*** Warning ***

FDA Drug Safety Communication: Changes to the Heparin Sodium USP Monograph

Safety Announcement

[04-07-2010] Laboratory studies performed at the request of the U.S. Food and Drug Administration (FDA) have shown that Heparin Sodium, USP (heparin) made under the new United States Pharmacopeia (USP) Monograph ("new heparin") has approximately 10% less blood-thinning (anticoagulant) activity compared to heparin prepared using the previous ("old") USP Monograph. The studies were performed in order to better understand the clinical impact of the change in potency for heparin.

The FDA first alerted the public to changes in the potency of heparin in a Public Health Alert in October 2009.

The results of these studies reinforce FDA's previous recommendation for healthcare professionals to exercise clinical judgment in determining the dose of heparin for a patient and consider the clinical circumstances where the potency decrease may require dosage adjustments and more frequent monitoring.

Healthcare professionals should be aware that heparin products, i.e., those made using both the old and the new USP standards may be available for some time. Healthcare professionals may wish to consider not using the products interchangeably. Pharmacies and hospitals may wish to consider separating the supplies of old and new heparin and exhausting the supplies of "old" heparin before transitioning to the "new" product (see Table below, "How to Identify Heparin Products made to the New USP Standard").

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals:

- Be aware that there is an approximate 10% decrease in the anticoagulant activity (potency) of the "new heparin" compared with the "old heparin."
- Continue to exercise clinical judgment in determining the dose of heparin.
- Continue to individualize heparin dosing to the specific patient/patient-specific clinical situation.
- Understand that the labeling for heparin, including the recommended doses for heparin has not changed.
- Consider those clinical circumstances where the potency decrease may require dosage adjustments and more frequent monitoring, such as where aggressive anticoagulation is essential to the treatment of the patient, including:

- pediatric patients undergoing extracorporeal membrane oxygenation
- adults and children undergoing cardiopulmonary bypass
- the treatment or prevention of life-threatening thromboses

- Report any adverse events associated with the use of heparin

Data Summary

Studies to assess differences in heparin activity were performed in animals (*in-vivo*) and in human plasma (*in-vitro*). The results of the human plasma and animal studies were consistent in demonstrating an approximate 10% decrease in heparin activity of the "new" heparin products compared to "old" heparin products. The average activated partial thromboplastin time (aPTT) response to a dose of heparin changed in a dose-proportional manner.

The same studies also demonstrated that there were large individual variations in aPTT responses to a given dose of heparin. Therefore, in a clinical setting, a 10% decrease in heparin dose might not be reflected in the results of an aPTT or ACT (Activated Clotting Time) for an individual patient.

Given the inherent individual variability in response to a dose of heparin, a 10% decrease in heparin activity (potency) is not likely to have clinical significance. However, special clinical situations such as cardiac surgery and/or use in pediatric patients may require more intensive monitoring to achieve optimal therapeutic response. Since heparin therapy is routinely titrated to each patient (there are many patient-specific factors that can influence heparin dosing) the usual method of individualizing dosing will continue to ensure patient safety.

Table to Distinguish Between "New" and "Old" Heparin

Since new heparin will be available, starting October 2009 there will likely be supplies of both the old and new heparin stocked for use in hospitals and pharmacies for a period of about three years. Facilities that have stocks of old and new heparin may wish to consider segregating stores of the old heparin from the new and using the "old" heparin products first. The table below provides information on how to distinguish between the old and new product and company website for additional information.

How to Identify Heparin Products made using the New USP Standard

Manufacturer	(Date) Availability of Lots Made to the New USP Standard	How to Identify the New Product	Additional Information/Company Contact
APP	October 2009	"N" will appear after the Expiration Date	http://www.appdrugs.com
B. Braun	October 2009	"N" will appear after the Lot Number	http://www.bbraunusa.com
Hospira	October 2009	Lot Numbers will begin with the number "82" or higher	http://www.hospira.com/Files/HeparinUSP.pdf
Baxter	October 2009	"N" will appear before the Lot Number	http://www.baxter.com/index.html

ICSI

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

Health Care Guideline:
Diagnosis and Treatment of Ischemic Stroke

Ninth Edition
June 2010

The information contained in this ICSI Health Care Guideline is intended primarily for health professionals and the following expert audiences:

- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- health care teaching institutions;
- health care information technology departments;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. If you are not one of the expert audiences listed above you are urged to consult a health care professional regarding your own situation and any specific medical questions you may have. In addition, you should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in your individual case.

This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. An ICSI Health Care Guideline rarely will establish the only approach to a problem.

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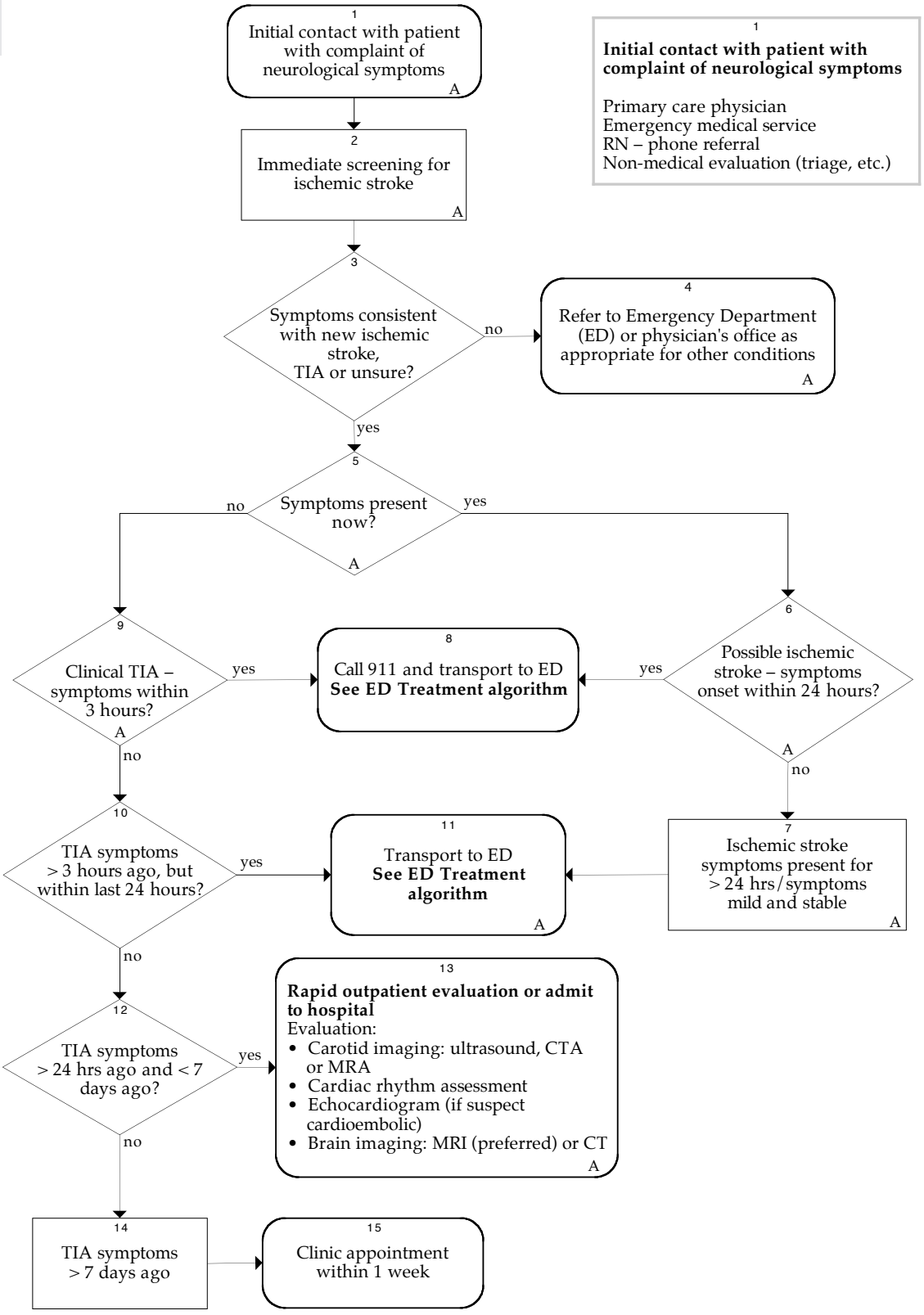
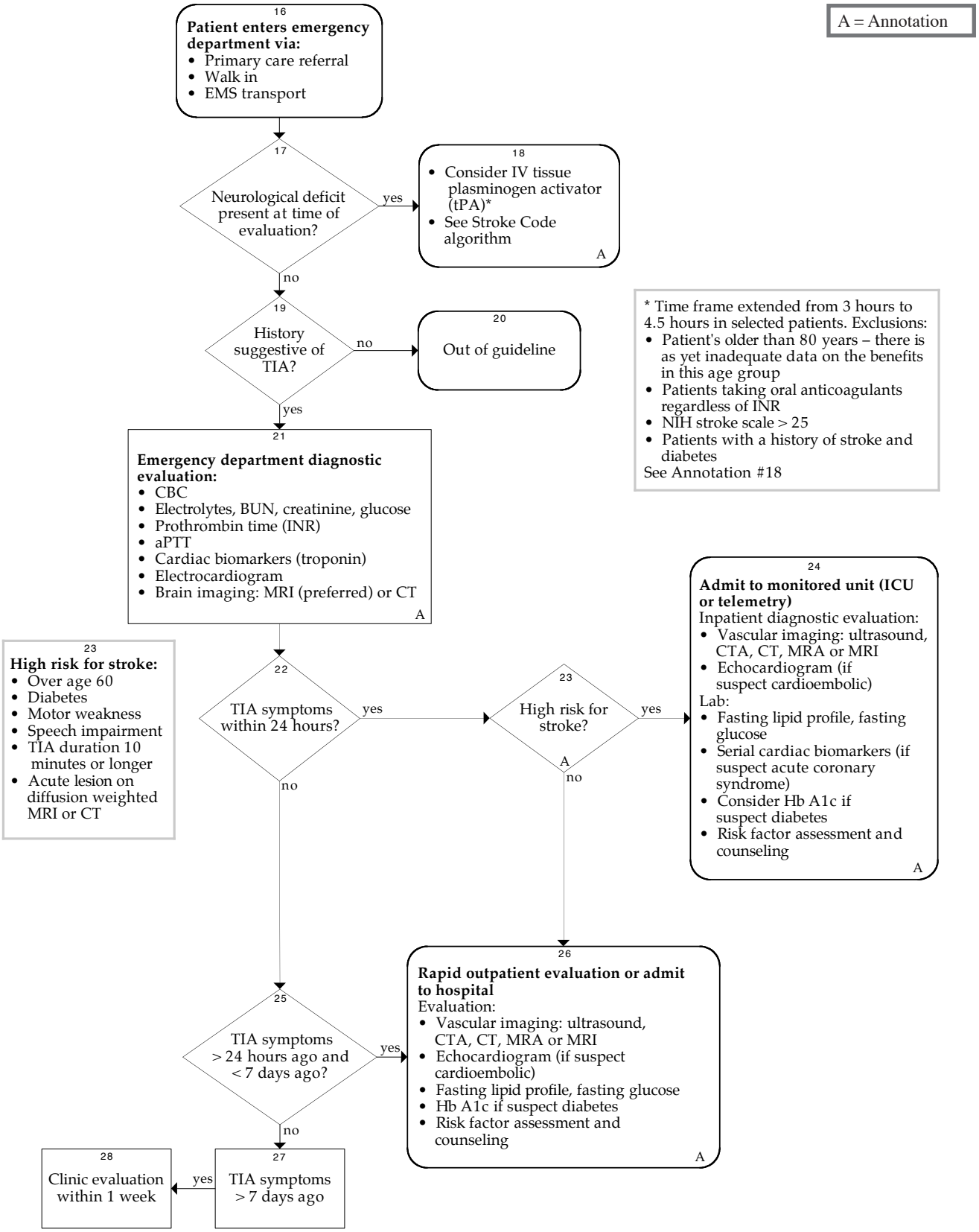
Health Care Guideline:
Diagnosis and Initial Treatment of Ischemic Stroke

Screening (Ambulatory) Algorithm

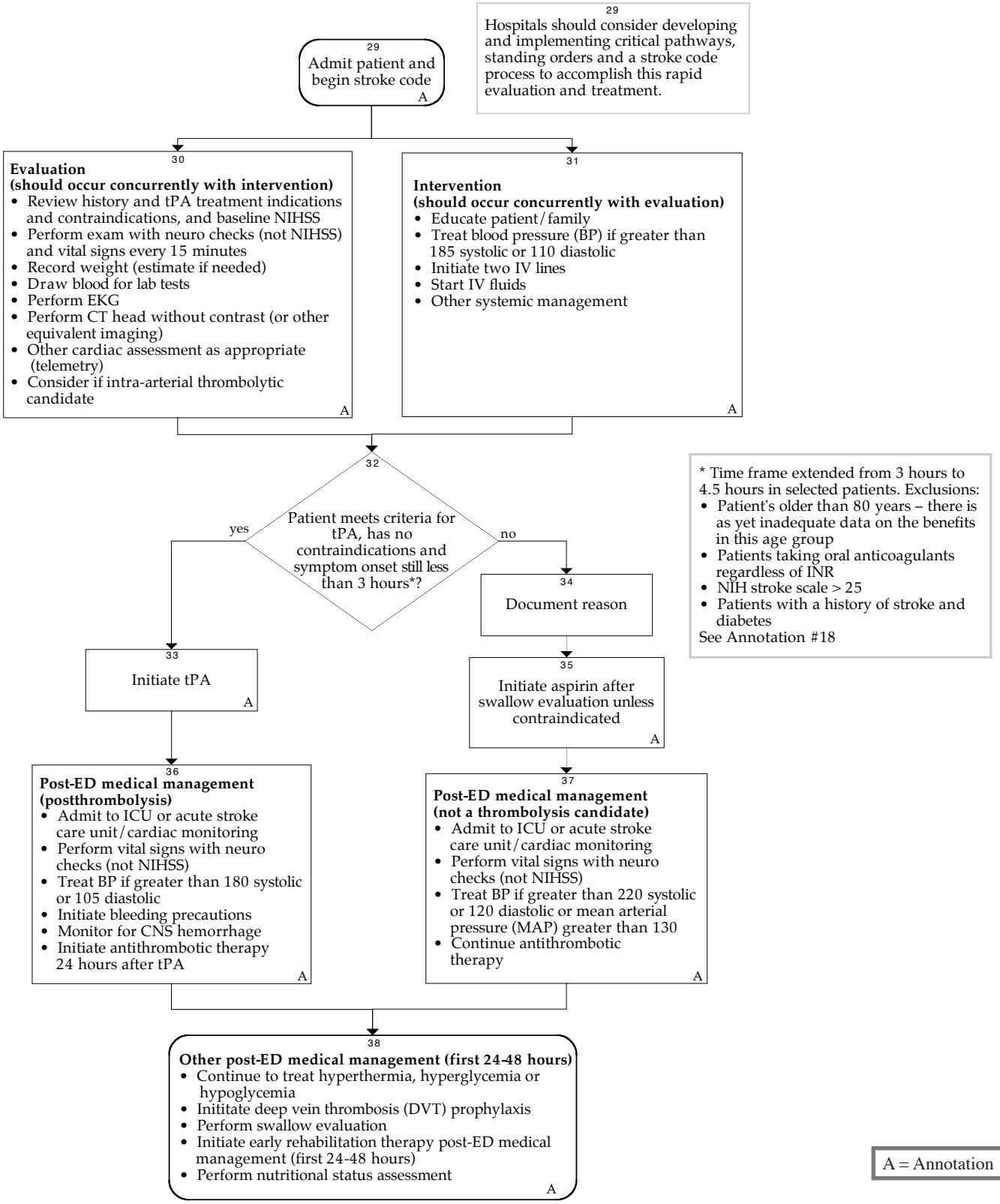
A = Annotation



Emergency Department (ED) Treatment Algorithm



Stroke Code Algorithm



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Foreword

Scope and Target Population

The scope of the following guideline is the 48 hours beginning when a patient age 18 years or older presents to a provider with symptoms of ischemic stroke or transient ischemic attack. For most stroke patients who are hospitalized, the guideline's temporal scope will expire before discharge. The guideline work group on Diagnosis and Initial Treatment of Ischemic Stroke recognizes that two time frames are critically important in the overall outcome, and fall outside the defined scope. They are prehospital care, and continuing care of stroke patients after 48 hours, which includes the development of a long-term secondary prevention strategy. While the group has not itself performed a systematic review of the primary evidence on these matters, we recommend the following guidelines from the American Heart Association/American Stroke Association.

A. Regarding prehospital care:

Acker, Joe E, et al. Implementation strategies for emergency medical services within stroke systems of care. A policy statement from the American Heart Association/American Stroke Association Expert Panel on Emergency Medical Services and the Stroke Council. *Stroke* 2007;116:3097-115.

B. Regarding continuing care after the initial 48 hours and secondary prevention:

1. Sacco RL, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/ American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:577-617.

2. Adams RJ, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke* 2008;39:1647-52.

Clinical Highlights and Recommendations

- Intravenous tPA continues to be a proven treatment for ischemic stroke when administered within recommended time parameters. *(Annotations #18, 29; Aim #3)*
- Intravenous tPA, if given, should be administered within three hours (4.5 hours in selected patients; see Annotation #18, "Consider IV Tissue Plasminogen Activator [tPA]/See Stroke Code Algorithm") of stroke onset and less than 60 minutes of arrival at the emergency department. *(Annotations #29, 30, 33; Aim #3)*
- Patients presenting with signs and symptoms of transient ischemic attack should be evaluated for risk of immediate future events using the ABCD2 score. *(Annotation #23; Aim #1)*
- Patients presenting with stroke onset who are not candidates for intravenous tPA should promptly be given aspirin, after exclusion of hemorrhage on CT scan. *(Annotation #35; Aim #3)*
- Education regarding early stroke symptoms, risk factors, diagnostic procedures, and treatment options should be offered to the patient and family. This should be documented in the patient chart. *(Annotation #31; Aim #6)*

- Medical management for prevention of complications within the initial 24-48 hours of diagnosis and initial treatment of ischemic stroke include: *(Annotation #38; Aim #5)*
  - manage blood pressure appropriately;
  - treat hyperthermia;
  - treat hypo- or hyperglycemia;
  - administer intravenous IV fluids;
  - initiate deep vein thrombosis prophylaxis;
  - perform swallow evaluation before oral intake, including medications;
  - initiate early rehabilitation and
  - perform nutritional status assessment.

Priority Aims

1. Increase the percentage of patients age 18 and over presenting within 3 hours, or up to 4.5 hours for patients meeting selected criteria of stroke onset who are evaluated within 10 minutes of arriving in the emergency department. *(Annotations #18, 29)*
2. Increase the percentage of patients at high risk for stroke presenting with TIA symptoms within 24 hours who are admitted to the hospital. *(Annotation #23)*
3. Increase the percentage of patients receiving appropriate thrombolytic and antithrombotic therapy for ischemic stroke (use of tPA and aspirin). *(Annotations #29, 30, 33, 35)*
4. Increase the percentage of non-tPA recipients who have hypertension appropriately managed in the first 48 hours of hospitalization or until neurologically stable. *(Annotation #37)*
5. Increase the percentage of stroke patients who receive appropriate medical management within the initial 24-48 hours of diagnosis for prevention of complications such as: *(Annotations #31, 38)*
   - Hypoglycemia and hyperglycemia
   - Hyperthermia
   - Dehydration
   - Hypoxia
   - Deep vein thrombosis
   - Aspiration
   - Immobility
   - Nutritional status decline
6. Improve patient and family education of patients with ischemic stroke in both the emergency department and the admitting hospital unit. *(Annotation #31)*

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Hospitals should consider developing and implementing critical pathways, standing orders and a stroke process to accomplish rapid evaluation and treatment. The process should expedite the evaluation and treatment of patients who are candidates for intravenous tPA and assure uniform, guideline-driven care for all patients with respect to issues like:
   - ongoing antithrombotic therapy,
   - management of blood pressure,
   - early mobilization, and
   - use of appropriate antiembolism treatment in the paralyzed patient.
2. A process should be in place for the patient and family that will rapidly orient them to the suspected diagnosis, emergency department process, tests to be preformed, tPA treatment and its risks, and other treatment measures to be considered. This could include both face-to-face interactions with the patient and family by the caregiver, as well as teaching tools in written form.

System Improvement

There is evidence that benchmarking can guide and drive quality improvement. Using essentially the same quality indicators as The Joint Commission (TJC) and ICSI, programs like the American Heart Association's Get With The Guidelines-Stroke *(LaBresh, 2008 [C]; Schwamm, 2009b [B])* and the Paul Coverdell National Acute Stroke Registry *(Stoeckle-Roberts, 2006 [C])* have been shown to improve the quality of stroke care.

Centers for Medicare and Medicaid Services

Beginning in 2010, hospitals submitting Medicare claims for stroke must let CMS know if they participate in a database registry for stroke care. For further information on the CMS Final FY 2010 Rule, refer to http://www.cms.gov.

The Joint Commission (TJC) Primary Stroke Center Certification

TJC offers certification as Primary Stroke Centers to hospitals that meet specific qualifications. The process is on the early recognition and management of stroke, and the scope of accreditation includes integrated efforts in public awareness, emergency medical services, emergency department and hospitalization *(Alberts, 2000 [R])*. The link is http://www.jointcommission.org/CertificationPrograms/PrimaryStrokeCenters. Beginning in October 2009, all TJC-accredited hospitals are required to submit the eight National Quality Forum-endorsed stroke consensus measures.

Among the requirements for TJC certification as a Primary Stroke Center is ongoing process improvement guided by data and benchmarking. The quality indicators chosen by TJC overlap with those developed by the ICSI Diagnosis and Initial Treatment of Ischemic Stroke guideline work group. The TJC quality indicators are:

1. Deep Vein Thrombosis (DVT) Prophylaxis*
2. Discharged on Antithrombotics*
3. Patients with Atrial Fibrillation Receiving Anticoagulation Therapy*
4. Thrombolytic Therapy Administered (in eligible patients)

5. Antithrombotic Therapy by End of Hospital Day Two
6. Discharged on Cholesterol Reducing Medication
7. Dysphagia Screening **
8. Stroke Education
9. Smoking Cessation/Advice Counseling **
10. Assessed for Rehabilitation

* Initial standard stroke measure set.

****** Note: indicators for 7 and 9 are not currently (as of 2010) required by the Joint Commission. The remaining eight indicators are required. These eight are also endorsed by the National Quality Forum.

Measures 1, 4, 5, 7 and 8 are similar to or identical to those measures listed in this document and within the scope of the guideline.

Related ICSI Scientific Documents

Guidelines

- Antithrombotic Therapy Supplement
- Hypertension Diagnosis and Treatment
- Palliative Care
- Venous Thromboembolism Diagnosis and Treatment
- Venous Thromboembolism Prophylaxis

Order Sets

- Admission for Ischemic Stroke for Patients Not Receiving tPA
- Admission for Ischemic Stroke for Patients Receiving tPA
- Venous Thromboembolism Prophylaxis for the Hospitalized Patient

Disclosure of Potential Conflict of Interest

ICSI has adopted a policy of transparency, disclosing potential conflict and competing interests of all individuals who participate in the development, revision and approval of ICSI documents (guidelines, order sets and protocols). This applies to all work groups (guidelines, order sets and protocols) and committees.

Participants must disclose any potential conflict and competing interests they or their dependents (spouse, dependent children, or others claimed as dependents) may have with any organization with commercial, proprietary, or political interests relevant to the topics covered by ICSI documents. Such disclosures will be shared with all individuals who prepare, review and approve ICSI documents.

Alejandro Rabinstein, MD disclosed receiving research/grant funding from Cardionet.

David Larson, MD disclosed receiving honorarium funding from Medicines Company and Heartscope; neither of which is related to the topic of stroke.

No other work group members disclosed potential conflicts of interest.

Introduction to ICSI Document Development

This document was developed and/or revised by a multidisciplinary work group utilizing a defined process for literature search and review, document development and revision, as well as obtaining input from and responding to ICSI members.

For a description of ICSI's development and revision process, please see the Development and Revision Process for Guidelines, Order Sets and Protocols at http://www.icsi.org.

Evidence Grading System

A. Primary Reports of New Data Collection:

Class A: Randomized, controlled trial

Class B: Cohort study

Class C: Non-randomized trial with concurrent or historical controls
Case-control study
Study of sensitivity and specificity of a diagnostic test
Population-based descriptive study

Class D: Cross-sectional study
Case series
Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M: Meta-analysis
Systematic review
Decision analysis
Cost-effectiveness analysis

Class R: Consensus statement
Consensus report
Narrative review

Class X: Medical opinion

Citations are listed in the guideline utilizing the format of *(Author, YYYY [report class])*. A full explanation of ICSI's Evidence Grading System can be found at http://www.icsi.org.

Algorithm Annotations

Screening (Ambulatory) Algorithm Annotations

1. Initial Contact with Patient with Complaint of Neurological Symptoms

This contact may occur with one of several medical system personnel, including primary care physicians, other medical specialty physicians, emergency medical services, nursing staff in a clinic or urgent care setting or even non-medical triage personnel. This does not refer to the emergency department evaluation. This contact may be by phone or in person. Potential staff contacts should be educated in the importance of stroke symptom recognition and the appropriate triage measures that should be taken.

2. Immediate Screening for Ischemic Stroke

This should include detail as to the location, severity, duration of symptoms and any aggravating or relieving factors. Symptoms that are commonly associated with ischemic stroke or transient ischemic attack (TIA) include:*

- sudden numbness or weakness of the face, arm or leg – especially on one side of the body;
- sudden mental confusion, trouble speaking or understanding;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden trouble seeing in one or both eyes;
- sudden severe headache with no known cause.

* List from American Stroke Association for public education

Recognition of stroke is a challenging first step in a race against time to save brain. Recognition starts with the patient, family or bystanders and must continue with emergency medical personnel and in the emergency department. Tools to facilitate recognition have been developed for these settings. For the public, two scales have been disseminated. The American Stroke Association, American Academy of Neurology and American College of Emergency Physicians have recently completed a public awareness campaign entitled "Give Me 5" emphasizing that stroke typically presents as problems of walking, talking, reaching, seeing and/or feeling. Another scale for the general public, has been developed by the National Stroke Association. It is entitled "FAST," emphasizing the importance of changes in the appearance of one's Face, difficult in raising Arms, abnormality of quality of Speech, and the imperative to intervene in a Timely manner to get help.

Scales have also been developed for emergency medical services (Cincinnati and Los Angeles scales) and for the emergency department itself (ROSIER [Recognition of Stroke in the Emergency Room] scale) *(Kidwell, 2000 [C]; Kothari, 1999 [C]; Nor, 2005 [C]).* These tools are listed in the Resource Table.

Symptoms of ischemic stroke can also, of course, be represented in atypical ways.

Clinical diagnoses with neurologic symptoms that may imitate or superficially resemble ischemic stroke or TIA include the following *(Adams, 2007 [R])*:

- **Migraine**

  Neurologic symptoms experienced with migraine tend to have a more gradual onset and slower development. However, the two problems may be indistinguishable.

- **Seizures**

  Although seizures typically consist of a "positive" phenomenon (jerking of a limb) rather than loss of neurologic function (weakness or paralysis of a limb), symptoms and signs during the ictus or in the postictal state may be similar to ischemic stroke (e.g., confusion or speech arrest during the ictus as in complex partial seizure, postictal confusion, postictal paralysis, and other sensory or visual phenomenon).

- **Syncope**

- **Transient global amnesia**

  This is characterized by a sudden onset antegrade and retrograde memory disturbance without other neurologic symptoms. If the patient experiences symptoms of transient global amnesia, it would be inappropriate to assume the diagnosis without a complete neurologic assessment.

- **Peripheral nerve disorders**

  Mononeuropathy and radiculopathy can often be distinguished from ischemic stroke by the anatomic distribution of the symptoms, and in the case of radiculopathy, by associated painful symptoms. Bell's palsy, vestibular neuritis and extraocular muscle imbalance due to cranial neuropathy may also imitate ischemic stroke; a complete history and neurologic examination are required to accurately differentiate from ischemic stroke.

- **Intracranial hemorrhage**

- **Other intracranial masses, e.g., tumor, abscess (often differentiated by computed tomography)**

  The mode of onset and early course tend to be more gradual in development but mimicry of stroke is not uncommon.

- **Psychogenic presentation**

  Psychogenic conditions or reactions such as anxiety, panic disorder, or conversion reactions must be considered in some cases.

- **Metabolic disorders**

  Hypoglycemia is the most common metabolic disorder producing neurologic symptoms that imitate stroke. A patient with known diabetes or liver disease should be screened for hypoglycemia.

This discussion is not meant to be detailed guide to discerning between ischemic stroke and other diagnoses. If there is any uncertainty as to symptom causation, the evaluation should proceed as though ischemic stroke or TIA is confirmed so as not to delay appropriate emergency treatment if indicated.

4. Refer to Emergency Department (ED) or Physician's Office as Appropriate for Other Conditions

Some of the diagnoses outlined in Annotation #2, "Immedidate Screening for Ischemic Stroke," may warrant emergency department evaluation because of the urgency of the problem itself or the inability of the contact person to distinguish the other condition from ischemic stroke *(Adams, 2007 [R])*. In these uncertain cases, the contact person should continue on to the Screening (Ambulatory) algorithm, box #5, "Symptoms Present Now?" See Appendix A, "Acute Stroke Care Networks."

5. Symptoms Present Now?

This annotation refers to ongoing symptoms suggestive of cerebral ischemia. If ischemic symptoms have resolved and were present for less than 24 hours, this is clinically defined as a transient ischemic attack (TIA).

Recently, a new definition of TIA has been proposed: TIA is a transient episode of neurologic dysfunction caused by focal brain, spinal cord or retinal ischemia without acute infarction *(Easton, 2009 [R])*.

Applying the definition requires imaging. The pre-imaging syndrome has been designated "acute neurovascular syndrome."

The work group will use "clinical TIA" in this document in lieu of acute neurovascular syndrome *(Easton, 2009 [R])*.

6. Possible Ischemic Stroke – Symptoms Onset within 24 Hours?

Key Point:

- The onset of symptoms should be defined as the last time the patient was known to be normal or at previous prestroke baseline.

If the symptoms resolve completely and then recur, for the purposes of determining whether thrombolysis can be considered for stroke, the time of onset would be the last time the patient was normal (just prior to the onset of the second set of symptoms.) Patients may be unable to give this information if they have an aphasia or mental confusion. Family members or other witnesses may need to give this information. If the patient was sleeping and awakened with the problem, the time of onset would be the moment the patient was last known to be normal just before falling asleep.

7. Ischemic Stroke Symptoms Present for > 24 Hours/Symptoms Mild and Stable

Patients with stable mild deficits present longer than 24 hours may be transported to the emergency department for evaluation and treatment by means other than 911. As a rule, they should be admitted to the hospital to assure thorough and expeditious evaluation and treatment. Outpatient evaluation and treatment is an acceptable alternative if it can be done as quickly as it could be done inpatient and if all goals of inpatient assessment (diagnosis of mechanism, initiation of appropriate secondary prevention, prevention of complications, early assessment for and deployment of rehabilitative services) can be successfully addressed. It should be appreciated that recurrence risk is high in the initial hours and days following a minor stroke, similar to the case of TIA (see below), hence expeditious assessment is warranted.

9. Clinical Transient Ischemic Attack (TIA) – Symptoms within Three Hours?

Patients presenting with history of clinical TIA may have neurological deficits of which they are not aware. To avoid missing the thrombolytic treatment window, patients with clinical TIAs presenting within three hours of symptom onset should be triaged like patients with stroke, i.e., call 911 *(Adams, 2007 [R])*.

11. Transport to Emergency Department (ED)

Patients should be taken to the emergency department expeditiously; use of 911 Emergency is at the provider's discretion. Alternatively, if such a program were available, the patient may be assessed in a specialized clinic or other program in which the evaluation can be carried out as quickly and treatment initiated as definitively as if the patient were admitted to the hospital. This work group otherwise recommends that the physician

strongly consider hospitalization for clinical TIA patients who appear within 24 hours of the event to expedite workup and possibly administer tPA if the deficit recurs.

13. Rapid Outpatient Evaluation or Admit to Hospital

Patients should receive rapid outpatient evaluation (TIA clinic or other program) or be admitted to the hospital as soon as possible *(Johnston, 2006 [R])*. In addition to a risk assessment for stroke, the patient should be diagnostically evaluated including:

- brain imaging: magnetic resonance imaging (MRI) (preferred because diffusion weighted sequences may identify patients at particularly high risk of early major recurrence – see annotations) or computed tomography
- vascular imaging: ultrasound (if symptoms suggest ischemia in the carotid distribution), computed tomography angiography (CTA) or magnetic resonance angiography (MRA)
- cardiac rhythm assessment; (monitor rhythm if admitted)
- echocardiogram (if suspect cardioembolic source)

Emergency Department (ED) Treatment Algorithm Annotations

18. Consider IV Tissue Plasminogen Activator (tPA)/See Stroke Code Algorithm

Key Points:

- Treatment with IV tPA is proven therapy for patients having ischemic stroke.
- Treatment with IV tPA should begin within three hours (180 minutes) or 4.5 hours (270 minutes in) selected patients. The eligibility for treatment in the 3-4.5 hour time window is similar to patients treated within 3 hours; with the following additional exclusions:
  - Patients older than 80 years – there is as yet inadequate data on the benefits in this age group
  - Patient taking oral anticoagulants regardless of INR
  - NIH stroke scale > 25
  - Patients with a history of stroke and diabetes
- Patients with persisting symptoms presenting to the emergency department within 150 minutes (or 240 minutes in selected patients) of symptom onset should be evaluated rapidly for treatment with IV tPA.
- Occasionally, patients may be able to receive IV tPA even if they present later than 150 minutes, (240 minutes in selected patients) if their workup, such as laboratory evaluation, has been completed and they have IV access in place.
- Intra-arterial thrombolysis may be an option for treatment in selected patients who are not IV tPA candidates due to being beyond the 3 to 4.5 hour time window (see Annotation #30 section "Consider If Intra-Arterial Recanalization Candidate").

Patients presenting to the emergency department soon after the onset of symptoms may be candidates for treatment with intravenous (IV) tissue plasminogen activator (tPA) and will therefore require a rapid evaluation and treatment initiation *(Albers, 2004 [R])*. (See Appendix A, "Acute Stroke Care Networks.") Although the time window from onset of symptoms to treatment can be up to 3 hours, i.e., 180 minutes (or 4 .5 hours, i.e., 270 minutes in selected patients), the evaluation in the emergency department will require at least 30 minutes in most cases (CT scan of head, laboratory tests performed and results have returned, IV access obtained, and neurological exam and history) *(Adams, 2007 [R])*. We have therefore chosen 150 minutes or 240 minutes in selected patients, as a practical cutoff time for this triage decision.

There are important exceptions to this time limitation guideline for triage of patients into the "stroke code" process. In certain instances, the time required for evaluation may be shorter, and "stroke code" may be feasible for patients presenting as late as 165 or 170 (255-260 minutes in selected patients) minutes after onset. One example would be the patient who is already in the hospital and has undergone the appropriate laboratory evaluation, has an IV access in place, and much of the history is already known. In that case, a brief neurologic exam and rapid evaluation with CT may be the only items required prior to treatment and could theoretically be performed in 10-15 minutes.

Initial Thrombolytic Trials

Thrombolytic therapy for ischemic stroke using intravenous tissue plasminogen activator (tPA) has now been tested in several large, randomized, placebo-controlled clinical trials. The National Institute of Neurological Disorders and Stroke (NINDS) stroke trial (actually a combination of two trials, one with a 24-hour and the other with a 90-day outcome measure) compared placebo with tPA at a dose of 0.9 mg/kg given within three hours of symptom onset in 624 patients *(National Institute of Neurological Disorders and Stroke tPA Study Group, 1995 [A])*. The time of stroke onset was strictly defined, blood pressure was maintained within a specified range, and other anticoagulant and antiplatelet drugs were avoided within the first 24 hours after treatment. The prespecified threshold for a clinically important difference at 24 hours was not met. However, at three months and one year *(Kwiatkowski, 1999 [A])*, there were significantly increased percentage of patients (11%-13%) with favorable outcomes in the tPA group, compared with controls. Results were consistent across all four of the standard outcome measures that were assessed. Treatment with tPA resulted in a significantly increased risk of symptomatic intracerebral hemorrhage (6.4% tPA treated vs. 0.6% in placebo group, $p < 0.001$). Mortality was lower at three months in those treated with tPA (17% vs. 21% in placebo treated), but this did not reach statistical significance. On the basis of the favorable results from these combined trials, the Federal Drug Administration approved tPA for use in the United States in 1996.

The European Cooperative Acute Stroke Study (ECASS) performed concurrent with the NINDS trial also compared intravenous tPA to placebo in a randomized, placebo-controlled trial in 620 patients. However, the study design was different in a number of respects, including longer time window to treatment (six hours), higher dose of tPA (1.1 mg/kg), and lack of strict blood pressure control *(Hacke, 1995 [A])*. Over 80% of the patients were treated between three and six hours after symptoms began. The intention-to-treat analysis did not demonstrate significant improvement in the primary outcome measure (combination of Barthel Index and modified Rankin Scale at three months). However, there was a high rate of major protocol violation (109 patients). In a secondary analysis including only the target population, there was a significant difference in favor of tPA treatment, but the margin was of questionable clinical significance.

In 1998, a third large tPA study was completed. ECASS II had a nearly identical protocol to the original ECASS study except that the tPA dose was lowered to 0.9 mg/kg *(Hacke, 1998 [A])*. A total of 800 patients were enrolled, and approximately 80% were treated three to six hours after stroke onset. The results indicated that there was no significant difference in neurological function between tPA and placebo patients. There was a trend in favor of treatment that did not reach statistical significance.

The Thrombolytic Therapy in Acute Ischemic Stroke Study sponsored by Genentech also used a six-hour time window, but was similar in other respects to the NINDS tPA trial *(Clark, 2000 [A])*. Only 15% of

patients were enrolled within three hours. Although a significantly higher percentage of tPA treated patients showed early improvement at 24 hours measured with the National Institutes of Health Stroke Scale (NIHSS), these findings were reversed at one month with the placebo group having a statistically higher percentage of patients showing improvement on this scale. Symptomatic intracerebral hemorrhage was significantly increased compared to placebo (11% vs. 0%), with the greatest risk of hemorrhage in patients treated between five and six hours.

Three similar large-scale clinical trials comparing intravenous streptokinase to placebo in a randomized trial design were performed concurrent with the NINDS tPA and ECASS studies *(Multicenter Acute Stroke Trial [MAST], 1996 [A]; Multicenter Acute Stroke Trial [MAST], 1995 [A])*. All three studies were terminated before completion because of safety concerns with excessive rates of intracerebral hemorrhagic complications and higher mortality in the treated groups.

These early studies support a limited use of intravenous tPA at a dose of 0.9 mg/kg with appropriate precautions and treatment beginning within 3 hours of symptom onset *(Ingall, 2004 [A])*. Following FDA approval of tPA for stroke, several reports of community experience with this treatment appeared in the literature *(Buchan, 2000 [A]; Charipar, 2008 [D]; Chiu, 1998 [D]; Hanson, 2000 [D]; Tanne, 1999 [D]; Wang, 2000a [D])*. Although clinical results for the most part have been concordant with those in the NINDS study, two of these reports document an increase in intracerebral hemorrhagic complications when patients were treated outside the NINDS protocol further supporting the importance of following the NINDS tPA study protocol.

The significance of early time to treatment was further emphasized by a secondary analysis of the NINDS tPA study population showing gradual decline in measured efficacy even within the three-hour time window *(Marler, 2000 [C])*. American Heart Association (AHA) consensus guidelines for the use of tPA have been published, and treating physicians are encouraged to evaluate patients for this treatment and initiate treatment with urgency *(Adams, 2007 [D])*. Another analysis using pooled data from all the early tPA trials suggested efficacy might be achieved even after the three-hour window (*ATLANTIS, ECASS, and NINDS tPA Study Group Investigators, 2004 [M]).*

Recent Thrombolytic Trials

ECASS III *(Hacke, 2008 [A])* was a multicenter trial conducted in Europe to evaluate intravenous recombinant tissue plasminogen activator (tPA or alteplase) versus placebo administered between 3 and 4.5 hours after onset of ischemic stroke symptoms. A total of 821 patients were enrolled, nearly one-third more than in NINDS, the United States trial that led to the adoption of tPA as the gold standard for the treatment of acute ischemic stroke within the first three hours after symptom onset. Both arms were acceptably well balanced, although initial stroke severity and previous history of stroke were greater in the placebo group.

Treatment with tPA was associated with a significant improvement in the rate of favorable functional outcome as defined by a modified Rankin of 0 or 1 (i.e., mild or no deficits). These rates were 52% for the tPA group and 45% for the placebo group (OR 1.34; 95% CI 1.02-1.76) in the intention-to-treat analysis. The benefit was more pronounced when only patients treated with tPA according to the protocol were analyzed (OR 1.47; 95% CI 1.10-1.97) and it was also present when a global outcome measure also including the NIHSS, the Barthel index and the Glasgow Outcome scale was used as the endpoint. Overall, the chances to regain full independence were 28% higher among patients treated with tPA, and 14 patients had to be treated for one additional patient to achieve a favorable outcome.

Mortality was not significantly different between the groups, but slightly higher in the placebo arm. The rate of symptomatic intracranial hemorrhage as defined by the NINDS criteria was 7.9% in the tPA group (versus 6.4% in the NINDS trial). Furthermore, only 2.4% of patients were thought to have worsened because of intracranial hemorrhage in the active treatment group.

The positive results of ECASS III are similar to these of a pooled analysis of previous tPA trials *(ATLANTIS, 2004 [M])*. Yet, some have expressed skepticism, pointing out the discrepancy with previous negative results

of ATLANTIS, a U.S. trial evaluating intravenous tPA versus placebo within five hours of stroke onset *(Clark, 1999 [A])*. ECASS III was different from the NINDS and ATLANTIS trials. The main difference with NINDS was the lower stroke severity of enrolled patients, which explains the much higher rate of complete or near complete recovery at 90 days in ECASS III (modified Rankin 0-1; 52% in ECASS III vs. 39% in NINDS in the tPA arm; and 45% in ECASS III vs. 26% in NINDS in the placebo arm). The main difference with ATLANTIS was the shorter time from symptom onset to enrollment in ECASS III (76% treated with tPA after 4 hours in ATLANTIS vs. 37% in ECASS III).

While attention to detail and critical analysis of the data are essential before applying trial results to change clinical practice, the results of ECASS III provide high-quality evidence supporting the use of intravenous tPA in acute stroke patients up to 4.5 hours after symptom onset. However, extending the therapeutic window for intravenous thrombolysis should not allow for complacency. It is very clear that thrombolytic treatment should be started as soon as possible. Thrombolysis is most effective when initiated within 90 minutes of symptom onset *(ATLANTIS, 2004 [M]),* and any delay decreases the benefit. Also, it will be prudent to be selective when extending the window to 4.5 hours. The criteria used for patient selection in ECASS III should be replicated when considering thrombolytic treatment between 3 and 4.5 hours after symptom onset in clinical practice. Age greater than 80, combined history of previous stroke and diabetes mellitus, use of anticoagulation regardless of INR and very high initial stroke severity (NIHSS > 25 or radiological evidence of infarction involving more than one-third of the middle cerebral artery territory) were exclusion criteria in ECASS III. Therefore, intravenous tPA in patients with these characteristics should continue to be used only within 3 hours of symptom onset.

Additional analysis of the ECASS III population confirmed the value of thrombolysis between 3 and 4.5 hours in all subgroups studied, although benefit was lower in patients > 65 years, and these patients also had higher risk of hemorrhage *(Bluhmki, 2009 [A])*. A separate analysis of the trial results concluded that 1 in 6 patients had a better outcome and 1 in 35 patients had a worse outcome after treatment with intravenous thrombolysis between 3 and 4.5 hours after symptom onset *(Saver, 2009 [M])*.

Based on the results of the ECASS III trial, the Stroke Council of the American Heart Association and the American Stroke Association recommended the administration of intravenous rtPA to eligible stroke patients presenting between 3 and 4.5 hours after stroke onset *(del Zoppo, 2009 [R])*. Yet obtaining written informed consent before administration of intravenous tPA between 3 and 4.5 hours of symptom onset may be advisable. **Extending the treatment window for intravenous tPA to 4.5 hours has not been approved by the Food and Drug Administration.**

(del Zoppo, 2009 [R])

21. Emergency Department (ED) Diagnostic Evaluation

Patients with a history of clinical TIA should be evaluated promptly *(Adams, 2007 [R])*. The following diagnostic evaluations should typically be performed *(Albers, 2002 [R]; Calvet, 2007 [D]; Coutts, 2005 [C]; Johnston, 2002 [R]).* The speed and venue of the assessment described below will depend on the currency of the symptoms and the physician's assessment of risk of early recurrence of clinical TIA or the development of stroke. The work group recommends that patients presenting less than 24 hours since initial clinical TIA with high risk symptoms (see Annotation #23, "High Risk for Stroke?") generally not leave the emergency department until the following are completed or scheduled within the next few hours on an inpatient basis.

- **Laboratory tests**
  - Complete blood count
  - Electrolytes (sodium, potassium, chloride, CO_2), BUN, creatinine, glucose
  - Prothrombin time/international normalized ratio (INR)

- Activated partial thromboplastin time (aPTT)
- Cardiac biomarkers (troponin)

- **Electrocardiogram**
- **Brain and vascular imaging (see below)**
  - Magnetic resonance imaging (MRI) (preferred)/magnetic resonance angiography (MRA)
  - Computed tomography (CT)/computed tomographic angiography (CTA)
  - CT/carotid ultrasound, if symptoms referable to carotid distribution

Brain Imaging

If the patient is not having symptoms at the time of presentation, a diffusion-weighted MRI (DW-MRI) is preferred, if available. Restricted proton diffusion in the setting of a clinical transient ischemic attack identifies higher risk of stroke. At this time, an MRA of the carotids and intracranial artery can be performed.

If MRI is not available, a CT of the head would be indicated and, if feasible, a CTA of the head and neck can also be performed.

(Boulanger, 2007 [B]; Douglas, 2003 [D]; Latchaw, 2009 [R])

Another approach for patients with symptoms referable to a carotid territory would be CT of the brain followed by carotid ultrasound as vascular imaging.

23. High Risk for Stroke?

Key Points:

- Risk of stroke is greatest in the immediate aftermath of clinical TIA or minor stroke.
- Features of presentation define those at highest risk.
- Hospitalization should be strongly considered for those at highest risk.
- Speed is key, whether the patient is hospitalized or undergoes expedited ambulatory management.

The major issues in dealing with clinical TIA patients is making the best decisions about the speed of workup, the appropriate evaluation to guide preventive therapy, and the most efficacious therapies to avert stroke. To make the best decisions the provider must know what the early risk of stroke is for the given patient, whether speed of workup and treatment matter, and, if so, what treatments should be deployed. Information about these points is just becoming available. That a clinical TIA is a risk factor for stroke is not new news. The traditional wisdom is that a patient has a 30%-40% risk of having a stroke in the five years following a clinical TIA. The more salient question is about the short-term risk.

Several studies have identified factors in patients presenting with clinical TIAs that predict progression to ischemic stroke. Older studies using a clinical definition of TIA (the neurologic syndrome prior to completion of imaging) examined factors predisposing to ischemic stroke within a time frame of months or years after the clinical TIA, but provide limited information as to acute risk. Examples of risk factors identified in these older studies include advanced age, presenting with more than four clinical TIAs in the two weeks prior to the index clinical TIA, and the comorbidities of hypertension, myocardial infarction, cardiac arrhythmia, and diabetes mellitus *(Dennis, 1990 [B]; Friday, 1997 [B]; Hankey, 1992 [B]; Kernan, 1991 [B]; Streifer, 1995 [D]*). The presentation of transient monocular blindness or amaurosis fugax generally confers a more

benign prognosis *(Dennis, 1989 [D]; Evans, 1994 [B]; Wilterdink, 1992 [M])*. Brown, et al., proposed an algorithm for triage and evaluation of patients with clinical TIA and minor ischemic stroke, citing these data to estimate specific risk *(Brown, 1994 [R]; Flemming, 2004 [R])*.

Data from recent studies also using a clincial definition of TIA are more relevant to the issue at hand in the emergency department (ED), i.e., the risk over the next few days and weeks. A cohort study described the early (one-week and three-month) risk of ischemic stroke, cardiovascular events, and death in 1,707 patients presenting with a diagnosis of clinical TIA to emergency departments within the Kaiser Permanente system in northern California *(Johnston, 2000 [B])*. Fifteen percent of the patients were admitted for further monitoring, and the rest were discharged from the emergency department. The risk of stroke or admission for other cardiovascular events (myocardial infarction, unstable angina, cardiac arrhythmia, congestive heart failure) were reported as follows:

Event	**7 days**	**3 months**
Stroke	6%*	10.5%
Clinical TIA		13%
Cardiovascular events		2.7%
Death		2.6%

* Over half occurred within two days.

Taken in total, 26.2% of clinical TIA patients returned to the hospital within three months with another cerebrovascular or cardiovascular event.

In multivariate analysis, five factors independently predicted higher risk:

- Age greater than 60 years
- Diabetes mellitus
- Clinical TIA lasting longer than 10 minutes
- Clinical TIA including weakness as a symptom
- Clinical TIA including abnormal speech as a symptom

The features comprise a risk stratification scheme known as the "California Score."

The same issue of early risk was examined in the population-based Oxford Vascular Study *(Coull, 2004 [B])*. The short-term fate of 87 consecutive Oxfordshire residents with clinical TIA or minor stroke was examined. Risk of stroke was 8% at one week, 11.5% at one month and 17.3% at three months. The risks were slightly higher after minor stroke (11.5%, 15% and 18.5%, respectively) at the three time intervals.

Yet another study examined patients with carotid stenosis randomized to medical therapy after first clinical TIA in the North American Symptomatic Carotid Endarterectomy Trial. The study found stroke risk of 5.5% at two days and 20.1% at 90 days following the qualifying clinical TIA, emphasizing that early risk is substantial after clinical TIA in this setting *(Eliasziw, 2004 [B])*. The study also showed that benefit of carotid endarterectomy in such patients drops significantly as time to the procedure exceeds two weeks from the ischemic event, arguing that speed of assessment and treatment are all-important *(Rothwell, 2004 [M])*.

Giles, in a meta-analysis of studies of stroke risk on day two and seven post-clinical TIA, reported that variability among reports of rates of stroke may relate to the setting in which the patients are seen for evaluation and whether treatments are offered *(Giles, 2007 [M])*.

From these studies it is clear that in general clinical TIA represents a potent short-term risk factor for stroke. From the Kaiser Permanente study, it is also suggested that risk is heterogeneous, i.e., some patients are at higher risk than others. If true, it might then be possible to identify those at highest short-term risk prospectively and reliably. They could be triaged to an expedited management track.

Confirmation information has now been accumulated. Analysis of the Oxfordshire population-based sample of clinical TIA episodes (n=209) yielded an "ABCD" score identifying those at high risk of stroke *(Rothwell, 2005 [B])*.

Table 1.

The elements of the scale from this derivation sample are:

A – for age	Over the age of 60 years	1 point
B – for blood pressure	A systolic greater than 140 mmHg or diastolic greater than 90 mmHg	1 point
C – for clinical features	Unilateral weakness Speech disturbance without weakness Other clinical features	2 points 1 point 0 points
D – for duration of symptoms	Symptoms lasting greater than 60 minutes Symptoms lasting 10-59 minutes Symptoms lasting less than 10 minutes	2 points 1 point 0 points

(Rothwell, 2005 [B])

The ABCD score was subsequently validated in a second population-based sample of clinical TIA episodes (n=190). The seven-day risks of stroke in the combined derivation and validation samples (n=299) were:

0-4 points (73% of combined samples): 0.4% (95% CI 0-1.1%)

5 points (18% of combined samples): 12.1% (4.2%-20.0%)

6 points (9% of combined samples): 31.4% (16.0%-46.8%)

Note the similarity of the ABCD score features, derived and validated in Great Britain, to those of the California Score described above. Next challenge was to demonstrate the generalizability of these approaches, i.e., to show the reliability of the prediction models in all patient groups and settings.

The ABCD scheme was applied in additional cohorts. One *(Cucchiara, 2006 [C])* found the scheme not as sensitive for high risk as originally reported, but the study used a different outcome set than the original report. The other *(Tsivgoulis, 2006 [C])* found the scheme very reliable in identifying high-risk patients. Both cohorts were already-hospitalized patients under care of neurologists. It might be argued that a more relevant setting to study the validity of the scheme would be in a community-based sample of patients seen by non-neurologists. Finally, retrospective analysis *(Bray, 2007 [C])* concluded that the ABCD score was highly predictive in identifying patients with clinical TIA at a high short-term risk of stroke.

More recently, the groups from Kaiser Permanente (California Score) and Oxford (ABCD Score) together, validated the two similar prognostic scores in four independent groups of patients and generated a new unified score (the ABCD2 Score) to predict the risk of stroke in the two days following a clinical TIA *(Johnston, 2007 [C])*. This new score was derived and validated in patients seen in emergency departments and outpatient clinics and is a more accurate predictor than either of the two previous scores (California Score and ABCD Score) in the derivation and validation groups. Also the score predicted the risk of stroke within two days, which is more useful in the outpatient setting. Data from the validation groups included 4,799 patients.

Table 2.

A – for age	60 years or older	1 point
B – for blood pressure	a systolic 140 mmHg or greater or diastolic of 90 mmHg or greater	1 point
C – for clinical features	Unilateral weakness Speech disturbance without weakness	2 points 1 point
D – for duration of symptoms	Symptoms lasting greater than 60 minutes Symptoms lasting 10-59 minutes Symptoms lasting less than 10 minutes	2 points 1 point 0 points
D – Diabetes		1 point

Based on these results, the authors suggest admitting patients who present with a clinical TIA and have a ABCD2 score of 4 or greater. Risk of stroke at two days:

Low risk (0-3 points): 1.0%

Moderate risk (4-5 points): 4.1%

High risk (6-7 points): 8.1%

These reports highlighted the frequent early occurrence of stroke and other cardiovascular events and the validity of risk stratification schemes. It has not been clear whether hospitalization or expedited outpatient management would mitigate high risk.

Very recently, it has been shown that deployment of streamlined systems that address clinical TIAs very quickly (e.g., within 24-48 hours) with definitive diagnostic testing and initiation of secondary prevention is associated with reducing the rate of early stroke (EXPRESS, SOS-TIA). These studies used historic cohorts as controls, randomization of rapid vs. slow assessment being ethically impossible. The EXPRESS Trial *(Rothwell, 2007 [C])*, for example, compared stroke rate at 90 days in clinical TIA patients treated in an expedited process with that of an historical control group in the same medical system. The expedited process reduced time from clinical TIA to initial assessment by stroke specialists from 3 days to less than 1 day and the time to initiation of secondary prevention from 20 days to 1 day. The 90-day risk fell from 10.3% to 2.1%. The expedited care systems that have been examined include outpatient assessments (EXPRESS, SOS-TIA) or in hospital protocols (FASTER) *(Kennedy, 2007 [A]; Lavallee, 2007 [D]; Rothwell, 2007 [C])*. Interestingly, these studies did not use stratification to select patients at higher risk. Even so, the studies showed value in expedited evaluation. Not clear at this point is what role stratification should play. It is also not clear what interventions made the difference in patient outcomes seen with the expedited systems.

What these data show is that not only are clinical TIAs dangerous and amenable to risk stratification, but also early medical management is associated with reduced risk. Based on what is known and acknowledging the continuing areas of uncertainty, the work group recommends that patients seen within 24-48 hours of initial clinical TIA be admitted to hospital or to a program of expedited outpatient assessment. The clinical factors outlined above that predict high risk of recurrence might influence decision-making in this patient group. Also, detection of ischemic infarct by diffusion-weighted MRI would confer risk similar to an ABCD2 score of 4 or greater. Caveats have already appeared in results of validation studies of the ABCD2 scale in other patient groups. While its validity has been confirmed in principle, the ABCD2 scale's sensitivity has been shown to be imperfect in these studies. Sensitivity improved if glucose >120 mg/dL and history of hypertension were included in a new scale in one experience *(Fothergill, 2009 [C])*, whereas

urgent vascular imaging and EKG monitoring for patients with < 4 points on the ABCD2 were advocated by others *(Amarenco, 2009 [C]; Ois, 2008 [D])*. Although the data available cannot define an appropriate triage decision for all patients, this information should serve as a guide for rational triage of the patient with clinical TIA. Certain diagnostic entities, if suspected, may require hospitalization for specific management, even with presentation later than 24-48 hours from clinical TIA occurrence or lower ABCD2 score (e.g., carotid or vertebral artery dissection, carotid stenosis, specific coagulopathy or arteriopathy, cerebral venous thrombosis). Not settled is whether the assessment of those at low risk can be safely pursued at a more leisurely pace or foregone altogether. At present, the work group is not prepared to recommend that patients be selected for hospitalization based solely on the ABCD2 scheme. It recognizes that it may be being used in that way in some hospitals in the region and encourages that the effectiveness of the approach be monitored in those hospitals.

In summary, the work group recommends consideration of hospitalization for patients with first clinical TIA within the past 24-48 hours to facilitate early deployment of lytic therapy, if necessary, and to expedite institution of definitive secondary prevention. For others, the risk stratification data described above might also justify hospitalization rather than expedited ambulatory management. Whatever the strategy, speed is key. Patients managed in the outpatient setting should be fully educated about the need to return immediately if symptoms recur, to allow use of lytic therapy.

(Goldstein, 2006; [R]; Johnston, 2006 [R]; Purroy, 2004 [R])

24. Admit to Monitored Unit (Intensive Care or Telemetry)

Patients with clinical TIA symptoms within 24-48 hours and at high risk for stroke (see Annotation #23, "High Risk for Stroke?") should be admitted to a monitored unit (ideally telemetry) for observation and further evaluations. Admitting patients expedites diagnostic evaluation, allows for ready access to fibrinolysis should the patient have an acute stroke, facilitates early carotid revascularization if indicated, and offers greater opportunity for risk factor modification for secondary stroke prevention. Again, expedited outpatient programs may be equivalent (see Annotation #26, "Rapid Outpatient Evaluation or Admit to Hospital").

The following diagnostic evaluations should be performed for inpatients *(Adams, 2007 [R]; Albers, 2002 [R]; Johnston, 2000 [R])*:

- **Brain and vascular imaging** *(Douglas, 2003 [D]; Latchaw, 2009 [R])*
  - Computed tomography (CT)/computed tomograhic angiographic (CTA)
  - CT/carotid ultrasound if symptoms referable to carotid distribution
  - Magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA)
- **Laboratory Tests**
  - Fasting lipid profile
  - Fasting glucose
  - Serial cardiac biomarkers if suspect acute coronary syndrome
  - Consider hemoglobin A1c if suspect diabetes
- **Echocardiogram**
- **Risk factor assessment and counseling**

26. Rapid Outpatient Evaluation or Admit to Hospital

Patients with clinical TIA symptoms that occurred more than 24 hours ago but within the last seven days should be evaluated as soon as possible *(Albers 2002 [R]; Johnston, 2002 [R])*. Organizations have started TIA clinics for the rapid evaluation of patients in the outpatient setting. Patients who cannot be evaluated rapidly as an outpatient should be admitted to the hospital. The following diagnostic evaluations should be performed within 48 hours:

- **Brain and vascular imaging** *(Douglas, 2003 [D]; Latchaw, 2009 [R])*
  - Magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA)
  - Computed tomography (CT)/computed tomography angiography (CTA)
  - CT/carotid ultrasound, if symptoms referable to carotid distribution
- **Consider echocardiogram**
- **Laboratory tests**
  - Fasting lipid profile
  - Fasting glucose
  - Consider hemoglobin A1c if suspect diabetes
- **Risk factor assessment and counseling**

Stroke Code Algorithm Annotations

29. Admit Patient and Begin Stroke Code

Key Points:

- The "door to first physician contact" goal is within 10 minutes.
- The "door to initiation of CT scan" goal is within 25 minutes.
- The "door to drug" goal for thrombolytic treatment is within 60 minutes.

The goal of the stroke code is to rapidly administer tPA in appropriately screened candidates. The onset of symptoms to treatment can be up to 180 minutes (or 270 minutes in selected patients); see Annotation #18, "Consider IV Tissue Plasminogen Activator [tPA]/see Stroke Code Algorithm," but the NIH recommendation of "door to drug" is within 60 minutes *(Adams, 2007 [R])*.

The work group uses the term "stroke code" to refer to a process in the emergency department for the rapid evaluation and treatment of patients who have presented in a time frame qualifying them for thrombolytic therapy. This process may take many forms. It might include a formal "stroke team" that is called whenever a possible candidate for tPA has presented, or it may include the emergency department staff who have been trained in the rapid evaluation and treatment of stroke patients. The stroke code concept should also be implemented in planning a rapid response to inpatient stroke. The general concept is one that includes the following:

- Rapid triage of patients as soon as they arrive in the emergency department
- Immediate initiation of phlebotomy for appropriate blood tests, followed by CT scan or other equivalent imaging

- First physician contact for history and exam occurring early in the emergency department visit. The NIH recommendation for timing of "door to first physician contact" for thrombolytic candidates is within 10 minutes
- Rapid access to the best neurologic and radiologic expertise for evaluation of the patient and interpretation of the CT scan prior to treatment

  This may include a neurologist and neuroradiologist present at the time of treatment. Alternatively, it may be a primary care physician with expertise in stroke diagnosis and administration of tPA and a general radiologist with expertise in reviewing head CT scans. Telemedicine may be used to provide expertise in one or both roles. The NIH recommendation for the timing of "door to initiation of CT scan" for thrombolytic candidates is within 25 minutes.
- Interpretation of the CT scan available within 20 minutes of test completion.
- Administration of tPA in appropriately screened candidates within 60 minutes. The NIH recommendation for the timing of "door to drug" for thrombolytic treatment is within 60 minutes *(Adams, 2007 [R]); Bock, 1999 [NA]).*

30. Evaluation (Should Occur Concurrently with Intervention)

Key Points:

- Apart from history and examination (NIHSS) relevant to thrombolytic therapy, CT scan and glucose, other tests are not necessary before administering IV tPA in most patients. Obtaining them should not delay treatment.
- Review tPA indications/contraindications and document whether patient is eligible.
- Perform baseline National Institutes of Health Stroke Scale (NIHSS).
- Perform non-contrast head CT to exclude hemorrhage.

Review History and tPA Treatment Indications and Contraindications, and Baseline NIHSS

Take a focused patient history, including a review of indications and contraindications for treatment with tPA *(Adams, 2007 [R])*.

Indications for tPA

- Acute onset of focal neurological symptoms, consistent with ischemic stroke in patients 18 years of age and older.
- Clearly defined onset of stroke less than 3 hours (4.5 hours in selected patients; see Annotation #18, "Consider IV Tissue Plasminogen Activator [tPA]/See Stroke Code Algorithm") prior to planned start of treatment.

  If the patient awakens with symptoms, onset is defined as the time when the patient was last known to be at his/her baseline neurological status prior to retiring.
- CT scan showing no evidence of intracranial hemorrhage, non-vascular lesions (e.g., brain tumor, abscess) or signs of advanced cerebral infarction such as sulcal edema, hemispheric swelling, or large areas of low attenuation consistent with extensive volume of infarcted tissue.
- Unlikelihood of stroke mimickers, e.g., postictal state.

- A patient with a seizure at the time of onset of stroke may be eligible for treatment as long as the physician believes that residual impairments are secondary to stroke and not a postictal phenomenon *(Adams, 2007 [R]).*

Contraindications for tPA

The clinical history, laboratory and radiological contraindications for thrombolytic therapy (tPA) that are listed below should be considered relative contraindications. Clinical judgement should weigh the patient's risk for receiving tPA compared with the benefits of thrombolytic therapy.

Clinical contraindications

- Clearly defined onset of stroke greater than 3 hours (4.5 hours in selected patients; see Annotation #18, "Consider IV Tissue Plasminogen Activator [tPA]/See Stroke Code Algorithm") prior to planned start of treatment; if the patient awakens with symptoms, onset is defined as the time of the last known baseline neurological status prior to retiring.
- Rapidly improving symptoms
- Mild stroke symptoms/signs (NIHSS less than four)
  - Sensory symptoms only
  - Ataxia without other deficits
  - Dysarthria without other deficits
  - Mild motor signs (non-disabling)
  - Visual field defect without other deficits

  On the other hand, deficits measured at one to three on the scale may be very disabling and warrant use of tPA, e.g., moderate isolated aphasia in a professional using language in his specialty, such as a journalist. Hence clinical judgment may override guidelines.
- An obtunded or comatose state in the setting of middle cerebral artery (MCA) stroke, relative contraindication
- Clinical presentation suggestive of subarachnoid hemorrhage, regardless of CT result
- Hypertension – systolic blood pressure (SBP) greater than 185 mmHg or diastolic blood pressure (DBP) greater than 110 mmHg

  Patients with a systolic blood pressure greater than 185 mmHg or diastolic blood pressure greater than 110 mmHg are excluded only if the blood pressure remains elevated on consecutive measurements, and if aggressive treatment is required to lower the blood pressure into an appropriate range.

  Throughout this guideline, the work group frequently refers to blood pressure limits that are represented as systolic/diastolic. These ranges are intended to show the blood pressure limits as excessively elevated when either the systolic level **OR** the diastolic level is above the threshold.

History contraindications

- Minor ischemic stroke within the last month
- Major ischemic stroke or head trauma within the last three months
- History of intracerebral or subarachnoid hemorrhage if recurrence risk is substantial
- Untreated cerebral aneurysm, arteriovenous malformation (AVM) or brain tumor
- Gastrointestinal or genitourinary hemorrhage within the last 21 days

- Arterial puncture at a non-compressible site within the last seven days or lumbar puncture within the last three days
- Major surgery or trauma within the last 14 days
- Clinical presentation suggestive of acute myocardial infarction (MI) or post-MI pericarditis
- Patient taking oral anticoagulants and INR greater than 1.7
- Patient receiving heparin within the last 48 hours and has an elevated aPTT
- Patient receiving low-molecular-weight heparin within the last 24 hours
- Pregnant, or possibly pregnant, female
- Known hereditary or acquired hemorrhagic diathesis or unsupported coagulation factor deficiency

Laboratory contraindications

Glucose should always be measured prior to giving tPA; other parameters should be checked before treatment if there is reason to believe they may be abnormal (e.g., INR and aPTT should be checked if patient has been exposed recently to warfarin or heparin or if there is history of liver disease).

- Glucose less than 50 or greater than 400 mg/dL
- Platelet count less than 100,000 mm^3
- INR greater than 1.7
- Elevated aPTT
- Positive pregnancy test

Radiology contraindications

- Intracranial hemorrhage
- Large area of low attenuation consistent with an infarcted brain

  Early changes of this type suggest that onset of symptoms occurred earlier than the history first indicated. Recheck patient history and time of symptom onset.
- Intracranial tumor, aneurysm, arteriovenous malformation (AVM) or other space-occupying lesion

Once indications and contraindications have been reviewed, the patient should be appropriately managed and documentation of why tPA was given or not given must occur.

Baseline NIHSS

A history and neurological examination must be performed to assess whether the presentation is consistent with a stroke diagnosis and to estimate the severity of the deficit *(Adams, 2007 [R])*. Use of the NIHSS by physicians and nursing staff is encouraged, as the scale provides a uniform method of evaluation to facilitate comparison between examiners' observations during the early hours of the stroke care. We encourage use of the NIHSS as an initial evaluation tool and after treatment to assess for change.

The NIHSS is a quantitative measure of neurologic deficit in stroke patients that covers the key aspects of the neurological exam, including level of consciousness and orientation, eye movements, visual fields, facial weakness, motor strength in limbs, coordination, sensation, language and comprehension of language, articulation, and neglect. It can be performed in rapid fashion (five to eight minutes), which is an important feature in this clinical setting *(Adams, 2007 [R]; Brott, 1992 [R])*.

The NIHSS has been demonstrated in several evaluations to have both validity and reliability as follows:

- Content validity
  - The items contained in the NIHSS were selected on the basis of expert opinion and literature review, thus satisfying the requirements for content validity (*Boysen, 1992 [R]*).
- Concurrent criterion validity
  - The NIHSS correlates with lesion volume on CT scan *(Brott, 1989 [D])*.
  - The NIHSS correlates with other measures of neurological outcome *(Duncan, 1992 [C])*.
- Construct validity
  - Factor analysis reported by Lyden et al. defined two constructs relating to right and left hemisphere function confirming construct validity of this scale (i.e., it is measuring what it was designed to measure). This final factor structure remained consistent in both tPA-treated and placebo patients over time after ischemic stroke treatment *(Lyden, 1999 [C])*.
- Predictive validity
  - The NIHSS predicts three-month outcome *(Adams, 1999 [B]; Muir, 1996 [C])*.
- Interrater and intrarater reliability
  - The NIHSS has been shown to be a reproducible measure, both comparing different examiners and comparing repeated evaluations by the same examiner. Reliability has been demonstrated for neurologists, other physicians and nursing caregivers *(Dewey, 1999 [C]; Goldstein, 1989 [C]; Goldstein, 1997 [C])*. Although the NIHSS was originally designed as a research tool, it has proven to be an excellent measure of neurologic status and can be an important tool for the standardization and communication of clinical information between nurse caregivers and between nurse caregivers and other health care professionals *(Spilker, 1997 [C])*.

Perform Vital Signs Every 15 Minutes with Neurological Checks (not NIHSS)

It is the standard of practice to perform a baseline NIHSS neurological assessment *(Adams, 2007 [R])*. For subsequent neuro checks, a less extensive tool is appropriate. Performing a full NIHSS assessment every 15 minutes is often not feasible and may not be a good use of time. There is not evidence showing that performing a full NIHSS assessment every 15 minutes improves patient outcomes or improves the assessment and early detection of changes in patient condition. Unfortunately, there is not a standard validated non-NIHSS neurological assessment that is utilized by health care providers or that has been studied.

The work group has gathered the abbreviated neurological assessments used by several organizations and proposes the following non-NIHSS neuro check as an option.

Level of Consciousness – measures the level of alertness and cognition of the patient

- Is the patient alert, alert with stimulation or requires repeated stimulation to remain alert, or comatose?
- Is the patient able to correctly mouth his/her name and age?
- Is the patient able to correctly follow simple commands of opening and closing his/her eyes?

Motor Functions – measures the motor functions and patient's ability to follow commands

- Is the patient able to perform a series of arm movements?
- Is the patient able to perform a series of leg movements?

Language Skills – measures the amount of aphasia and dysarthria in response to asking patients to describe an item or read several sentences

See Appendix B for an example of non-NIHSS neuro check forms

The work group would like to encourage organizations to measure the use of non-NIHSS assessment tools to grow the evidence in this area.

Record Weight (estimate if needed)

Draw Blood for Lab Tests

Necessary/critical laboratory tests (results must be available before treatment in all cases):

- Glucose
- PT/INR (if patient on warfarin)

Recommended laboratory tests (results must be available before treatment if physical exam and/or patient history indicates the possibility of abnormal results):

- Complete blood count (CBC) with platelet count
- Electrolytes, BUN, creatinine
- PT/INR, aPTT

Others to consider:

- Troponin
- AST

These tests are used to evaluate for dehydration, metabolic disorders that might influence neurologic status (especially hypoglycemia and hyperglycemia), hematologic disorders such as polycythemia that may affect cerebral perfusion, or coagulopathies that could affect the treatment decision *(Adams, 2007 [R])*. Prior to administration of tPA, the glucose level should be reviewed. If the patient is known to be on warfarin or has received heparin within the last 24 hours, the prothrombin time and partial thromboplastin time must be reviewed prior to treatment. A urine or serum pregnancy test should be obtained in women of childbearing potential if there is substantial reason to believe the patient may be pregnant.

Perform Electrocardiography (EKG)

An EKG should be performed for the purpose of screening for concomitant cardiac disease, either acute or chronic, that may impact immediate treatment decisions.

Perform CT Head without Contrast (or Other Equivalent Imaging)

A CT scan without contrast must be performed prior to treatment with tPA, primarily for the purpose of excluding hemorrhage. Early signs of infarct should also be sought as this finding confers greater risk of symptomatic intracerebral hemorrhage with tPA treatment *(Adams, 2007 [R])*. It has been recently shown that MRI scans of the brain with diffusion- and susceptibility-weighted (gradient echo) sequences are much more sensitive than CT in detecting new infarction and chronic hemorrhage as well as of equal sensitivity for acute hemorrhage *(Chalela, 2007 [C]; Fiebach, 2004 [C]; Latchaw, 2009 [R])*. Consequently, when it is possible to perform MRI as quickly as CT with equally expert and timely interpretation, MRI may be used in this situation. Whichever is used, it is recommended that the greatest level of radiologic expertise possible be obtained for interpretation, with the caveat that this CT reading should not create excessive delays in the evaluation and treatment process. A procedure for rapid teleradiography CT readings should be organized and in place if needed to provide this expertise quickly.

Other Cardiac Assessment as Appropriate (Telemetry)

Consider If Intra-Arterial Recanalization Candidate

Intra-arterial thrombolytic therapy may be a treatment option for selected patients presenting in an early time frame but beyond the 3 hour (or 4.5 hours in selected patients; see Annotation #18, "Consider IV Tissue Plasminogen Activator [tPA]/See Stroke Code Algorithm") time window for intravenous tPA *(Adams, 2007 [R])*.

The availability of this option will be institution dependent, and patients must be highly selected. If considering this treatment option for a patient, a physician must explain to the patient and family that this is beyond standard of usual care and has substantial risk. Despite the limitations of available study data, in cases of more severe presentation with basilar artery or middle cerebral artery or basilar artery occlusion, intra-arterial thrombolytic treatment may be appropriate because the prognosis without treatment is poor.

If the patient is an appropriate candidate for this treatment, consideration should be given to immediate transfer to an institution offering this intervention. If an endovascular interventionist skilled in this technique is available elsewhere, the patient should be mobilized quickly. See also Appendix A, "Acute Stroke Care Networks."

Middle cerebral artery occlusion

Criteria for consideration of angiographic evaluation for intra-arterial treatment:

- Middle cerebral artery (MCA) occlusion defined by:
  - Symptom complex consistent with this vascular distribution:
    - Contralateral hemiplegia and facial weakness
    - Contralateral hemisensory loss
    - Aphasia if ischemia is on left, "neglect" if on right
    - Commonly, contralateral homonymous visual field deficit, reduced level of arousal, eye deviation toward side of brain ischemia (away from side of weakness)
  - MCA "clot sign" on baseline pretreatment CT scan with appropriate clinical presentation
  - CT angiogram, MRA or transcranial doppler (TCD) demonstration of the occlusion with appropriate clinical presentation

Treatment should begin greater than 3 hours (or 4.5 hours in selected patients (see Annotation #18, "Consider IV Tissue Plasminogen Activator [tPA]/See Stroke Code Algorithm") but less than 6 hours from onset of symptoms.

In the case of middle cerebral artery occlusion, the estimated degree of benefit may seem to be less dramatic than that with basilar occlusion, but the supporting studies offer a superior level of evidence. In the first of two PROACT studies (Prolyse in Acute Cerebral Thromboembolism Study), an improved rate of recanalization was established when comparing use of intra-arterial recombinant pro-urokinase (r-proUK) plus IV heparin to intra-arterial infusion of placebo plus IV heparin (57.7% versus 14.3%, 2p=0.017) *(del Zoppo, 1998 [A])*. This was a small phase II trial (n=40, 26 received r-proUK and 14 received placebo). Clinical efficacy was not a primary endpoint and it was not established in this study. In PROACT II intra-arterial r-proUK plus IV heparin (n=121) was compared to IV heparin alone (n=59) *(Furlan, 1999 [A])*. Significant clinical benefit with treatment was established, showing a 15% absolute increase in the percentage of patients with good outcome at three months (primary outcome measure was modified Rankin score of two or less). The complication of symptomatic intracerebral hemorrhage was higher than that seen in the NINDS IV tPA study (10.2% vs. 6.4% respectively) *(National Institute of Neurological Disorders and Stroke tPA Stroke*

Study Group, 1995 [R]). However, the pretreatment severity of stroke in PROACT II was also higher than that in the NINDS study, probably accounting for this excess of hemorrhagic complications.

Despite these promising results, r-proUK was not approved by the FDA for the indication of ischemic stroke, and r-proUK has never been available in the U.S. for any indication. The results of PROACT II, however, have served as a proof of principle for the efficacy of an intra-arterial lytic approach to proximal MCA (M_1 or M_2 segment) occlusion in the three- to six-hour time frame. It should be recalled that the available lytic agent, tPA, has not been examined in a randomized trial of the intra-arterial route. In summary, intra-arterial tPA thrombolysis is recommended (Class I) for treatment within six hours of onset of middle cerebral artery occlusion (level of evidence B). It should not preclude IV tPA in patients that otherwise qualify (Class I, level of evidence A) *(Meyers, 2009 [R])*.

Basilar artery occlusion

- Basilar artery (BA) occlusion defined by the following.
  - Symptom complex consistent with this vascular distribution:
    - Quadriparesis, sometimes with posturing bulbar dysfunction (dysarthia, dysphagia, dysphonia)
    - Typically dysconjugate eye movement deficits
    - Commonly, depressed level of arousal, respiratory abnormalities
  - Hyperdense "clot sign" in basilar artery on baseline non-contrast CT scan with appropriate clinical presentation
  - CT angiogram, MRA or transcranial doppler (TCD) demonstration of the occlusion with appropriate clinical presentation

Treatment should begin greater than three hours but less than 12 hours from onset of symptoms.

The occurrence of acute basilar artery occlusion with bilateral brainstem symptoms is typically a catastrophic neurological event portending a poor prognosis if reperfusion does not occur, with estimations of over 75% mortality and severe disability in survivors *(Archer, 1977 [D]; Caplan, 1983 [D]; Kubik, 1946 [D])*. Several investigators have reported their results in series of treated patients with basilar thrombosis using intra-arterial urokinase or tPA, showing recanalization rates between 40% and 78% and good outcome by various measures in 20% to 50% *(Becker, 1996 [D]; Brandt, 1996 [D]; Cross, 1997 [D]; Gonner, 1998 [D]; Hacke, 1988 [C]; Wijdicks, 1997 [D]; Zeumer, 1993 [D])*. These are dramatic results when compared to the natural history of this disease as reported in the literature.

There are no randomized, controlled trials of cases of basilar occlusion comparing intravenous tPA to intra-arterial thrombolysis within 3 hours of symptom onset or intra-arterial therapy to placebo controls in any time window, but the limited number of patients presenting with this specific entity would make this a difficult undertaking. In patients presenting within a 3 hour time window, (4.5 hours in select patients; see Annotation #18, "Consider IV Tissue Plasminogen Activator [tPA]/See Stroke Code algorithm") the work group suggests that IV tPA be administered. Subsequent intra-arterial treatment may be considered in some centers.

Newer approaches

Other approaches to acute reperfusion are under study. One has been to combine the speed of the intravenous therapy with the superior recanalization effect of intra-arterial administration. The Emergency Management of Stroke (EMS) Bridging Trial was a small study (n=35) comparing combined use of intravenous and intra-arterial tPA in patients presenting within the three-hour time window *(Lewandowski, 1999 [A])*. This study demonstrated the feasibility of the combined intravenous/intra-arterial approach showing better recanalization rates when compared to intra-arterial treatment alone. The study was too small to adequately assess

efficacy and safety. A larger study (n=80) by the Interventional Management of Stroke (IMS) Investigators compared efficacy and safety of the approach using matched historical controls from the NINDS IV tPA trial *(IMS Study Investigators, 2004 [A])*. Efficacy was slightly greater and safety similar to the historical IV-tPA-treated patients. A randomized trial is ongoing.

Another approach uses mechanical rather than chemical clot removal. The two most common devices for mechanical reperfusion are the MERCI (mechanical embolus removal in cerebral ischemia) catheter (a corkscrew-shaped retrieval device) and the Penumbra system (which relies on clot suctioning and mechanical disruption through separation). The MERCI and Multi-MERCI trials showed that recanalization could be safely achieved in up to 70% patients presenting within eight hours after occlusion of a proximal artery, e.g., internal carotid, MCA, BA, vertebral artery *(Gobin, 2004 [D]; Smith, 2008, [D])*. Recanalization rates exceeding 80% have been reported with the penumbra system in patients with similar characteristics in a single study funded by Penumbra, Inc. *(Penumbra Pivotal Stroke Trial Investigators, The, 2009 [D])*. FDA has approved both of these devices for treatment of patients with acute ischemic stroke. The utility of these devices in improving clinical outcomes remains unclear (Class IIb, level of evidence B) *(Meyers, 2009 [R])*.

At this point in time, there are no studies comparing intravenous to intra-arterial therapy within the 3 hour or 4.5 hour windows. Intravenous treatment with tPA is proven effective in this time frame. Intra-arterial thrombolysis with the agents currently available for use has theoretic advantages in certain stroke types (demonstrated large vessel occlusion of the internal carotid, middle cerebral or basilar arteries), but its superiority in producing improved clinical outcomes remains unproved. Also, there are logistic difficulties with intra-arterial catheter technique that may delay the time to intervention, thus limiting the benefit for these patients. For these reasons, treatment within the 4.5 hour time window with intra-arterial instead of intravenous thrombolysis cannot be recommended for these large vessel occlusion cases. Centers with expertise in use of this technique or mechanical clot removal should be encouraged to continue utilizing intra-arterial chemical or mechanical thrombolysis in appropriate candidates presenting beyond the 4.5 hour time window chemical (intra-arterial tPA) presentation within a 4.5 to 6-hour time window for MCA occlusion – M_1 or M_2 segment, and 4.5 to 12 hours for BA occlusion; mechanical clot removal presentation time within a 4.5 to 8-hour time window for MCA occlusion, 4.5 to 12 hours for BA occlusion while collecting outcome data and reporting their experience to the medical community. Even more desirable, these same centers should be participating in randomized, controlled trials so that the efficacy of these approaches can be fully established and their roles in the acute ischemic stroke treatment armamentarium can be clarified for all.

Emerging Technologies

Several groups have reported use of imaging to support decisions about reperfusion therapies *(Albers, 2006 [C]; Furlan, 2006 [A]; Hacke, 2005 [A])*. MR and CT technologies can provide information about the status of the vascular supply and parenchyma of acutely ischemic brain. Vascular studies (MRA, CTA) demonstrate presence and location of occlusive thrombus, as well as collateral channels. This knowledge enables the offending thrombus to be targeted more precisely and may expand reperfusion options to intra-arterial chemical or mechanical means. Special CT and MR imaging protocols measure cerebral transit time, blood flow, blood volume and in the case of MR, presence or absence of cytotoxic edema characteristic of infarcting or infarcted brain by detecting restricted proton diffusion. From these parenchymal data, presence and extent of penumbra vs. infarct can be inferred.

It has been argued that information available from these technologies may be of equal or greater importance as time elapsed since symptom onset in deciding whether and how to undertake a reperfusion therapy. The hypothetical ideal reperfusion scenario is when a vascular occlusion is identified and the parenchymal signature is that of penumbra with little or no infarct. On theoretical grounds, treating in such a scenario might be defended even if the time limit were exceeded. A small randomized trial recently supported this idea by showing that intravenous tPA may be beneficial beyond 3 hours compared with placebo in patients with perfusion-diffusion "mismatch" (i.e., a larger volume of brain with reduced flow than that of already

infarcted tissue) using perfusion- and diffusion-weighted MRI *(Davis, 2008 [A])*. Interestingly, patients without mismatch improved as much as those with mismatch in this underpowered study. Analysis of the same patients examining clinical-diffusion mismatch (i.e., deficit more severe than expected considering area of restricted proton diffusion) also found that mismatch did not predict efficacy of IV tPA in a prolonged time window *(Ebinger, 2009 [A])*. The science has been made more difficult because of the complexity of the technology, lack of standardized metrics, and variability among patients in important factors such as robustness of collaterals *(Miteff, 2009 [D])*. Also, the role of mismatch detection in selecting patients has been confused in recent studies that are simultaneously examining other issues, such as newer chemical agents, as well as the efficacy of imaging in selecting patients for recanalization therapy *(Hacke, 2009 [A]; Parsons, 2009 [A])*.

Management protocols using such approaches are being assessed in several hospitals in this region. Their use to supersede time-based reperfusion policies, though supported by emerging information, must still be considered outside of standard care. In conclusion, the accuracy and usefulness of such studies have not been well established (Class IIb, level of evidence B) *(Latchaw, 2009 [R])*.

31. Intervention (Should Occur Concurrently with Evaluation)

Key Points:

- Treating elevated blood pressure is necessary before administering tPA. Other treatments listed below are not necessary prior to therapy and should not delay its administration.
- Patients with a systolic blood pressure greater than 185 mmHg or diastolic blood pressure greater than 110 mmHg are excluded if the blood pressure remains elevated on consecutive measurements despite treatment with approved measures (e.g., labetolol, nitroglycerin ointment USP 2%, or nicardipine) or if aggressive treatment is required to lower the blood pressure into an appropriate range (e.g., nitroprusside drip).
- Prevent dehydration in patients by maintaining euvolemia with isotonic fluids. Hypotonic fluids should be avoided because they promote brain swelling.

Educate Patient and Family

A process should be in place for educating the patient and family to the suspected diagnosis, emergency department (ED) process, tests to be performed, tPA treatment and its risks, and other treatment measures to be considered. This could include face-to-face interaction by the caregiver with the patient and family, as well as teaching tools in written form. Education should be documented in the medical record.

Treat Hypertension If Blood Pressure Greater than 185 Systolic or 110 Diastolic

Patients with a systolic blood pressure (BP) greater than 185 mmHg or diastolic blood pressure greater than 110 mmHg are excluded from this annotation only if the blood pressure remains elevated on consecutive measurements *(Adams, 2007 [R])*, and if aggressive treatment is required to lower the blood pressure into an appropriate range (e.g., if more than a few doses of any medication is required or if nitroprusside drip is required).

Guidelines for blood pressure management in this setting have been slowly evolving *(Adams, 2007 [R]; International Society of Hypertension Group, 2003 [R]; Powers, 1993 [R]; Stead, 2004 [M]; Strandgaard, 1996 [R])*.

A full understanding of this issue requires understanding of the physiology. Cerebral blood flow (CBF) is regulated by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance

(CVR) (CBF=CPP/CVR). CPP represents the difference between arterial blood pressure forcing the blood into the cerebral circulation and the venous back pressure. Under normal circumstances, the venous back pressure is negligible and CPP is equal to arterial blood pressure. Normally, changes in blood pressure (or CPP) over a wide range have little effect on CBF. This phenomenon, termed autoregulation, is mediated via changes in the CVR. An increase in CPP (or arterial blood pressure) produces vasoconstriction and a decrease produces vasodilatation. This autoregulation keeps the cerebral blood flow at a steady level over a range of 60-150 mmHg mean arterial pressure. In individuals with chronic hypertension, the range for autoregulation is shifted upwards so that they may be more tolerant of higher blood pressure and less tolerant of lower blood pressure (decreased cerebral blood flow).

Acute ischemic stroke will cause a change in autoregulation in the ischemic zone by two mechanisms:

First, when an artery is occluded, a central core of severe ischemia is produced. This is surrounded by a zone with less reduction in blood flow termed the penumbra where perfusion is maintained by collateral circulation. The blood vessels in the penumbra are maximally dilated, and for that reason blood flow through them may be completely dependent on blood pressure.

Second, during the acute period, the phenomenon of autoregulation even outside of the penumbra can be impaired in patients both with and without persistent arterial occlusion, changing the autoregulation curve so that maintenance of blood flow is completely dependent on the blood pressure.

These abnormalities in autoregulation may persist for days or weeks. There is evidence to suggest that there is slow improvement in disordered autoregulation in the acute period. But early on, lowering the blood pressure may reduce blood flow to critical levels in the ischemic region, potentially extending the area of infarct. This is supported by data from both animal and human studies *(Christensen, 2002 [D]; Powers, 1993 [R])*.

Although the potential dangers of lowering arterial blood pressure in patients with acute ischemic stroke are accepted theory influencing practice, documentation of actual risk is based on a few published case reports *(Britton, 1980 [D]; Grossman, 1996 [R]; Lavin, 1986 [D])*. The theoretical adverse effects of overtreatment are substantial. Whether carefully controlled treatment of hypertension in acute stroke might be beneficial has not been adequately studied.

A Cochrane review (2003) consisting of 34 randomized controlled trials and 5,368 patients examined the effect of various drugs on blood pressure (BP) during the first 72 hours of acute ischemic stroke (AIS). Drugs shown to actually reduce BP included oral and IV calcium channel blockers, oral beta-blockers, glyceryl trinitrate, ACE inhibitors, prostacyclin (PGI2), and streptokinase. The effect of blood pressure reduction was not clear, likely due to the significant imbalances in baseline blood pressure between treatment and control groups. Outcomes examined included early death and overall case fatality. The review concluded that there is insufficient evidence to evaluate the effect of altering blood pressure on outcome after acute ischemic stroke. Another systematic review demonstrated increased mortality, early deterioration, and dependency associated with higher blood pressure in the acute stroke setting *(Willmot, 2003 [M])*. A recent placebo controlled trial in patients with stroke due to ischemia or hemorrhage assessed safety and outcome efficacy of early BP reduction. Subjects were not on BP medications before the trial and had early post-stroke systolic blood pressure > 160 mmHg. Goal was reduction to 145-155 mmHg or by 15%. The trial was stopped when its funding ran out. It was underpowered to detect efficacy but suggested that mild BP reduction within 36 hours with labetolol or lisinopril was safe *(Potter, 2009 [A])*.

The above review includes the IST trial *(Leonardi-Bee, 2002 [A])*, which demonstrated a U-shaped curve when BP was plotted against survival (i.e., increased mortality at lowest and highest pressure with lowest mortality at systolic pressure around 150 mmHg). Other investigators have reported a similar finding i.e., a U-shaped relationship with adverse outcomes in patient groups not treated with thrombolytic agents *(Castillo, 2004 [D])* and treated with tPA *(Ahmed, 2009 [B])*, providing grounds for the current consensus-based guidelines to treat BP if it exceeds arbitrarily derived thresholds established according to thrombolysis status

(see Table 3, "Approach to Elevated Blood Pressure in Acute Ischemic Stroke") *(Adams, 2007 [R])*. To be anticipated is more research to gather evidence about what the thresholds should actually be.

Taking the above studies into consideration, the AHA issued a revised 2007 edition of "Guidelines for the Early Management of Patients with Acute Ischemic Stroke" *(Adams, 2007 [R])*. In the absence of unambiguous data, these consensus-based guidelines recommend the following measures for treatment of BP in patients with acute ischemic stroke (AIS).

Table 3.

Approach to Elevated Blood Pressure in Acute Ischemic Stroke	
A. Not eligible for thrombolytic therapy	
Blood Pressure Level mm/Hg	**Treatment**
Systolic BP < 220 or diastolic < 120	Observe unless other end-organ involvement, e.g., aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy. Treat other symptoms of stroke such as headache, pain, agitation, nausea and vomiting Treat other acute complications of stroke including hypoxia, increased intracranial pressure, seizures or hypoglycemia.
Systolic BP > 220 or diastolic BP >120	- Labetalol 10-20 mg IV over 1-2 mins. May repeat or double every 10 mins. (max. dose 300 mg in 24 hours) **or** - Nicardipine 5 mg/hr IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/hr every 5 mins. to maximum of 15 mg/hr. *Aim for 15% reduction of BP
Diastolic BP > 140	Nitroprusside 0.5mcg/kg/min IV infusion as initial dose with continuous BP monitoring (max dose of 10 mcg/kg/min) *Aim for 10-15% reduction of BP
B. Eligible for Thrombolytic Therapy	
Pretreatment	
Blood Pressure Level mmHg	
Systolic BP > 185 or diastolic BP > 110	- Labetalol 10-20 mg IV over 1-2 mins. May repeat x 1; **or** - Nitroglycerin ointment USP 2% 1-2 inches; **or** - Nicardipine infusion @ 5 mg/hr, titrate up by 2.5 mg/hr at 5-15 min intervals; max dose 15 mg/hr; when desired BP attained, reduce to 3 mg/hr *** If BP does not decline and remains > 185/100 DO NOT administer tPA**
During and After Treatment with rtPA	
Monitor BP	Monitor BP every 15 minutes during treatment; following treatment, check BP every 15 mins for 2 hours, then every 30 mins for 6 hrs, then every hour for 16 hours.
Blood Pressure Level mmHg	
BP 180- 230/105-120 mmHg	- Labetalol 10-20 mg IV over 1-2 mins, may repeat every 10-20 mins (max dose 300 mg in 24 hours); **or** - Labetalol 10 mg IV followed by an infusion at 2-8 mg/min (max dose 300 mg in 24 hours)
BP > 230/121-140 mmHg	- Labetalol 10-20 mg IV over 1-2 mins, may repeat every 10-20 mins (max dose 300 mg in 24 hours); **or** - Labetalol 10 mg IV followed by an infusion at 2-8 mg/min (max dose 300 mg in 24 hours); **or** - Nicardipine infusion 5 mg/hr, titrate to desired effect, may increase 2.5 mg/hr q 5- 15 mins; max dose of 15 mg/hr. - If BP not controlled, consider nitroprusside infusion 0.5 mcg/kg/min (max dose of 10 mcg/kg/min)

The information in Table 3 was compiled from manufacturer package inserts, www.epocrates.com, www.micromedex.com, www.uptodate.com, www.pdr.net and is current as of April 1, 2010. For the most up-to-date medication and prescribing information, consult with your pharmacy or consider the following sources: http://www.epocrates.com, http://www.micromedex.com, http://www.uptodate.com, http://www.pdr.net.

Initiate Two Intravenous Lines

Two IV lines should be started so that tPA may have a dedicated line.

Start Intravenous Fluids

Treatment with a 0.9% normal saline at a rate of 75-125 cc/hr or 2-3 L/day should be administered to avoid dehydration *(Adams, 2007 [R])*. The rate may be adjusted for febrile patients. IV fluids are particularly important, of course, for patients in whom oral intake is prevented or limited by swallowing problems. Dehydration is fairly common on admission in stroke patients.

Hemorrheologic disturbances may be a factor in limiting cerebral blood flow in the setting of ischemic stroke. Attempts to affect blood viscosity by lowering hematocrit to increase blood flow and oxygen delivery have suggested the possibility of a useful therapeutic intervention *(Thomas, 1977 [C]; Wade, 1983 [D])*. Results have been mixed in studies of hemodilution techniques that attempt to decrease blood viscosity utilizing phlebotomy and volume expansion with dextran or pentastarch. Although there were promising results in small clinical trials, when subjected to more rigorous study with large controlled trials, this treatment was unsuccessful *(Italian Acute Stroke Study Group, 1988 [A]; Scandinavian Stroke Study Group, 1987 [A])*. Although proponents of this treatment have argued that results would be improved with earlier time-to-treatment, a more individualized approach with treatment decisions, or a more aggressive hypervolemic hemodilution approach, additional large-scale trials have not been undertaken. In fact, use of a hypervolemic approach in order to further raise cardiac output by volume expansion was complicated in some cases by cerebral edema and increased mortality, raising questions regarding the safety of this treatment *(Hemodilution in Stroke Study Group, 1989 [A])*. Therefore, hemodilution therapy is not recommended since the clinical benefit has not been established and the possibility of risk due to the development of cerebral edema has been suggested. Also, there is a risk of heart failure.

However, in the general medical management of patients with stroke, it is important to administer adequate fluids to avoid the development of dehydration or to treat it when present since dehydration with relative hypotension and hemoconcentration may impair cerebral blood flow *(Thomas, 1977 [C])*. Dehydration with hemoconcentration may also increase the risk of thrombus formation and recurrent embolization in cardiogenic stroke *(Arboix, 1998 [B]; Yasaka, 1993 [R]; Yasaka, 1990 [C])*. Therefore, it is suggested that isotonic intravenous fluids be administered to not only those admitted with dehydration or at risk for dehydration due to problems with swallowing, but to all stroke patients. Hypotonic fluids should be avoided because they promote brain swelling.

Other Systemic Management

Based on patient's presentation, other management may be required to control hyperthermia, hypothermia, hyperglycemia, hypoglycemia, hypotension, hypovolemia and/or hypoxia. (For additional information, please see Annotation #38, "Other Post-Emergency Department Medical Management [First 24-48 Hours]").

33. Initiate tPA

Treatment should consist of tPA 0.9 mg/kg intravenously to a maximum dose of 90 mg. Ten percent of this dose should be given as a bolus over one to two minutes and the remainder infused over one hour *(Adams, 2007 [R])*. This dosing may be based upon actual or estimated weight.

35. Initiate Aspirin After Swallow Evaluation Unless Contraindicated

Key Points:

- Aspirin should be given orally, rectally or via nasogastric tube promptly in patients who are not tPA candidates unless contraindicated (aspirin allergy, gastrointestional [GI] bleeding). A bedside swallow test should be performed in the emergency department before oral administration of aspirin.
- There is no evidence to support therapeutic anticoagulation with unfractionated heparin, low-molecular-weight heparin or heparinoids. There is, as yet, insufficient evidence to decide whether specific subgroups of ischemic stroke (e.g., dissection, cardio-embolism with intra-cardiac clot) will benefit from therapeutic anticoagulation.
- If a decision is made to use continuous heparin infusion, boluses should be avoided, and aPTT should be maintained in the 1.5-2 times baseline range.
- Low-dose prophylactic parenteral anticoagulation (e.g., enoxaparin, 40 mg subcutaneously daily) is beneficial for prevention of deep vein thrombosis (DVT) or PE (pulmonary embolism) in stroke patients with limited mobility.

Aspirin

Patients who are not candidates for tPA should be given aspirin promptly in a dose of 325 mg *(Adams, 2007 [R])* orally, rectally or by nasogastric tube and should be continued on a similar daily dose *(Albers, 2004 [R])*. Exceptions to this approach would be justified in those with contraindications to aspirin therapy (e.g., aspirin allergy, gastrointestinal hemorrhage). For patients with an aspirin allergy, 75 mg of clopidogrel may be reasonable. Intravenous or oral loading with 150-600 mg of clopidogrel establishes antiplatelet effect more rapidly; however, efficacy in this setting is unproven.

Initiation of aspirin therapy should be withheld for 24 hours for patients who have received tPA.

Although the benefits of aspirin therapy for long-term preventive therapy for stroke are well established, the use of aspirin to improve outcome in the acute treatment setting has also been demonstrated. Large randomized controlled trials have identified a small but measurable benefit with use of aspirin in the first 48 hours following ischemic stroke onset *(Bath, 2001b [A]; Chinese Acute Stroke Trial Collaborative Group, 1997 [A]; International Stroke Trial Collaborative Group, 1997 [A]; Sandercock, 1993 [M])*.

The studies together demonstrate benefit of small magnitude, but with statistical significance in the following outcome measures:

- Early recurrent ischemic stroke – 7 fewer per 1,000 treated ($p < 0.0001$)
- Death from any cause – 4 fewer per 1,000 treated ($p=0.05$)
- Death or early recurrence of non-fatal stroke – 9 fewer per 1,000 treated ($p=0.001$)
- Death or dependency at discharge or six months – 13 fewer per 1,000 treated ($p=0.007$)

Also, the measured hazard appears to be small and statistically insignificant:

- Hemorrhagic stroke or transformation – 2 more per 1,000 in ASA treated ($p=0.06$)

Considerations with Heparin Use

In contrast, to the proof of efficacy for aspirin, results from the International Stroke Trial provide powerful evidence against the routine use of any heparin regimen as intensive as the moderate-dose subcutaneous regimen utilized in this very large clinical trial (unfractionated heparin – 12,500 units subcutaneous twice daily) *(International Stroke Trial Collaborative Group, 1997 [A]).*

The commonly cited indications of vertebrobasilar distribution ischemia or ischemic stroke in the setting of atrial fibrillation were analyzed separately and there was no measurable benefit in these specific subgroups. Similarly, the weight of available data regarding use of full-dose low-molecular-weight heparin for the acute treatment of stroke does not support their routine use for limiting disability or decreasing mortality in this setting *(Publications Committee for the Trial of ORG 10172 in Acute Ischemic Stroke, 1998 [A])*.

In summary, the routine use of acute anticoagulation treatment with unfractionated heparin, low-molecular-weight heparin, or heparinoid in acute ischemic stroke is not supported by the available evidence *(International Stroke Trial Collaborative Group, 1997 [A])*. This treatment does not appear to improve clinical outcome from the index stroke. There may be subgroups that benefit, but further studies of this problem are required for confirmation.

Despite these discouraging results, the use of continuous heparin infusion in acute stroke has continued to be common in clinical practice *(Albers, 2004 [R]; Berge, 2000 [A]; Coull, 2002 [M]; Diener, 2001 [A])*.

Given these data, if the decision is made to use full-dose continuous heparin infusion for a specific indication (e.g., large vessel atherothrombosis or dissection), physicians are strongly encouraged to discuss with their patients the lack of proof for this therapy and to detail the potential hazards.

Heparin use for venous thromboembolism (VTE) prophylaxis

For patients at high risk for VTE where pharmacologic prophylaxis is contraindicated, intermittent pneumatic compression (IPC) should be used if the patient is confined to bed. Thigh-length graduated compression elastic stockings have been shown not to be effective *(CLOTS Trials Collaboration, 2009 [A])*. See also Annotation #38, "Other Post-Emergency Department Medical Management (First 24-48 Hours)" *(Kamphnisen, 2005 [R]).*

See the ICSI Venous Thromboembolism Prophylaxis guideline for more information.

36. Post-Emergency Department (ED) Medical Management (Postthrombolysis)

- **Admit** to intensive care unit or acute stroke care unit/cardiac monitoring.
- **Perform vital signs and neurological checks (not NIHSS National Institutes of Health Stroke Scale)** every 15 minutes for two hours, then every 30 minutes for six hours, then every 60 minutes for 24 hours (recommend use of an abbreviated NIHSS for neurological checks). (See Appendix B, "Non-NIHSS Neuro Check.")
- **Treat blood pressure (BP) if greater than 180/105**
  - First 24 hours: Treat if systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 105 mmHg.
  - Monitor BP and any corresponding neurological changes in the emergency department and first few days of hospitalization.

- **Initiate bleeding precautions:**
  - Avoid placement of central venous access or arterial puncture for the first 24 hours.
  - Avoid placement of an indwelling bladder catheter during drug infusion and for at least 30 minutes after infusion ends.
  - Avoid insertion of a nasogastric tube, if possible, during the first 24 hours.
  - Avoid use of anticoagulant, antiplatelet, or non-steroidal anti-inflammatory agents for the first 24 hours.
  - Monitor for central nervous system (CNS) hemorrhage.
- **If any signs of CNS hemorrhage** (e.g., neurological deterioration, development of severe headache, sudden severe elevation of BP, or new nausea or vomiting) or signs of major systemic hemorrhage, institute the following measures:
  - Discontinue infusion of thrombolytic drug.
  - Obtain hemoglobin, hematocrit, partial thromboplastin time, prothrombin time/INR, platelet count, fibrinogen (also type and cross match if transfusions will be needed).
  - Obtain surgical consultation if necessary.
  - Obtain emergent CT head without contrast if CNS hemorrhage suspected.
- **Initiate antithrombotic therapy** 24 hours after tPA administration (antiplatelet agent or anticoagulant as appropriate).

37. Post-Emergency Department (ED) Medical Management (Not a Thrombolysis Candidate)

Treat Blood Pressure If Greater than 220/120 mmHg or Mean Arterial Pressure Greater than 130 mmHg

Recommendations – ischemic stroke, **not** a tPA candidate:

- Admit to the intensive care unit or acute stroke care unit and perform cardiac monitoring.
- Perform vital signs with neuro checks (not National Institutes of Health Stroke Scale).
- Treat BP only if systolic blood pressure (SBP) is greater than 220 mmHg, diastolic blood pressure (DBP) is greater than 120 mmHg, and/or mean arterial pressure (MAP) is greater than 130 mmHg.
- Use easily titrated agents, choosing those with the least effect on cerebrovasculature (labetolol, nitroglycerin ointment USP 2% or nicardipine). American Heart Association (AHA) recommendations support oral dosing if the patient has passed a bedside swallow test. If not, intravenous agents should be used.

  Dosing examples:

labetalol oral	100-200 mg by mouth initially and every two hours as needed, up to 800 mg total in 24 hours
	or
labetalol IV	10-20 mg IV over 1-2 min., repeat or double dose every 10-20 min.

nitroglycerin ointment USP 2%	1 to 2 inches
nicardipine	5 mg/hr IV infusion, titrate for BP control, increasing 2.5 mg/hr every 5 min. to maximum of 15 mg/hr
nitroprusside	0.5 mcg/kg/min IV; titrate for BP control as needed up to 10 mcg/kg/min

- Avoid agents that tend to cause precipitous drops in BP (e.g., sublingual calcium channel blockers).
- Treat hypotension (IV fluids; treat congestive heart failure or arrhythmia and consider pressors).
- Monitor BP and any corresponding neurological changes in the emergency department and first few days of hospitalization. Avoid overtreating BP.

In patients with markedly increased blood pressure on presentation with acute stroke, measured reduction (e.g., 15% reduction targeted for the first 24 hours) is reasonable. The threshold for initiating such treatment remains 220 mmHg systolic and/or 120 mmHg diastolic. This is despite preliminary evidence that initiating treatment at a lower level may be safe and beneficial *(CHHIPS, 2008 [NA])*. In patients who are on an antihypertensive medication program at the time of the ischemic stroke, these medications should generally be withheld for the initial 24 hours. They should be reinstated after 24 hours, assuming that oral or tube administration is possible and hypotension is not present *(Adams, 2007 [R])*. Many potential reasons for deviating from this general principle exist. For example, suspension of a beta-blocker in a patient with coronary heart disease may be dangerous, and discontinuation of clonidine may cause rebound hypertension.

- Continue antithrombotic therapy

38. Other Post-Emergency Department Medical Management (First 24-48 Hours)

Continue to Treat Hyperthermia, Hyperglycemia or Hypoglycemia

Treat Hyperglycemia

Hyperglycemia may adversely influence clinical outcome.

- Early identification of patients with hyperglycemia in the setting of acute ischemic stroke or in those at risk for cerebral ischemia (ED evaluation of glucose level) is recommended *(Leigh, 2004 [C]; Ribo, 2005 [C])*.
- Avoid any agents or factors that might induce hyperglycemia.
  - Eliminate glucose from IV solutions using normal saline (recommended).
  - Avoid use of corticosteroids, even in those patients with cerebral edema, as they are not helpful and may be harmful. Separate recommendations are needed for those on maintenance corticosteroids for concurrent conditions, and treatment decisions are left to the discretion of the physician.
- Use appropriate measures to maintain euglycemia, carefully avoiding hypoglycemia.
- Continue to monitor glucose with bedside testing in those receiving treatment in order to maintain euglycemia.

Most observational studies document either increased mortality or decreased functional outcome, or both, with higher glucose. Some have speculated that early hyperglycemia in the setting of acute stroke is simply a marker of physiologic stress and an epiphenomenon in those who have suffered severe stroke *(Bruno, 1999*

[B]; Jorgensen, 1994 [B]; Kiers, 1992 [B]; Woo, 1990 [B]). Others have documented that it is an independent predictor of poor outcome and propose that it has a causative role *(Baird, 2003 [D]; Lindsberg, 2004 [R]; Parson, 2002 [D])*. Despite the extensive body of literature describing this relationship, a definitive clinical trial aimed at intervention to improve outcome is still lacking. A study utilized a continuous infusion of insulin, glucose and potassium in the setting of acute ischemic stroke *(Gray, 2007 [A])*. The trial was discontinued due to low enrollment. When stopped, it showed no benefit by the primary (mortality) or secondary (death or disability) endpoints. Significant but modest reductions in glucose level, as well as blood pressure, were seen in those randomized to the active treatment. The study was underpowered and had other limitations, making its negative results not definitive. It remains unclear whether early hyperglycemia in the setting of acute stroke is a marker of physiologic stress or an independent predictor of poor outcome. Usual management of hyperglycemia (glucose levels greater than 140 mg/dL) with gentle dosing of subcutaneous insulin, avoiding hypoglycemia, in a timely manner during acute ischemia would seem prudent until ongoing clinical trials address the appropriateness of more aggressive treatment measures *(Adams, 2007 [R])*.

Initiate Deep Vein Thrombosis (DVT) Prophylaxis

Consider DVT prophylaxis in any patient admitted to the hospital with lower extremity weakness related to an ischemic stroke. The risk of DVT is high (25%-50%), and prophylaxis with parenteral anticoagulant decreases the incidence (10% to 20%). The risk of pulmonary embolism appears to be decreased, as well, although numbers have been small and statistical significance not achieved *(Counsell, 2001 [M])*.

All patients should receive patient education that includes signs and symptoms of venous thromboembolism (VTE) and therapy options, and encouraged to ambulate early and perform flexion/extension exercises *(Geerts, 2004 [R])*. Thigh-length graduated elastic compression stockings have been shown in a randomized trial not to be effective in reducing risk of deep vein thrombosis after stroke *(Clots Trials Collaboration, The, 2009 [A])*. Intermittent pneumatic compression should be considered for patients at high risk for VTE who have contraindications to pharmacologic prophylaxis *(Clots Trials Collaboration, The, 2009 [A])*.

The PREVAIL Trial recently compared the low-molecular-weight enoxaparin (40 mg/day) with unfractionated heparin (5,000 units twice daily) for 10 days after stroke preventing walking. There was a 43% reduction in the incidence of venous thromboembolism in the enoxaparin group (10%), compared with the unfractionated heparin group (18%). Overall bleeding rates were similar. Based on this trial, low-molecular-weight heparin is superior to unfractionated heparin in prevention of venous thromboembolism after stroke with inability to ambulate *(Sherman, 2007 [A])*.

Low-molecular-weight heparin is renally cleared. For patients with a CrCl less than 30 mL/min, use unfractionated heparin. The patient should be monitored for the possible development of heparin-induced thrombocytopenia (HIT) and bleeding. Obtain a platelet count and hemoglobin every other day, beginning on the second day of heparin therapy.

See the ICSI Antithrombotic Therapy Supplement and the Venous Thromboembolism Prophylaxis guideline.

Perform Swallow Evaluation

Pneumonia is a common finding among patients with acute strokes, its incidence ranging from 6% to 32% *(Perry, 2001 [M])*, and it is associated with stroke-related dysphagia symptoms. Implementation of a coordinated swallow evaluation on all acute stroke patients has been shown to significantly decrease the incidence of pneumonia among patients with acute stroke *(Odderson, 1995 [D])*. This study used a screening tool consisting of three components: 1) the patient is alert, follows simple requests, has a clear, strong voice, and can produce a strong cough; 2) the patient can handle his/her own secretions without difficulty and can swallow ice chips and sips of ice water briskly; and 3) The larynx elevates completely at the time of

swallowing, the voice remains clear after swallow and there is no coughing afterward. (See Appendix C, "Stroke Dysphagia Screen.")

Dysphagia screening, performed in the emergency department, is an easy and effective way to identify stroke patients who are eligible for early oral medications and nutrition *(Turner-Lawrence, 2009 [C])*.

The work group recommends that a bedside swallow test be performed prior to the patient's ingestion of anything by mouth (including oral aspirin or other medications). This screen should be performed in the emergency department by a physician or nurse and should include pre-specified screening questions identifying patients at high risk for aspiration. If the result of the screening tool is negative, bedside swallow evaluation shall be performed using 2-3 ounces of water. If no clinical signs of aspiration occur, the patient may receive medications, including aspirin, by mouth. If the result of the screening tool is positive or if bedside swallow evaluation reveals clinical signs of aspiration, the patient shall be given nothing by mouth, referred for a formal swallow evaluation to be performed by a speech language pathologist, and aspirin administered via nasogastric tube or per rectum. If this swallow screen is not to be performed in the emergency department, aspirin should be administered rectally or via nasogastric tube.

Bedside swallow assessment or more a formal swallow evaluation, and dietary adjustments based on this information, have not been adequately evaluated in sufficiently powered randomized clinical trials. Because these interventions are safe and have a reasonable probability of improving care by decreasing complications, it is reasonable to advocate their use in this setting despite absence of proof of efficacy. Several previously published guidelines advocate these practices *(Bath, 2001a [M])*.

Initiate Rehabilitation Early

Early mobilization within 48 hours of admission, in the form of early initiation of appropriate rehabilitation swivels or other nursing intervention, is advocated for the purpose of preventing complications related to immobility, including deep vein thrombosis, contractures, joint disorders, and pressure sores/decubitus ulcers *(Adams, 1994 [R]; Helgason, 1997 [R])*. This recommendation is not based on existing randomized trial data, and it is unlikely that such a trial will be carried out in the future.

Perform Nutritional Status Assessment

Assessment of the patient's baseline nutritional status and the implementation of treatments to correct any major nutritional problems are recommended *(Adams, 2007 [R])*. Poor nutritional status in patients admitted for stroke is associated with increased morbidity and mortality *(FOOD Trial Collaboration, 2003 [B])*. However, a trial did not find benefit in administering nutritional supplementation *(Food Trial Collaboration, 2005 [A])*.

Early Treatment of Ischemic Brain Edema

Although ischemic brain swelling typically peaks between three and five days after stroke onset, marked early swelling (in the first 24-48 hours) causing mass effect and tissue shift can occur in the most severe cases ("malignant" ischemic brain edema). Low attenuation changes exceeding two-thirds of the middle cerebral artery territory and large areas of hypoperfusion on perfusion scans (computed tomography [CT] perfusion or magnetic resonance perfusion) on initial radiological evaluation are associated with high risk of developing malignant brain edema. Patients with these features should be strictly monitored with serial neurological examinations, ideally in a stroke unit. Repeating CT scan of the brain to evaluate for progression of regional mass effect is indicated if the patient develops any signs of neurological deterioration. The value of serial CT scans of the brain in the absence of clinical changes remains to be established.

Decompressive hemicraniectomy with durotomy improves survival and functional outcome *(Vahedy, 2007 [M])*. The optimal timing of the procedure is not well established, but most experts recommend early intervention. Improvement in functional outcome has been shown only for patients 60 years old or younger.

Osmotherapy (mannitol 20% or hypertonic saline) may be used to treat ischemic brain edema, but there is very limited data supporting its value *(Bardutzky, 2007 [R])*. Mannitol 20% is usually administered as a bolus of 1-2 g/kg of body weight, followed by repeated boluses as needed for neurological decline or scheduled doses of 0.25 to 0.5 g/kg every four to six hours. In patients with established signs of herniation, a rescue dose of 23.4% of saline solution (30 cc) may be useful *(Koenig, 2008 [D])*.

Hyperventilation should be avoided except for mild to moderate hyperventilation (target pCO_2 30-34 mmHg) for brief periods of time because of the risk of exacerbating ischemia by causing vasoconstriction.

Treat Hyperthermia

The acutely injured brain, whether due to trauma or ischemia, is inordinately susceptible to the damaging effects of brain temperature elevation. This fact is well supported by both animal and human studies *(Ginsberg, 1998 [R]; Terént, 1981 [B])*.

Interventions for patients with temperatures of greater than 99.5ºF (37.5ºC) include appropriate dosing of acetaminophen (1 gram orally or 650 mg rectally every four to six hours, not to exceed 4-6 grams in 24 hours) and regular monitoring of temperature status (every four hours). A recent phase III trial of this approach in patients with 36-39ºC failed to identify benefit in primary analysis and does not support routine use of acetaminophen for normothermic patients for cooling, although possible benefit was shown post hoc in those with mild to moderate temperature elevation in the 37-39ºC range *(den Hertog, 2009 [A])*. For those patients with extreme hyperthermia, greater than 103ºF (39.4ºC), aggressive interventions, including cooling blankets and ice packs, are encouraged. Causes for temperature elevation should be sought and treated.

In human studies, early hyperthermia in acute stroke is associated with increased risk of poor outcome, higher mortality and increased infarct volume *(Azzimondi, 1995 [B]; Castillo, 1998 [D]; Hajat, 2000 [M]; Reith, 1996 [B])*. The causality and the relationship of temperature elevation to these poor outcomes are not fully understood. Whether intervention with cooling methods will result in improved outcomes is unknown.

Appendix A – Acute Stroke Care Networks

Two advances in ischemic stroke care, IV tPA and coordinated inpatient care processes (often considered together as "stroke unit care"), are known to improve outcomes. The urgency, complexity and potential risks of the former and training required for the latter challenge the resources of emergency rooms and hospitals that may care for only a few ischemic stroke patients each year. A recent national survey showed that 64% of all United States hospitals had not administered IV tPA for stroke during the two-year sampling interval (2005-07), and 40% of Americans live in counties in which no hospitals have substantial experience with IV tPA administration *(Kleindorfer, 2009 [C])*. At the same time, hospitals with large volumes of such patients have developed "frontline" capability driven by local competition and supported by quality improvement programs offered through The Joint Commission (TJC), the American Heart Association, National Stroke Association, CDC, and others. Currently there exist significant care inequities across the region.

In contrast to those who arrive at frontline stroke hospitals, stroke patients in remote/rural areas in our state and region are likely not to have access to advantages of informed, urgently deployed reperfusion techniques (especially IV tPA but also intra-arterial chemical and mechanical reperfusion therapies for selected cases) and stroke unit care during their hospitalizations. It is likely that outcomes are impacted by low rates of IV tPA use, suboptimal patient selection for IV tPA, and hospital processes that are not guideline based. In fact, one might calculate from number-needed-to-treat metrics that many poor outcomes each year in Minnesota might result from disparities in care based on geography.

Ad hoc systems have been developed in Minnesota and elsewhere to eliminate the disparities in care resulting from geographic exigencies *(Frey, 2005 [D]; Hoody, 2008 [D]; Rymer, 2003 [D]; Silliman, 2003 [D]; Silverman, 2005 [D]; Switzer, 2008 [R]; Switzer, 2009 [R]; Vaishnav, 2008 [D]; Wang, 2000b [D]; Wang, 2003 [D]; Wang, 2004 [D])*. Typically the systems that have evolved provide support for remote/rural emergency rooms and hospitals by neurologists or other stroke experts who are physically located elsewhere, usually at a frontline hospital. A single frontline hospital (a "hub") may provide support for several remote/rural emergency rooms and hospitals ("spokes"). Several models of support have evolved. In some models, the stroke cases are transferred to the frontline stroke center. Models include:

- Field to comprehensive stroke center transport – For example, a ground ambulance or helicopter is deployed by regional EMS to a farmhouse, and the patient is transport to a frontline stroke center without intermediate hospitalization, i.e., "spokeless." This model has not proliferated beyond a few areas.
- "Trip to drip" – A stroke expert or team of experts travels quickly to the remote/rural emergency room or hospital to provide or supervise acute care. This model is limited by distances and availability of mobile stroke experts/teams.
- "Ship and drip" – The stroke patient is transferred prior to initiation of reperfusion therapies from remote/rural emergency room or hospital to a frontline stroke center.
- "Drip and ship" – After assessment of eligibility with input of supportive expert, IV tPA is started at the remote/rural hospital, and the patient is immediately transported to the front line stroke center.
- "Drip and keep" – IV tPA is given with support as above, and the patient remains at remote/rural hospital for acute hospitalization.

There is considerable latitude for individual variation within these models. For example, the formality of expectations between the hub and spoke varies from casual (e.g., a phone call to a hospital neurology consulting line) to explicit, including expectation for 24/7 availability of a stroke expert on the hub side and for formal training, ongoing education, joint protocol development, and joint post-stroke care planning on the spoke side. The form of communication from hub to spoke varies from simple phone call to phone call/teleradiography to telemedicine/teleradiography.

Literature supports the feasibility and safety of administering IV tPA in all of these models. There is level I evidence showing that compared with phone call alone, telemedicine avoids protocol deviations in administration of IV tPA *(Meyer, 2008 [A])*. The trial was not powered to analyze actual outcomes.

Working relationships between individual stroke centers and remote/rural hospitals and emergency rooms will necessarily and appropriately be customized according to the unique circumstances and goals of the entities. It seems prudent, however, that these evolving relationships be guided by basic principles. The work group makes the following recommendations:

- Agreements between hub and spokes should be formal, as opposed to ad hoc.
- Hub should provide 24/7 availability of support for reperfusion therapies by one or several of the following:
  - telephone +/- teleradiography
  - telemedicine +/- teleradiography
- Protocols defining care processes between hub and spoke should be jointly developed and support the agreed-upon model, e.g., 3, 4 or 5.
- Initial and ongoing education of spoke personnel relevant for the care model should be provided.
- Initial and ongoing training of spoke personnel (e.g., NIHSS performance and interpretation, conducting an informed consent discussion regarding IV tPA) relevant to the care model should be provided.
- There should be joint planning for stroke unit care at hub (models 3 and 4) or spoke (model 5) and case follow-up. Planning for optimal care of non-reperfusion cases should also be provided.

(Schwamm, 2009a [R]; Schwamm, 2009c [R])

Appendix B – Non-NIHSS Neuro Check

Function & Measurement Format	**Scores:**						
Level of Consciousness: 0=Alert 1=Not alert, but arousable with minimum stimulation 2=Not alert, requires repeated stimulation to attend 3=Coma							
LOC Questions: Ask Patient the Month and His/Her Age 0=Answers both correctly 1=Obeys one correctly 2=Both incorrect							
LOC Commands: Ask Patient to Open and Close Eyes 0=Opens both correctly 1=Obeys one correctly 2=Both incorrect							
Motor Functions: Arms 0=Normal extension arms 90º or 45º for 10 seconds without drift 1=Drift 2=Some effort against gravity 3=No effort against gravity 4=No movement 9=Untestable – Joint fused or limb amputated **(Do not include this in total score)**							
Motor Functions: Legs 0=Normal – hold leg 30º position for 5 seconds 1=Drift 2=Some effort against gravity 3=No effort against gravity 4=No movement 9=Untestable – Joint fused or limb amputated							
Best Language 0=No aphasia 1=Mild to moderate 2=Severe aphasia 3=Mute							
Dysarthria 0=Normal articulation 1=Mild to moderate slurring of words 2=Near unintelligible or unable to speak 3=Mute							

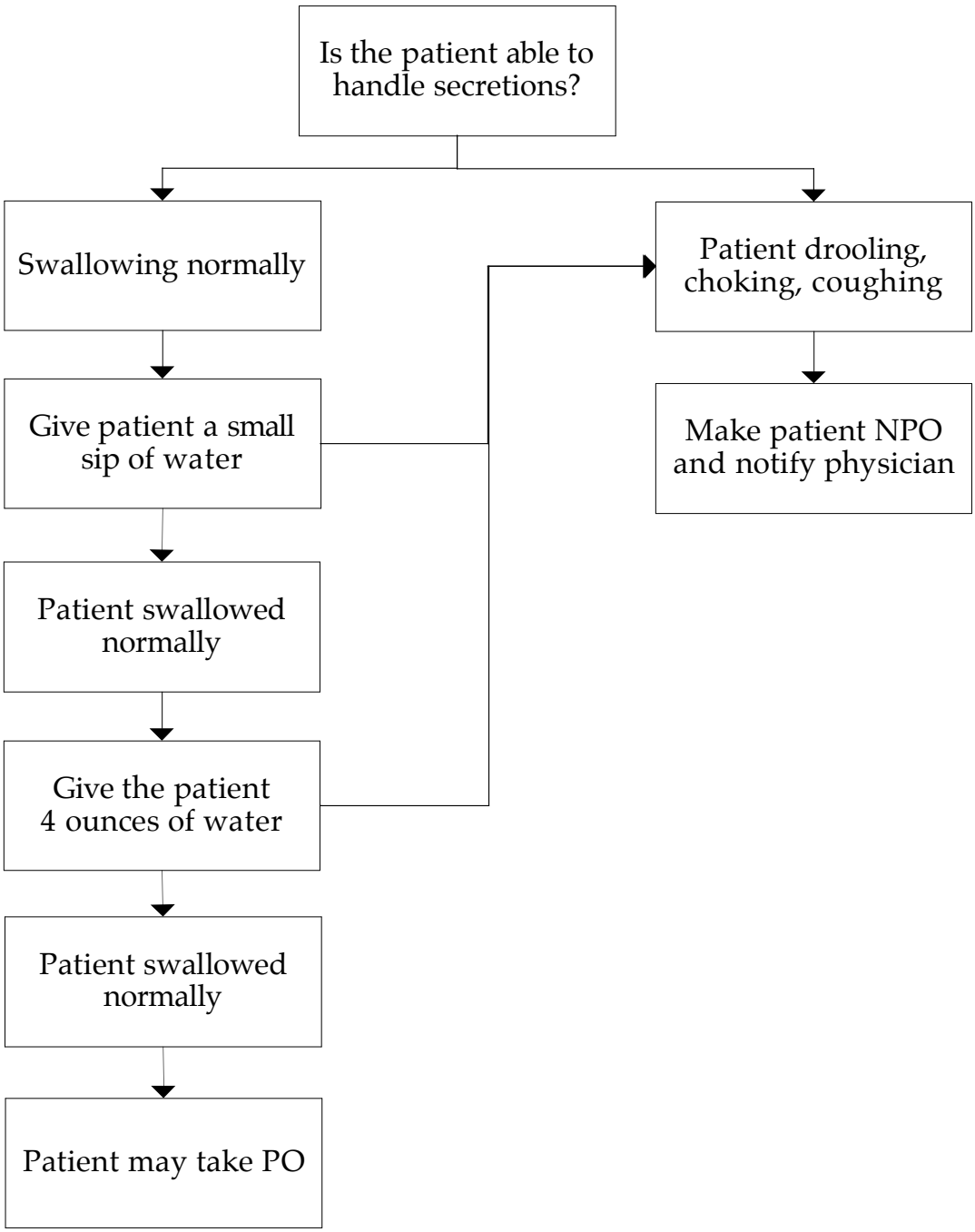
Appendix C – Stroke Dysphagia Screen

Who should be assessed?

Patients who present with clinical TIA, stroke or stroke symptoms.

How do you assess?

Use this algorithm for a quick three-step process!



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Brief Description of Evidence Grading

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

A full explanation of these designators is found in the Foreword of the guideline.

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This section provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Priority Aims and Suggested Measures
- Key Implementation Recommendations
- Knowledge Resources
- Resources Available

Priority Aims and Suggested Measures

1. Increase the percentage of patients age 18 and over presenting within 3 hours, or up to 4.5 hours for patients meeting selected criteria of stroke onset who are evaluated within 10 minutes of arriving in the emergency department.

   Possible measure for accomplishing this aim:

   a. Percentage of patients presenting within 3 hours, or up to 4.5 hours for patients meeting selected criteria of stroke onset who are evaluated by a physician within 10 minutes of arriving in the emergency department.

2. Increase the percentage of patients at high risk for stroke presenting with clinical TIA symptoms within 24 hours who are admitted to the hospital.

   Possible measure for accomplishing this aim:

   a. Percentage of patients admitted to the hospital who have documentation of clinical TIA symptoms within the last 24 hours.

3. Increase the percentage of patients receiving appropriate thrombolytic and antithrombotic therapy for ischemic stroke (use of tPA and aspirin).

   Possible measures for accomplishing this aim:

   a. Percentage of eligible patients with ischemic stroke treated with tPA.

   b. Percentage of patients who are not candidates for tPA treatment who receive aspirin within 24 hours of hospitalization, after a negative head CT, unless contraindicated.

   c. Percentage of patients receiving tPA according to guideline. (Refer to Annotations #29 and 30). (This is similar to TJC process measure.)

   d. Percentage of patients with stroke symptoms who are candidates for tPA with a "door to drug" time (time of arrival to time of drug administration) of less than 60 minutes.

   e. Percentage of patients with stroke symptoms who undergo a computed tomography scan within 25 minutes of arrival in the emergency department.

4. Increase the percentage of non-tPA recipients who have hypertension appropriately managed in the first 48 hours of hospitalization or until neurologically stable.

   Possible measure for accomplishing this aim:

   a. Percentage of non-tPA recipients who have hypertension appropriately managed according to the guideline.

5. Increase the percentage of stroke patients who receive appropriate medical management within the initial 24-48 hours of diagnosis for prevention of complications such as:

   - Hypoglycemia and hyperglycemia
   - Hyperthermia
   - Dehydration
   - Hypoxia
   - Deep vein thrombosis

- Aspiration
- Immobility
- Nutritional status decline

Possible measures for accomplishing this aim:

a. Percentage of patients who receive appropriate intervention for hypoglycemia and hyperglycemia.

b. Percentage of patients who receive appropriate intervention for hyperthermia.

c. Percentage of patients who receive intravenous fluids.

d. Percentage of patients who receive appropriate treatment for hypoxia.

e. Percentage of patients with ischemic stroke with paralysis or other reason for immobility receiving appropriate prevention for venous thromboembolism (subcutaneous heparin or pneumatic compression device).

f. Percentage of patients who are at risk for aspiration who receive an early swallow evaluation.

g. Percentage of patients mobilized from bed within 48 hours of admission.

6. Improve patient and family education of patients with ischemic stroke in both the emergency department and the admitting hospital unit.

   Possible measures for accomplishing this aim:

   a. Percentage of patients presenting in the emergency department with ischemic stroke for whom patient/family education is documented in the medical record.

   b. Percentage of patients admitted to a hospital unit with ischemic stroke for whom patient/family education is documented in the medical record.

Measurement Specification

Possible Success Measure #5f

Percentage of patients who are at risk for aspiration who receive an early swallow evaluation.

Population Definition

Adults patients (18 years and older) initially presenting with acute symptoms of ischemic stroke.

Data of Interest

Patients who are already identified as nothing by mouth upon presentation of acute ischemic symptoms.

Numerator/Denominator Definitions

Numerator: # of patients who were screened for dysphagia before taking any food, fluids or medication (including aspirin) by mouth.

Denominator: # of all patients screened for acute ischemic stroke.

Method/Source of Data Collection

Concurrent and retrospective data collection through administrative data/claims data, and medical record.

Time Frame Pertaining to Data Collection

Data may be collected monthly or quarterly. For The Joint Commission primary stroke center certification, data reporting is quarterly with monthly data points.

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Hospitals should consider developing and implementing critical pathways, standing orders and a stroke process to accomplish rapid evaluation and treatment. The process should expedite the evaluation and treatment of patients who are candidates for intravenous tPA and assure uniform, guideline-driven care for all patients with respect to issues like:
   - ongoing antithrombotic therapy,
   - management of blood pressure,
   - early mobilization, and
   - use of appropriate antiembolism treatment in the paralyzed patient.
2. A process should be in place for the patient and family that will rapidly orient them to the suspected diagnosis, emergency department process, tests to be preformed, tPA treatment and its risks, and other treatment measures to be considered. This could include both face-to-face interactions with the patient and family by the caregiver, as well as teaching tools in written form.

System Improvement

There is evidence that benchmarking can guide and drive quality improvement. Using essentially the same quality indicators as The Joint Commission (TJC) and ICSI, programs like the American Heart Association's Get With The Guidelines-Stroke *(LaBresh, 2008 [C]; Schwamm, 2009b [B])* and the Paul Coverdell National Acute Stroke Registry *(Stoeckle-Roberts, 2006 [C])* have been shown to improve the quality of stroke care.

Centers for Medicare and Medicaid Services

Beginning in 2010, hospitals submitting Medicare claims for stroke must let CMS know if they participate in a database registry for stroke care. For further information on the CMS Final FY 2010 Rule, refer to http://www.cms.gov.

The Joint Commission (TJC) Primary Stroke Center Certification

TJC offers certification as Primary Stroke Centers to hospitals that meet specific qualifications. The process is on the early recognition and management of stroke, and the scope of accreditation includes integrated efforts in public awareness, emergency medical services, emergency department and hospitalization *(Alberts, 2000 [R])*. The link is http://www.jointcommission.org/CertificationPrograms/PrimaryStrokeCenters. Beginning in October 2009, all TJC-accredited hospitals are required to submit the eight National Quality Forum-endorsed stroke consensus measures.

Among the requirements for TJC certification as a Primary Stroke Center is ongoing process improvement guided by data and benchmarking. The quality indicators chosen by TJC overlap with those developed by the ICSI Diagnosis and Initial Treatment of Ischemic Stroke guideline work group. The TJC quality indicators are:

1. Deep Vein Thrombosis (DVT) Prophylaxis*
2. Discharged on Antithrombotics*
3. Patients with Atrial Fibrillation Receiving Anticoagulation Therapy*
4. Thrombolytic Therapy Administered (in eligible patients)

5. Antithrombotic Therapy by End of Hospital Day Two
6. Discharged on Cholesterol Reducing Medication
7. Dysphagia Screening **
8. Stroke Education
9. Smoking Cessation/Advice Counseling **
10. Assessed for Rehabilitation

* Initial standard stroke measure set.

**** Note: indicators for 7 and 9 are not currently (as of 2010) required by the Joint Commission. The remaining eight indicators are required. These eight are also endorsed by the National Quality Forum.

Measures 1, 4, 5, 7 and 8 are similar to or identical to those measures listed in this document and within the scope of the guideline.

Knowledge Products and Resources

Criteria for Selecting Resources

The following resources were selected by the Diagnosis and Treatment of Ischemic Stroke guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

Resources Available to ICSI Members Only

ICSI has a wide variety of knowledge resources that are ***only*** available to ICSI members (these are indicated with an asterisk in far left-hand column of the Resources Available table). In addition to the resources listed in the table, ICSI members have access to a broad range of materials including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Knowledge Resources, go to http://www.icsi.org/improvement_resources. To access these materials on the Web site, you must be logged in as an ICSI member.

The resources in the table on the next page that are not reserved for ICSI members are available to the public free-of-charge.

Resources Available

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	Academy of Neurology	Practice guidelines and tools	Health Care Providers	http://www.aan.com/go/practice/guidelines
	AHA/ASA	Top Ten Things to Know: Use of Telemedicine within Stroke Systems of Care	Health Care Providers	http://www.american-heart.org/presenter.jhtml?identifier=3066480
	AHA/ASA	Top Ten Things to Know: Recommendations for Implementation of Telemedicine within Stroke Systems of Care	Health Care Providers	http://www.american-heart.org/downloadable/heart/12417282768842009050 7_topTenTelemedicinePolicy.pdf
	ASA (American Stroke Association)	• Comprehensive Web site • Patient education resources	Health Care Providers; Patients and Families	http://www.strokeassociation.org
	Association of Black Cardiologists	• Patient education resources	Health Care Providers; Patients and Families	http://www.abcardio.org
	The Brain Attack Coalition	• Contains tools for health care professionals developing systems to enable the rapid diagnosis and treatment of acute stroke • Patient education resources	Health Care Providers; Patients and Families	http://www.stroke-site.org/
	Demaerschalk	This article offers a practical presentation of how telemedicine can be set up for stroke. Helpful information for those considering entry to telestroke arrangements.	Health Care Providers	Mayo Clinic Proc. 2009;84(1):53-64 Stroke Telemedicine
	GLRSN (Great Lakes Regional Stroke Network)	• Comprehensive Web site • Patient education resources	Health Care Providers; Patients and Families	http://tigger.uic.edu/depts/glstrknet/
	Gropen	A report from a cutting-edge consortium which prioritizes system and policy changes to implement stroke systems of care. Recommendations for multistate regional collaboratives to decrease rural/urban disparities through uniform stroke care systems.	Health Care Providers	Stroke 2009;40;1793-1802 Regional Implementation of the Stroke Systems of Care Model: Recommendations of the Northeast Cerebrovascular Consortium
	Minnesota Stroke Association	• Patient education resources	Patients and Families	http://www.strokemn.org/

* Available to ICSI members only.

Resources Available

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	NSA (National Stroke Association)	• Comprehensive Web site • Patient education resources • Links to survivor/caregiver products and services and additional related Web sites	Health Care Providers; Patients and Families	http://www.stroke.org
	NINDS (National Institute of Neurological Disorders and Stroke)	• Links to clinical trials • Vontains entire discussion and guidelines for system change to address stroke treatment	Health Care Providers; Patients and Families	http://www.ninds.nih.gov/
	Neuroscience Nurses Association	• Professional association's Web site	Health Care Providers	http://www.aann.org
	Web MD	Site for medical information for general public	Patients and Families	http://webmd.com/stroke/default.htm

* Available to ICSI members only.