0.94). There was no difference in one-year mortality between groups (52% vs. 69%, adjusted OR=0.58, 95% CI 0.24-1.38), or the number of patients discharged home between groups (27% vs. 52%, adjusted OR=1.60, 95% 0.62-4.00).

Link to Evidence Table 3.7 and References available on website at www.strokebestpractices.ca
**Best Practice Recommendation 3.8**  
**Early Management of Patients Considered for Hemicraniectomy**

### 3.8
Hemicraniectomy should be considered in younger patients in the early stages of malignant middle cerebral artery territory ischemic stroke [Evidence Level B].

#### 3.8.1 Patient Selection

i. Patients who meet the following criteria alone or in combination should be considered for Hemicraniectomy [Evidence Level A]:
   a. Patients between the age of 18 and 60 years;
   b. For children under 18 years, emerging evidence supports early Hemicraniectomy in children with progressive malignant MCA syndrome [Evidence Level C];
   c. Malignant middle cerebral artery territory ischemic stroke;
   d. Infarction size greater than 50% MCA territory on visual inspection, or an ischemic lesion volume greater than 150 cm³;
   e. GCS less than eight within 24 hours after stroke onset and following reperfusion treatment;
   f. Worsening GCS, NIHSS, CNS, or PedNIHSS scale scores, or imaging indications of worsening edema at any time from presentation.

ii. If patient location is initially outside a comprehensive stroke centre, patient should have expedited transfer to tertiary or quaternary centre where advanced stroke care and neurosurgical services are available [Evidence Level C].

#### 3.8.2 Initial Clinical Evaluation

i. Urgent consult with a stroke specialist for assessment and for determination to involve neurosurgery [Evidence Level C].

ii. For patients who meet criteria for potential hemicraniectomy during initial assessment, an urgent neurosurgical consultation should be initiated, either in-person or via telemedicine (Telestroke services) [Evidence Level C].

iii. Initiate a discussion with patient, family members and legal decision-maker regarding a potential Hemicraniectomy [Evidence Level C].
   a. Key issues to be discussed with decision-makers include: stroke diagnosis and prognosis untreated, the risks of surgery, the possible and likely outcomes following surgery, and the patient’s previously expressed wishes concerning their treatment in the event of catastrophic illness.

#### 3.8.3 Patient Management Prior to Hemicraniectomy Surgery

i. Once decision for hemicraniectomy has been confirmed, surgery should take place within 48 hours of initial presentation [Evidence Level A].

ii. Patients should be transferred to an intensive care unit or neuro step-down unit for close and frequent monitoring of neurological status prior to surgery [Evidence Level B].
   a. Monitoring should include assessments of level of consciousness (e.g., using Glasgow Coma Scale), symptom worsening severity, and blood pressure at least hourly, and more frequently as individual patient condition requires [Evidence
 Level C].

b. If changes in status occur, the stroke team and neurosurgeon should be notified immediately for re-evaluation of patient [Evidence Level C]. Change in status may include level of drowsiness/consciousness, change in Glasgow Coma Scale, change in CNS score by 1 point or change in NIHSS score by 4 points.

c. Repeat or serial CT scans are recommended for patients when a change in neurological status resulting in deterioration occurs [Evidence Level C].

iii. Initiate acute BP management to treatment for high blood pressure [Evidence Level B]. Refer to Recommendation 3.3 for additional information.

iv. Hyperosmotic therapy with 20% mannitol or 3% hypertonic saline may be used in the preoperative period if required [Evidence Level C].

v. The head of the patient’s bed should be elevated 30 degrees [Evidence Level C], and patient and family members should be educated about proper head positioning [Evidence Level C].

vi. Hyperventilation should be avoided prior to surgery, except mild hyperventilation for brief periods if required [Evidence Level C].

vii. All anticoagulants should be withheld prior to hemicraniectomy [Evidence Level B].

viii. Corticosteroids not recommended as a management strategy for increased intracranial pressure for patients awaiting hemicraniectomy [Evidence Level A].

ix. If hydrocephalus occurs, it may be managed by an external ventricular drain (EVD) placed by a neurosurgeon [Evidence Level C].

x. Patients’ temperature and pain levels should be monitored frequently and elevations in temperature or pain should be treated [Evidence Level C].

xi. Education should be provided to patients and families regarding stroke, hemicraniectomy and possible issues following hemicraniectomy (such as post-stroke depression, residual deficits and level of function, and other discharge considerations) [Evidence Level C].

Rationale

The morbidity and mortality for the routine care of patients with malignant hemispheric strokes is higher than other stroke subgroups, and there is evidence to support that, in selected cases, hemicraniectomy may significantly reduce mortality and lead to improvement in patient outcomes. Consideration for hemicraniectomy must be individualized; there is a strong need for careful clinical consideration and patient selection. Decisions regarding hemicraniectomy involve several members of the multidisciplinary stroke team, including neurology, neurosurgery, intensive care and nursing through a collaborative and coordinated system of care.

System Implications

- Timely access to diagnostic services such as neuro-imaging, with protocols for prioritizing potential stroke patients.
- Timely access to specialized stroke care (i.e. a neuro-intensive care unit) and neurosurgical specialists for consultation and patient management, including rapid referral process if neurosurgical services not available within the initial treating hospital.
- Access to organized stroke care, ideally stroke units with a critical mass of trained staff and
an interprofessional stroke team.
   - Education for emergency department, and hospital staff on the characteristics and urgency for management of severe stroke patients.

### Performance Measures

1. **Risk-adjusted mortality rates for severe stroke patients who undergo Hemicraniectomy (in-hospital, 30-day and one year) (core).**
2. Percentage of hemicraniectomy patients who experience intraoperative complications and/or mortality during surgery or within first 24 hours post-operatively.
3. Distribution of functional ability measured by standardized functional outcome tools at time of discharge from hospital.

**Measurement Notes:**
- Mortality rates should be risk-adjusted for age, gender, stroke severity and comorbidities
- Time interval measurements should start from symptom onset of known or from triage time in the emergency department as appropriate.

### Implementation Resources and Knowledge Transfer Tools

- Canadian Stroke Best Practices Table 3.3A Screening and Assessment Tools for Acute Stroke
- Canadian Stroke Best Practices Table 3.3B Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack
- HSF Stroke Nurses Assessment Pocket Cards
  
  http://www.heartandstroke.on.ca/site/c.pvi3leNWJwE/b.5852913/k.AC4B/Order_Resources/apps/ka/ct/contactcustom.asp

### Summary of the Evidence

Three randomized controlled trials (RCT) from France (DECIMAL), Germany (DESTINY) and the Netherlands (HAMLET) have compared decompressive hemicraniectomy plus medical treatment to medical treatment alone for the management of malignant middle cerebral artery (MCA) infarct (Vahedi et al., 2007b; Juttler et al., 2007; Hofmeijer et al., 2009). These trials have comparable inclusion criteria and primary outcome measures as determined by modified Rankin Scale (mRS) and mortality.

Results from these three studies were pooled in a recent Cochrane Review (Cruz-Flores, Berge, & Whittle, 2012). In patients 60 years of age or younger, decompressive hemicraniectomy was significantly associated with reduced risk of death at the end of follow-up (OR = 0.19, 95% CI 0.09 to 0.37) and the risk of death or severe disability (mRS > 4) at 12 months (OR = 0.26, 95% CI 0.13 to 0.51). Decompressive hemicraniectomy was also associated with a non-significant trend towards increased survival with severe disability (mRS of 4 or 5; OR = 2.45, 95% CI 0.92 to 6.55). No significant between group differences were found for the combined outcome death or moderate disability (mRS 4-6) at the end of follow-up (OR = 0.56, 95% CI 0.27 to 1.15) (Cruz-Flores et al., 2012). By contrast, in a previous review of the same three trials it was reported that decompressive hemicraniectomy reduced the risk of death or moderate disability (mRS 4-6) (Cruz-Flores et al., 2012; Vahedi et al., 2007a). This discrepancy may be explained by the difference in inclusion criteria between the two reviews: the Cochrane Review included all patients enrolled in the 3 RCTs, including those operated within 96 hours (from the HAMLET trial), whereas the previous analysis only included patients treated within 48 hours of stroke onset (Cruz-Flores et al., 2012; Vahedi et al., 2007a).
The upper age limit for decompressive hemicraniectomy in malignant MCA infarct has been a focus of debate, as previous reviews have found that older age is associated with poorer prognosis (Gupta, Connolly, Mayer, & Elkind, 2004; McKenna, Wilson, Caldwell, & Curran, 2012). For example, McKenna et al. reported that patients 60 years of age and older have a higher mortality rate and poorer outcome following decompressive hemicraniectomy, as compared to younger patients (McKenna et al., 2012). Similarly, in the DECIMAL trial's surgical group, younger age correlated with better outcomes at 6 months (r = 0.64, p < 0.01) (Vahedi et al., 2007b). Conversely, authors from the HAMLET trial reported that there was a tendency towards greater benefit of surgery in patients between the ages of 51–60 as compared to patients 50 years of age or younger, although this finding did not reach significance (Hofmeijer et al., 2009).

As the maximum enrolment age in DECIMAL, DESTINY, and HAMLET was ≤ 60, these trials are of limited value in terms of identifying an appropriate age limit for decompressive hemicraniectomy. However, in a more recent RCT (n=47), the effectiveness of decompressive hemicraniectomy was investigated in patients up to 80 years of age (Zhao et al., 2012). Decompressive hemicraniectomy within 48 hours of stroke onset was significantly associated with a reduction in mortality at both 6- (12.5 vs. 60.9 %, p = 0.001) and 12-month follow-up (16.7 vs. 69.6 %, p < 0.001) (Zhao et al., 2012). In a subgroup analysis of participants’ ≥ 60 years of age, Zhao et al. reported that 31.2% of patients in the surgical arm had an unfavourable outcome (mRS 5–6) at 6 months, as compared to 92.3 % (12/13) in the medical arm (absolute risk reduction = 61.1%; 95 % CI 34.1 to 88.0) (Zhao et al., 2012). Similar findings were reported for the 12-month follow-up (ARR = 62.5%; 95% CI 38.8 to 86.2) (Zhao et al., 2012). A recent retrospective study investigating decompressive hemicraniectomy in older adults compared the outcomes of individuals aged between 61-70 years and those > 70 years of age (Inamasu et al., 2013). The mortality rate was significantly higher among those in the older cohort (60% vs. 0%, p = 0.01) (Inamasu et al., 2013). The authors concluded that decompressive hemicraniectomy should have a limited role in the treatment of patients > 70 years of age, whereas more research is needed exploring the use of this surgery for those 61-70 years old (Inamasu et al., 2013).

Timely surgical intervention is an important consideration when deciding whether to perform decompressive hemicraniectomy. Results from the HAMLET trial demonstrate that for patients randomized to decompressive hemicraniectomy within 48 hours of stroke onset, there is a reduction in both mortality and poor outcome when compared to those receiving standard medical treatment only (Hofmeijer et al., 2009). However, in patients who were randomized between 48 and 96 hours following stroke onset, no significant effect of surgical treatment was found in terms of either mortality rate or outcome (Hofmeijer et al., 2009). A similar trend revealing the benefits of decompression hemicraniectomy within 48 hours of stroke onset was reported in the pooled analysis conducted by Vahedi and colleagues. However, in a subgroup analysis comparing those treated less than 24 hours with those treated more than 24 hours following stroke onset, no differences in outcome were reported (Vahedi et al., 2007a). Taken together, these findings suggest that the appropriate time interval to perform decompressive hemicraniectomy is within 48 hours (Vahedi et al., 2007a); however, further research is need to determine if earlier treatment (e.g., with 24 hours) is associated with superior outcomes.

Quality of life and depression symptomatology were assessed at a one-year follow-up in the HAMLET trial (Hofmeijer et al., 2009). Patients who received decompressive hemicraniectomy had significantly lower mean physical summary scores on the SF-36 Quality of Life scale, as compared with those treated with medical care only (29 vs. 36; mean difference = -8, 95% CI -14 to -1, p = 0.02) (Hofmeijer et al., 2009). No significant differences were found between the two treatment groups with respect to the mental summary score of the SF-36 score, mood, or the proportion of patients or carers dissatisfied with treatment (Hofmeijer et al., 2009).

In summary, based on currently available data, decompressive hemicraniectomy within 48 hours of stroke onset decreases mortality in patients with malignant middle cerebral infarction between the ages of 18-60.
years (Vahedi et al., 2007b; Juttler et al., 2007; Hofmeijer et al., 2009; Vahedi et al., 2007a; Cruz-Flores et al., 2012). In addition, evidence suggests that the benefit of decompressive hemicraniectomy in mortality reduction is not associated with an increase in severely disabled survivors (Vahedi et al., 2007b; Juttler et al., 2007; Hofmeijer et al., 2009; Vahedi et al., 2007a; Cruz-Flores et al., 2012). Nevertheless, the consideration for decompressive hemicraniectomy must be individualized with careful patient selection and clinical consideration.

Link to Evidence Table 3.8 and References available on website at www.strokebestpractices.ca