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## Part 9: Adult Stroke

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## Part 9: Adult Stroke

Each year in the United States about 700 000 people of all ages suffer a new or repeat stroke. Approximately 158 000 of these people will die, making stroke the third leading cause of death in the United States.<sup>1,2</sup> Many advances have been made in stroke prevention, treatment, and rehabilitation.<sup>3,4</sup> For example, fibrinolytic therapy can limit the extent of neurologic damage from stroke and improve outcome, but the time available for treatment is limited.<sup>5,6</sup> Healthcare providers, hospitals, and communities must develop systems to increase the efficiency and effectiveness of stroke care.<sup>3</sup> The “7 D’s of Stroke Care”—detection, dispatch, delivery, door (arrival and urgent triage in the emergency department [ED]), data, decision, and drug administration—highlight the major steps in diagnosis and treatment and the key points at which delays can occur.<sup>7,8</sup>

This chapter summarizes the management of acute stroke in the adult patient. It summarizes out-of-hospital care through the first hours of therapy. For additional information about the management of acute ischemic stroke, see the AHA/American Stroke Association (ASA) guidelines for the management of acute ischemic stroke.<sup>9,10</sup>

### Management Goals

The goal of stroke care is to minimize brain injury and maximize patient recovery. The AHA and ASA developed a community-oriented “Stroke Chain of Survival” that links actions to be taken by patients, family members, and healthcare providers to maximize stroke recovery. These links are

- Rapid recognition and reaction to stroke warning signs
- Rapid emergency medical services (EMS) dispatch
- Rapid EMS system transport and hospital prenotification
- Rapid diagnosis and treatment in the hospital

The AHA ECC stroke guidelines focus on the initial out-of-hospital and ED assessment and management of the patient with acute stroke as depicted in the algorithm Goals for Management of Patients With Suspected Stroke (Figure). The time goals of the National Institute of Neurological Disorders and Stroke (NINDS)<sup>11</sup> are illustrated along the left side of the algorithm as clocks with a sweep hand depicting the goal in minutes from ED arrival to task completion to remind the clinician of the time-sensitive nature of management of acute ischemic stroke.

The sections below summarize the principles and goals of stroke assessment and management, highlighting key controversies, new recommendations, and training issues. The text refers to the numbered boxes in the algorithm.

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### Stroke Recognition and EMS Care

#### Stroke Warning Signs

Identifying clinical signs of possible stroke (Box 1) is important because fibrinolytic treatment must be provided within a few hours of onset of symptoms.<sup>5,12</sup> Most strokes occur at home, and only half of all victims of acute stroke use EMS for transport to the hospital.<sup>13–15</sup> In addition, stroke victims often deny or rationalize<sup>16</sup> their symptoms. This can delay EMS access and treatment and result in increased morbidity and mortality. Even high-risk patients fail to recognize the signs of a stroke.<sup>16</sup> Community and professional education is essential,<sup>17</sup> and it has successfully increased the proportion of stroke victims treated with fibrinolytic therapy.<sup>18,19</sup>

The signs and symptoms of a stroke may be subtle. They include sudden weakness or numbness of the face, arm, or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; or sudden severe headache with no known cause.

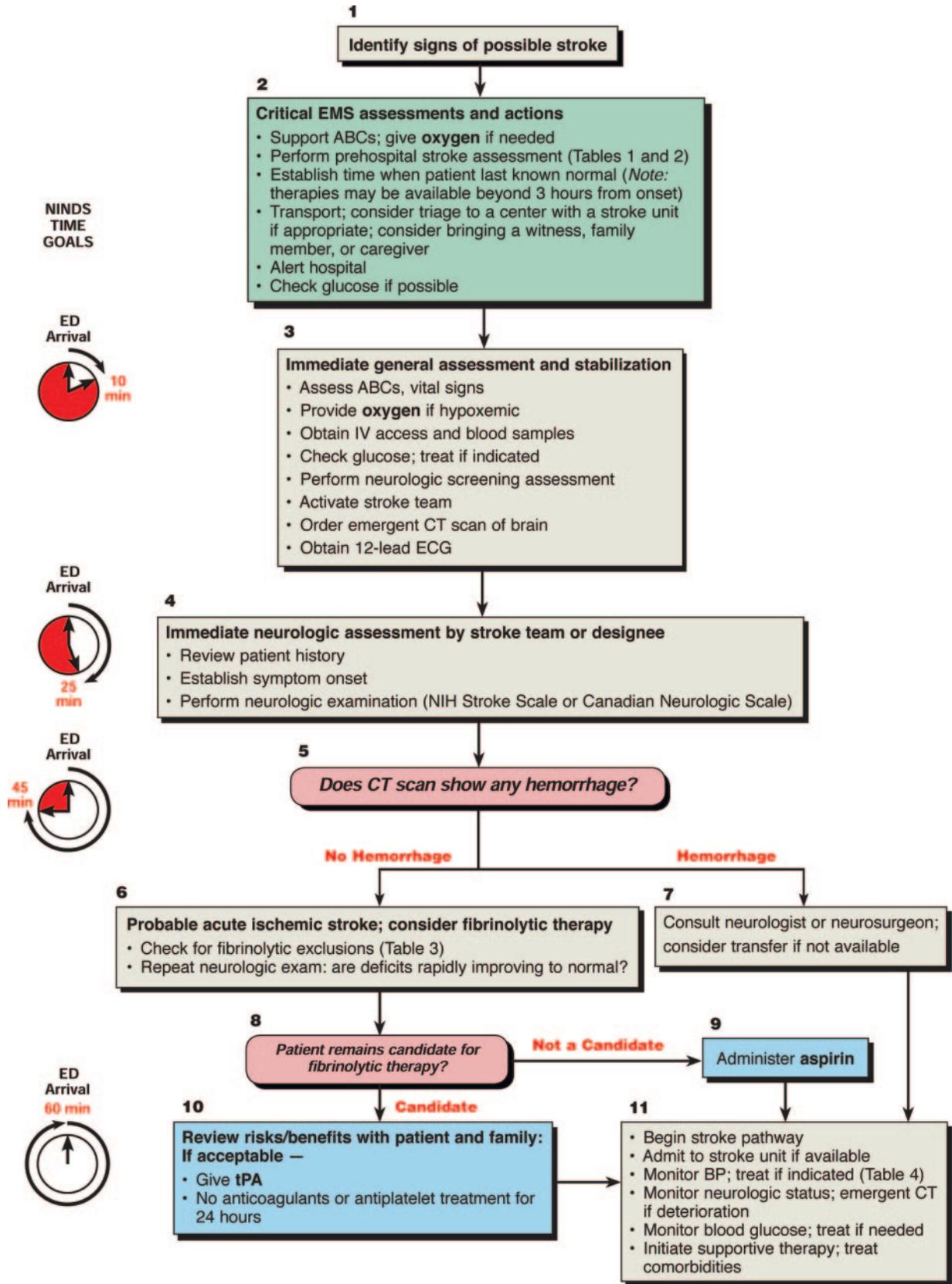
#### EMS Dispatch

Currently <10% of patients with acute ischemic stroke are ultimately eligible for fibrinolytic therapy because they fail to arrive at the receiving hospital within 3 hours of onset of symptoms.<sup>20–24</sup>

EMS systems must provide education and training to minimize delays in prehospital dispatch, assessment, and transport. Emergency medical dispatchers must identify potential stroke victims and provide high-priority dispatch to patients with possible stroke. EMS providers must be able to support cardiopulmonary function, perform rapid stroke assessment, establish time of onset of symptoms (or last time the patient was known to be normal), triage and transport the patient, and provide prearrival notification to the receiving hospital (Box 2).<sup>25–28</sup>

#### Stroke Assessment Tools

EMS providers can identify stroke patients with reasonable sensitivity and specificity, using abbreviated out-of-hospital tools such as the Cincinnati Prehospital Stroke Scale (CPSS)<sup>27,29–31</sup> (Table 1) or the Los Angeles Prehospital Stroke Screen (LAPSS) (Table 2).<sup>32,33</sup> The CPSS is based on physical examination only. The EMS provider checks for 3 physical findings: facial droop, arm weakness, and speech abnormalities. The presence of a single abnormality on the CPSS has a sensitivity of 59% and a specificity of 89% when scored by prehospital providers.<sup>30</sup> The LAPSS requires the examiner to rule out other causes of altered level of consciousness (eg, history of seizures, hypoglycemia) and then identify asymmetry in any of 3 examination categories: facial smile or grimace, grip, and arm strength. The LAPSS has a specificity of 97% and a sensitivity of 93%.<sup>32,33</sup>

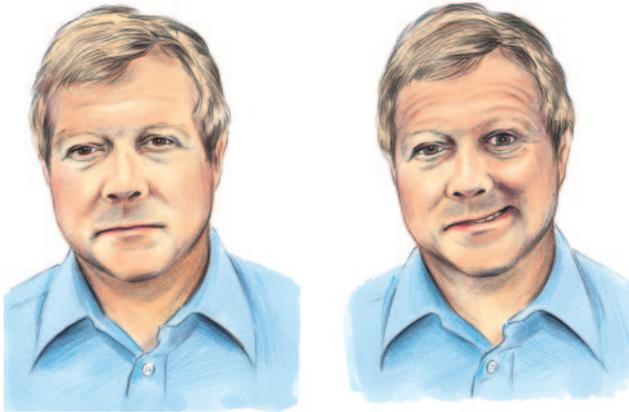


Goals for Management of Patients With Suspected Stroke Algorithm.

**TABLE 1. The Cincinnati Prehospital Stroke Scale****Facial Droop (have patient show teeth or smile):**

- Normal—both sides of face move equally
- Abnormal—one side of face does not move as well as the other side

Left: normal. Right: stroke patient with facial droop (right side of face).  
Kothari R, et al. *Acad Emerg Med.* 1997;4:986–990.

**Arm Drift (patient closes eyes and holds both arms straight out for 10 seconds):**

- Normal—both arms move the same or both arms do not move at all (other findings, such as pronator drift, may be helpful)
- Abnormal—one arm does not move or one arm drifts down compared with the other

**Abnormal Speech (have the patient say “you can’t teach an old dog new tricks”):**

- Normal—patient uses correct words with no slurring
- Abnormal—patient slurs words, uses the wrong words, or is unable to speak

Interpretation: If any 1 of these 3 signs is abnormal, the probability of a stroke is 72%.

With standard training in stroke recognition, paramedics have demonstrated a sensitivity of 61% to 66% for identifying patients with stroke.<sup>31,34,35</sup> After training in using a stroke assessment tool, paramedic sensitivity for identifying patients with stroke increased to 86% to 97% (LOE 3 to 5).<sup>33,36,37</sup> Therefore, all paramedics and emergency medical technicians-basic (EMT-basic) should be trained in the recognition of stroke using a validated, abbreviated out-of-hospital screening tool, such as the CPSS or the LAPSS (Class IIa).

**Transport and Care**

Once EMS providers suspect the diagnosis of stroke, they should establish the time of onset of symptoms. This time represents time zero for the patient. If the patient wakes from sleep or is found with symptoms of a stroke, time zero is the last time the patient was observed to be normal. EMS providers must rapidly deliver the patient to a medical facility capable of providing acute stroke care and provide prearrival notification to the receiving facility.<sup>25</sup>

EMS providers should consider transporting a witness, family member, or caregiver with the patient to verify the time of onset of stroke symptoms. En route to the facility

providers should support cardiopulmonary function, monitor neurologic status, and if authorized by medical control, check blood glucose.

Patients with acute stroke are at risk for respiratory compromise from aspiration, upper airway obstruction, hypoventilation, and (rarely) neurogenic pulmonary edema. The combination of poor perfusion and hypoxemia will exacerbate and extend ischemic brain injury, and it has been associated with worse outcome from stroke.<sup>38</sup> Although one small randomized clinical trial (LOE 2)<sup>39</sup> of selected stroke patients suggested a transient improvement in clinical deficit and MRI abnormalities following 8 hours of high-flow supplementary oxygen (by face mask), a larger quasi-randomized trial (LOE 3)<sup>40</sup> did not show any clinical benefit from routine administration of low-flow (3 L/min) oxygen for 24 hours to all patients with ischemic stroke. In contrast, the administration of supplementary oxygen to the subset of stroke patients who are hypoxemic is indirectly supported by several studies showing improved functional outcomes and survival of stroke patients treated in dedicated stroke units in which higher supplementary oxygen concentrations were used (LOE 7).<sup>38,39,41,42</sup>

Both out-of-hospital and in-hospital medical personnel should administer supplementary oxygen to hypoxemic (ie, oxygen saturation <92%) stroke patients (Class I) or those with unknown oxygen saturation. Clinicians may consider giving oxygen to patients who are not hypoxemic (Class IIb).

The role of stroke centers and stroke units continues to be debated.<sup>43</sup> Initial evidence<sup>44–50</sup> indicated a favorable benefit from triage of stroke patients directly to designated stroke centers (Class IIb), but the concept of routine out-of-hospital triage of stroke patients requires more rigorous evaluation.

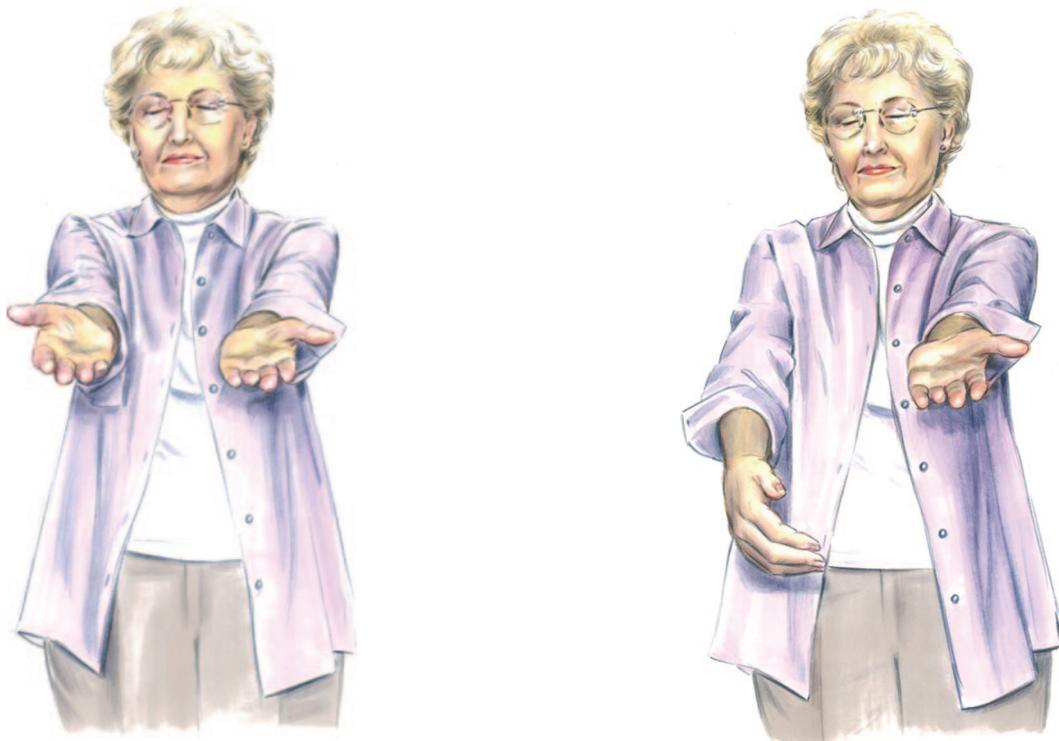
Each receiving hospital should define its capability for treating patients with acute stroke and should communicate this information to the EMS system and the community. Although not every hospital is capable of organizing the necessary resources to safely administer fibrinolytic therapy, every hospital with an ED should have a written plan describing how patients with acute stroke are to be managed in that institution. The plan should detail the roles of healthcare professionals in the care of patients with acute stroke and define which patients will be treated with fibrinolytic therapy at that facility and when transfer to another hospital with a dedicated stroke unit is appropriate (Class IIa).

Multiple randomized clinical trials and meta-analyses in adults (LOE 1)<sup>51–54</sup> document consistent improvement in 1-year survival rate, functional outcomes, and quality of life when patients hospitalized with acute stroke are cared for in a dedicated stroke unit by a multidisciplinary team experienced in managing stroke. Although the studies reported were conducted outside the United States in in-hospital units that provided both acute care and rehabilitation, the improved outcomes were apparent very early in the stroke care. These results should be relevant to the outcome of dedicated stroke units staffed with experienced multidisciplinary teams in the United States. When such a facility is available within a reasonable transport interval, stroke patients who require hospitalization should be admitted there (Class I).

**TABLE 2. Los Angeles Prehospital Stroke Screen (LAPSS)**

For evaluation of acute, noncomatose, nontraumatic neurologic complaint. If items 1 through 6 are all checked “Yes” (or “Unknown”), provide prearrival notification to hospital of potential stroke patient. If any item is checked “No,” return to appropriate treatment protocol. Interpretation: 93% of patients with stroke will have a positive LAPSS score (sensitivity=93%), and 97% of those with a positive LAPSS score will have a stroke (specificity=97%). Note that the patient may still be experiencing a stroke if LAPSS criteria are not met.

Criteria	Yes	Unknown	No
1. Age >45 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. History of seizures or epilepsy absent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Symptom duration <24 hours	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. At baseline, patient is not wheelchair bound or bedridden	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Blood glucose between 60 and 400	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Obvious asymmetry (right vs left) in any of the following 3 exam categories (must be unilateral):	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Equal</b>	<b>R Weak</b>	<b>L Weak</b>
Facial smile/grimace	<input type="checkbox"/>	<input type="checkbox"/> Droop	<input type="checkbox"/> Droop
Grip	<input type="checkbox"/>	<input type="checkbox"/> Weak grip <input type="checkbox"/> No grip	<input type="checkbox"/> Weak grip <input type="checkbox"/> No grip
Arm strength	<input type="checkbox"/>	<input type="checkbox"/> Drifts down <input type="checkbox"/> Falls rapidly	<input type="checkbox"/> Drifts down <input type="checkbox"/> Falls rapidly



One-sided motor weakness (right arm).

Kidwell CS, Saver JL, Schubert GB, Eckstein M, Starkman S. Design and retrospective analysis of the Los Angeles prehospital stroke screen (LAPSS). *Prehosp Emerg Care.* 1998;2:267–273.

Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field: prospective validation of the Los Angeles Prehospital Stroke Screen (LAPSS). *Stroke.* 2000;31:71–76.

### In-Hospital Care

#### Initial ED Assessment and Stabilization

Protocols should be used in the ED to minimize delay to definitive diagnosis and therapy.<sup>28</sup> As a goal, ED personnel should assess the patient with suspected stroke within 10 minutes of arrival in the ED (Box 3). General care includes

assessment and support of airway, breathing, and circulation and evaluation of baseline vital signs. We recommend that providers administer oxygen to hypoxemic patients in the ED (Class I) and consider oxygen administration for patients without hypoxemia (Class IIb).

Establish or confirm intravenous (IV) access and obtain blood samples for baseline studies (blood count, coagulation studies, blood glucose, etc). Promptly treat hypoglycemia. The ED physician should perform a neurologic screening assessment, order an emergent computerized tomography (CT) scan of the brain, and activate the stroke team or arrange consultation with a stroke expert.

A 12-lead ECG does not take priority over the CT scan, but it may identify a recent acute myocardial infarction or arrhythmias (eg, atrial fibrillation) as the cause of an embolic stroke. If the patient is hemodynamically stable, treatment of other arrhythmias, including bradycardia, premature atrial or ventricular contractions, or defects or blocks in atrioventricular conduction, may not be necessary.<sup>55</sup> There is general agreement to recommend cardiac monitoring during the initial evaluation of patients with acute ischemic stroke to detect atrial fibrillation and potentially life-threatening arrhythmias.<sup>10</sup>

### Assessment

The stroke team, another expert, or an emergency physician with access to remote stroke expert support will review the patient history and verify time of onset of symptoms (Box 4).<sup>56–58</sup> This may require interviewing out-of-hospital providers, witnesses, and family members to establish the time that the patient was last known to be normal. Neurologic assessment is performed incorporating either the National Institutes of Health (NIH) Stroke Scale or Canadian Neurologic Scale (see the ASA website: [www.strokeassociation.org](http://www.strokeassociation.org)).

Management of hypertension in the stroke patient is controversial. For patients eligible for fibrinolytic therapy, however, control of blood pressure is required to reduce the potential risk of bleeding. If a patient who is otherwise eligible for treatment with tissue plasminogen activator (tPA) has elevated blood pressure, providers can try to lower it to a systolic pressure of <185 mm Hg and a diastolic blood pressure of <110 mm Hg. Because the maximum interval from onset of stroke until effective treatment of stroke with tPA is limited, most patients with sustained hypertension above these levels (ie, systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg) cannot be treated with IV tPA (Table 4).<sup>9,10</sup>

Ideally the CT scan should be completed within 25 minutes of the patient's arrival in the ED and should be read within 45 minutes of ED arrival (Box 5). Emergent CT or magnetic resonance imaging (MRI) scans of patients with suspected stroke should be promptly evaluated by a physician with expertise in interpretation of these studies.<sup>59,60</sup> During the first few hours of an ischemic stroke, the noncontrast CT scan may not indicate signs of brain ischemia. If the CT scan shows no evidence of hemorrhage, the patient may be a candidate for fibrinolytic therapy (Boxes 6 and 8).

If hemorrhage is noted on the CT scan, the patient is not a candidate for fibrinolytic therapy. Consult a neurologist or neurosurgeon and consider transfer as needed for appropriate care (Box 7).

If hemorrhage is not present on the initial CT scan and the patient is not a candidate for fibrinolytic therapy for other reasons, consider administration of aspirin (Box 9) either

rectally or orally after the patient is screened for dysphagia (see below). Admit the patient to a stroke unit (if available) for careful monitoring (Box 11). Although the aspirin is not a time-critical intervention, it is appropriate to administer aspirin in the ED if the patient is not a candidate for fibrinolysis.

### Fibrinolytic Therapy (Boxes 6, 8, and 10)

If the CT scan shows no hemorrhage, the probability of acute ischemic stroke remains. The physician should review the inclusion and exclusion criteria for IV fibrinolytic therapy (Table 3) and perform a repeat neurologic examination (incorporating the NIH Stroke Scale or Canadian Neurologic Scale). If the patient's neurologic signs are spontaneously clearing (ie, function is rapidly improving toward normal) and is near baseline, fibrinolytic administration is not recommended (Box 6).<sup>10</sup>

As with all medications, fibrinolytics have potential adverse effects. The physician must verify that there are no exclusion criteria, consider the risks and benefits to the patient, and be prepared to monitor and treat any potential complications. The major complication of IV tPA for stroke is symptomatic intracranial hemorrhage. This complication occurred in 6.4% of the 312 patients treated in the NINDS trials<sup>5</sup> and 4.6% of the 1135 patients treated in 60 Canadian centers.<sup>61</sup> A meta-analysis of 15 published case series on the open-label use of tPA for acute ischemic stroke in general clinical practice shows a symptomatic hemorrhage rate of 5.2% of 2639 patients treated.<sup>62</sup> Other complications include orolingual angioedema (occurs in about 1.5% of patients), acute hypotension, and systemic bleeding. In one large prospective registry, major systemic bleeding was uncommon (0.4%) and usually occurred at the site of femoral groin puncture for acute angiography.<sup>61,63</sup>

If the patient remains a candidate for fibrinolytic therapy (Box 8), the physician should discuss the risks and potential benefits of the therapy with the patient or family if available (Box 10). After this discussion, if the patient/family elects to proceed with fibrinolytic therapy, give the patient tPA and begin the stroke pathway of care (see below). Neither anticoagulants nor antiplatelet treatment is administered for 24 hours after administration of tPA, typically until a follow-up CT scan at 24 hours shows no hemorrhage.

Several studies (LOE 1)<sup>5,12,61</sup> have documented a higher likelihood of good to excellent functional outcome when tPA is administered to adult patients with acute ischemic stroke within 3 hours of onset of symptoms. These results are obtained when tPA is administered by physicians in hospitals with a stroke protocol that rigorously adheres to the eligibility criteria and therapeutic regimen of the NINDS protocol. These results have been supported by subsequent 1-year follow-up,<sup>64</sup> reanalysis of the NINDS data,<sup>65</sup> and a meta-analysis (LOE 1).<sup>66</sup> Evidence from prospective, randomized (LOE 1)<sup>5,12,65,67</sup> studies in adults also documents a greater likelihood of benefit the earlier treatment is begun. Many physicians have emphasized the flaws in the NINDS trials.<sup>68,69</sup> But additional analyses of the original NINDS data by an independent group of investigators confirmed the validity of the results,<sup>65</sup> veri-

**TABLE 3. Fibrinolytic Checklist**

Use of tPA in Patients With Acute Ischemic Stroke

All boxes must be checked before tPA can be given.

Note: The following checklist includes FDA-approved indications and contraindications for tPA administration for acute ischemic stroke. A physician with expertise in acute stroke care may modify this list.

*Inclusion Criteria (all Yes boxes in this section must be checked):*

**Yes**

- Age 18 years or older?
- Clinical diagnosis of ischemic stroke with a measurable neurologic deficit?
- Time of symptom onset (when patient was last seen normal) well established as <180 minutes (3 hours) before treatment would begin?

*Exclusion Criteria (all No boxes in "Contraindications" section must be checked):*

**Contraindications:**

**No**

- Evidence of intracranial hemorrhage on pretreatment noncontrast head CT?
- Clinical presentation suggestive of subarachnoid hemorrhage even with normal CT?
- CT shows multilobar infarction (hypodensity greater than one third cerebral hemisphere)?
- History of intracranial hemorrhage?
- Uncontrolled hypertension: At the time treatment should begin, systolic pressure remains >185 mm Hg or diastolic pressure remains >110 mm Hg despite repeated measurements?
- Known arteriovenous malformation, neoplasm, or aneurysm?
- Witnessed seizure at stroke onset?
- Active internal bleeding or acute trauma (fracture)?
- Acute bleeding diathesis, including but not limited to
  - Platelet count <100 000/mm<sup>3</sup>?
  - Heparin received within 48 hours, resulting in an activated partial thromboplastin time (aPTT) that is greater than upper limit of normal for laboratory?
  - Current use of anticoagulant (eg, warfarin sodium) that has produced an elevated international normalized ratio (INR) >1.7 or prothrombin time (PT) >15 seconds?\*
- Within 3 months of intracranial or intraspinal surgery, serious head trauma, or previous stroke?
- Arterial puncture at a noncompressible site within past 7 days?

**Relative Contraindications/Precautions:**

Recent experience suggests that under some circumstances—with careful consideration and weighing of risk-to-benefit ratio—patients may receive fibrinolytic therapy despite one or more relative contraindications. Consider the pros and cons of tPA administration carefully if any of these relative contraindications is present:

- Only minor or rapidly improving stroke symptoms (clearing spontaneously)
- Within 14 days of major surgery or serious trauma
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Recent acute myocardial infarction (within previous 3 months)
- Postmyocardial infarction pericarditis
- Abnormal blood glucose level (<50 or >400 mg/dL [ $<2.8$  or  $>22.2$  mmol/L])

\*In patients without recent use of oral anticoagulants or heparin, treatment with tPA can be initiated before availability of coagulation study results but should be discontinued if the INR is >1.7 or the partial thromboplastin time is elevated by local laboratory standards.

fying that improved outcomes in the tPA treatment arm persist even when imbalances in the baseline stroke severity among treatment groups is corrected.<sup>70</sup>

Administration of IV tPA to patients with acute ischemic stroke who meet the NINDS eligibility criteria is recommended if tPA is administered by physicians in the setting of a clearly defined protocol, a knowledgeable team, and institutional commitment (Class I). It is important to note that the superior outcomes reported in both community and tertiary care hospitals in the NINDS trials have been difficult to replicate in hospitals with less experience in, and institutional commitment to, acute stroke care.<sup>71,72</sup> There is strong evi-

dence to avoid all delays and treat patients as soon as possible. Failure to adhere to protocol is associated with an increased rate of complications, particularly the risk of symptomatic intracranial hemorrhage.<sup>71,73</sup>

Community hospitals have reported outcomes comparable to the results of the NINDS trials after implementing a stroke program with a focus on quality improvement.<sup>61,74,75</sup> The experience of the Cleveland Clinic system is instructive.<sup>71,75</sup> A quality improvement program increased compliance with the tPA treatment protocol in 9 community hospitals, and the rate of symptomatic intracerebral hemorrhage fell from 13.4% to 6.4%.<sup>75</sup>

TABLE 4. Approach to Elevated Blood Pressure in Acute Ischemic Stroke<sup>9</sup>

Blood Pressure Level, mm Hg	Treatment
<b>A. Not eligible for fibrinolytic therapy</b>	
Systolic $\leq$ 220 OR diastolic $\leq$ 120	Observe unless other end-organ involvement (eg, aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy) Treat other symptoms of stroke (eg, headache, pain, agitation, nausea, vomiting) Treat other acute complications of stroke, including hypoxia, increased intracranial pressure, seizures, or hypoglycemia
Systolic $>$ 220 OR diastolic 121 to 140	Labetalol 10 to 20 mg IV for 1 to 2 min May repeat or double every 10 min (max dose 300 mg) OR Nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/h every 5 min to max of 15 mg/h Aim for a 10% to 15% reduction in blood pressure
Diastolic $>$ 140	Nitroprusside 0.5 $\mu$ g/kg per minute IV infusion as initial dose with continuous blood pressure monitoring Aim for a 10% to 15% reduction in blood pressure
<b>B. Eligible for fibrinolytic therapy</b>	
<b>Pretreatment</b>	
Systolic $>$ 185 OR diastolic $>$ 110	Labetalol 10 to 20 mg IV for 1 to 2 min May repeat 1 time or nitropaste 1 to 2 in
<b>During/after treatment</b>	
1. Monitor blood pressure	Check blood pressure every 15 min for 2 h, then every 30 min for 6 h, and finally every hour for 16 h
2. Diastolic $>$ 140	Sodium nitroprusside 0.5 $\mu$ g/kg per minute IV infusion as initial dose and titrate to desired blood pressure
3. Systolic $>$ 230 OR diastolic 121 to 140	Labetalol 10 mg IV for 1 to 2 min May repeat or double labetalol every 10 min to maximum dose of 300 mg, or give initial labetalol dose, then start labetalol drip at 2 to 8 mg/min OR Nicardipine 5 mg/h IV infusion as initial dose and titrate to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h; if blood pressure is not controlled by labetalol, consider sodium nitroprusside
4. Systolic 180 to 230 OR diastolic 105 to 120	Labetalol 10 mg IV for 1 to 2 min May repeat or double labetalol every 10 to 20 min to maximum dose of 300 mg, or give initial labetalol dose, then start labetalol drip at 2 to 8 mg/min

There is a relationship between violations of the NINDS treatment protocol and increased risk of symptomatic intracerebral hemorrhage and death.<sup>62</sup> In Germany there was an increased risk of death after administration of tPA for acute ischemic stroke in hospitals that treated  $\leq$ 5 patients per year, which suggests that clinical experience is an important factor in ensuring adherence to protocol.<sup>63</sup> Adding a dedicated stroke team to a community hospital can increase the number of patients with acute stroke treated with fibrinolytic therapy and produce excellent clinical outcomes.<sup>76</sup> These findings show that it is important to have an institutional commitment to ensure optimal patient outcomes.

Evidence from 2 prospective randomized studies in adults and a meta-analysis<sup>77,78</sup> and additional case series<sup>79–86</sup> documented improved outcome from therapies such as intra-arterial tPA. Thus, for patients with acute ischemic stroke who are not candidates for standard IV fibrinolysis, administration of intra-arterial fibrinolysis in centers that have the resources and expertise available may be considered within the first few hours after the onset of symptoms (Class IIb). Intra-arterial administration of tPA has not yet been approved by the US Food and Drug Administration (FDA).

### General Stroke Care

Admit the patient to a stroke unit (if available) for careful observation (Box 11), including monitoring of blood pressure and neurologic status and treatment of hypertension if indicated (Table 4). If the patient's neurologic status deteriorates, order an emergent CT scan to determine if cerebral edema or hemorrhage is responsible for the deterioration and treat if possible.

Hyperglycemia is associated with worse clinical outcome in patients with acute ischemic stroke than is normoglycemia,<sup>87–94</sup> but there is no direct evidence that active glucose control improves clinical outcome.<sup>95,96</sup> There is evidence that insulin treatment of hyperglycemia in other critically ill patients improves survival rates (LOE 7 for stroke).<sup>97</sup> For this reason administration of IV or subcutaneous insulin may be considered (Class IIb) to lower blood glucose in patients with acute ischemic stroke when the serum glucose level is  $>$ 10 mmol/L ( $>$ about 200 mg/dL).

Additional stroke care includes support of the airway, oxygenation and ventilation, and nutritional support. Administer approximately 75 to 100 mL/h of normal saline to maintain euvolemia if needed. Seizure prophylaxis is not recommended, but we recommend treatment of acute seizures

followed by administration of anticonvulsants to prevent further seizures.<sup>98</sup> Monitor the patient for signs of increased intracranial pressure. Continued control of blood pressure is required to reduce the potential risk of bleeding (see Table 4).

All patients with stroke should be screened for dysphagia before anything is given by mouth. A simple bedside screening evaluation involves asking the patient to sip water from a cup. If the patient can sip and swallow without difficulty, the patient is asked to take a large gulp of water and swallow. If there are no signs of coughing or aspiration after 30 seconds, then it is safe for the patient to have a thickened diet until formally assessed by a speech pathologist. Medications may be given in applesauce or jam. Any patient who fails a swallow test may be given medications such as aspirin rectally or if appropriate via the IV, intramuscular, or subcutaneous route.

### Temperature Control

Treat fever  $>37.5^{\circ}\text{C}$  ( $99.5^{\circ}\text{F}$ ). Hyperthermia in the setting of acute cerebral ischemia is associated with increased morbidity and mortality.<sup>99–102</sup>

Induced hypothermia can exert neuroprotective effects following stroke.<sup>103–111</sup> Hypothermia has been shown to improve survival and functional outcome in patients following resuscitation from ventricular fibrillation (VF) sudden cardiac arrest (LOE 1<sup>112</sup>; LOE 2<sup>113</sup>), but it has not been shown to be effective for acute ischemic stroke in controlled human trials. In some small human pilot studies and in animal models, hypothermia ( $33^{\circ}\text{C}$  to  $36^{\circ}\text{C}$ ) for acute ischemic stroke has been shown to be relatively safe and feasible (LOE 3 to 5).<sup>106,109,110</sup> Although effects of hypothermia on both global and focal cerebral ischemia in animals have been promising,<sup>111</sup> cooling to  $\leq 33^{\circ}\text{C}$  appears to be associated with increased complications, including hypotension, cardiac arrhythmias, cardiac failure, pneumonia, thrombocytopenia, and a rebound increase in intracranial pressure during rewarming.<sup>104,105,107,108,111</sup>

Ongoing larger clinical trials of induced hypothermia will likely increase our understanding of the role of hypothermia in acute cerebral ischemia. There is insufficient scientific evidence to recommend for or against the use of hypothermia in the treatment of acute ischemic stroke (Class Indeterminate).

### Summary

Advances in stroke care will have the greatest effect on stroke outcome if care is delivered within a system designed to improve both efficiency and effectiveness. The ultimate goal of stroke therapy is to maximize functional recovery.

### References

1. *Know the Facts, Get the Stats: Our Guide to Heart Disease, Stroke and Risks*. Dallas, Tex: American Heart Association; 2002. Publication No. 55-0576 2002-04.
2. American Heart Association. *Heart Disease and Stroke Statistics—2006 Update*. Dallas, Tex: American Heart Association. In press.
3. Schwamm LH, Pancioli A, Acker JE III, Goldstein LB, Zorowitz RD, Shephard TJ, Moyer P, Gorman M, Johnston SC, Duncan PW, Gorelick P, Frank J, Stranne SK, Smith R, Federspiel W, Horton KB, Magnis E, Adams RJ. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. *Circulation*. 2005;111:1078–1091.
4. Dobkin BH. Clinical practice: rehabilitation after stroke. *N Engl J Med*. 2005;352:1677–1684.

5. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333:1581–1587.
6. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA*. 2000;283:1145–1150.
7. Hazinski M. D-mystifying recognition and management of stroke. *Curr Emerg Cardiac Care*. 1996;7:8.
8. Acute stroke: current treatment and paradigms. In: Cummins RO, Field JM, Hazinski MF, eds. *ACLS: Principles and Practice*. Dallas, Tex: American Heart Association; 2003:437–482.
9. Adams H, Adams R, Del Zoppo G, Goldstein LB. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update: a scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. *Stroke*. 2005;36:916–923.
10. Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. *Stroke*. 2003;34:1056–1083.
11. Marler JR, Jones PW, Emr M, eds. *Setting New Directions for Stroke Care: Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke*. Bethesda, Md: National Institute of Neurological Disorders and Stroke; 1997.
12. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768–774.
13. Barsan WG, Brott TG, Olinger CP, Adams HP Jr, Haley EC Jr, Levy DE. Identification and entry of the patient with acute cerebral infarction. *Ann Emerg Med*. 1988;17:1192–1195.
14. Barsan WG, Brott TG, Broderick JP, Haley EC, Levy DE, Marler JR. Time of hospital presentation in patients with acute stroke. *Arch Intern Med*. 1993;153:2558–2561.
15. Pepe PE, Zachariah BS, Sayre MR, Floccare D. Ensuring the chain of recovery for stroke in your community. Chain of Recovery Writing Group. *Prehosp Emerg Care*. 1998;2:89–95.
16. Feldmann E, Gordon N, Brooks JM, Brass LM, Fayad PB, Sawaya KL, Nazareno F, Levine SR. Factors associated with early presentation of acute stroke. *Stroke*. 1993;24:1805–1810.
17. Lyden P, Rapp K, Babcock T, et al. Ultra-rapid identification, triage, and enrollment of stroke patients into clinical trials. *J Stroke Cerebrovasc Dis*. 1994;2:106–113.
18. Morgenstern LB, Staub L, Chan W, Wein TH, Bartholomew LK, King M, Felberg RA, Burgin WS, Groff J, Hickenbottom SL, Saldin K, Demchuk AM, Kalra A, Dhingra A, Grotta JC. Improving delivery of acute stroke therapy: the TLL Temple Foundation Stroke Project. *Stroke*. 2002;33:160–166.
19. Morgenstern LB, Bartholomew LK, Grotta JC, Staub L, King M, Chan W. Sustained benefit of a community and professional intervention to increase acute stroke therapy. *Arch Intern Med*. 2003;163:2198–2202.
20. Cocho D, Belvis R, Marti-Fabregas J, Molina-Porcel L, Diaz-Manera J, Aleu A, Pagonabarraga J, Garcia-Bargo D, Mauri A, Marti-Vilalta JL. Reasons for exclusion from thrombolytic therapy following acute ischemic stroke. *Neurology*. 2005;64:719–720.
21. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. *Neurology*. 2005;64:654–659.
22. Katzan IL, Hammer MD, Hixson ED, Furlan AJ, Abou-Chebl A, Nadzam DM. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol*. 2004;61:346–350.
23. Kleindorfer D, Kissela B, Schneider A, Woo D, Khoury J, Miller R, Alwell K, Gebel J, Szaflarski J, Pancioli A, Jauch E, Moomaw C, Shukla R, Broderick JP. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. *Stroke*. 2004;35:e27–e29.
24. O'Connor R, McGraw P, Edelson L. Thrombolytic therapy for acute ischemic stroke: why the majority of patients remain ineligible for treatment. *Ann Emerg Med*. 1999;33:9–14.
25. Sayre MR, Swor RA, Honeykutt LK. Prehospital identification and treatment. In: Marler JR, Jones PW, Emr M, eds. *Setting New Directions for Stroke Care: Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke*. Bethesda, Md: National Institute of Neurological Disorders and Stroke; 1997:35–44.

26. Zachariah B, Dunford J, Van Cott CC. Dispatch life support and the acute stroke patient: making the right call. In: *Proceedings of the National Institute of Neurological Disorders and Stroke*. Bethesda, Md: National Institute of Neurological Disorders and Stroke; 1991:29–33.
27. Kothari R, Barsan W, Brott T, Broderick J, Ashbrock S. Frequency and accuracy of prehospital diagnosis of acute stroke. *Stroke*. 1995;26:937–941.
28. A systems approach to immediate evaluation and management of hyperacute stroke: experience at eight centers and implications for community practice and patient care. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. *Stroke*. 1997;28:1530–1540.
29. Kothari R, Hall K, Brott T, Broderick J. Early stroke recognition: developing an out-of-hospital NIH Stroke Scale. *Acad Emerg Med*. 1997;4:986–990.
30. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati Prehospital Stroke Scale: reproducibility and validity. *Ann Emerg Med*. 1999;33:373–378.
31. Smith WS, Isaacs M, Corry MD. Accuracy of paramedic identification of stroke and transient ischemic attack in the field. *Prehosp Emerg Care*. 1998;2:170–175.
32. Kidwell CS, Saver JL, Schubert GB, Eckstein M, Starkman S. Design and retrospective analysis of the Los Angeles Prehospital Stroke Screen (LAPSS). *Prehosp Emerg Care*. 1998;2:267–273.
33. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field: prospective validation of the Los Angeles prehospital stroke screen (LAPSS). *Stroke*. 2000;31:71–76.
34. Ellison SR, Gratton MC, Schwab RA, Ma OJ. Prehospital dispatch assessment of stroke. *Mo Med*. 2004;101:64–66.
35. Wojner AW, Morgenstern L, Alexandrov AV, Rodriguez D, Persse D, Grotta JC. Paramedic and emergency department care of stroke: baseline data from a citywide performance improvement study. *Am J Crit Care*. 2003;12:411–417.
36. Smith WS, Corry MD, Fazackerley J, Isaacs SM. Improved paramedic sensitivity in identifying stroke victims in the prehospital setting. *Prehosp Emerg Care*. 1999;3:207–210.
37. Zweifler RM, York D, et al. Accuracy of paramedic diagnosis of stroke. *J Stroke Cerebrovasc Dis*. 1998;7:446–448.
38. Langhorne P, Tong BL, Stott DJ. Association between physiological homeostasis and early recovery after stroke. *Stroke*. 2000;31:2518–2519.
39. Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, Buonanno FS, Gonzalez RG, Sorensen AG. A pilot study of normobaric oxygen therapy in acute ischemic stroke. *Stroke*. 2005;36:797–802.
40. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke*. 1999;30:2033–2037.
41. Evans A, Perez I, Harraf F, Melbourn A, Steadman J, Donaldson N, Kalra L. Can differences in management processes explain different outcomes between stroke unit and stroke-team care? *Lancet*. 2001;358:1586–1592.
42. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? *Stroke*. 1999;30:917–923.
43. International Liaison Committee on Resuscitation. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2005;112:III-1–III-136.
44. Chapman KM, Woolfenden AR, Graeb D, Johnston DC, Beckman J, Schulzer M, Teal PA. Intravenous tissue plasminogen activator for acute ischemic stroke: a Canadian hospital's experience. *Stroke*. 2000;31:2920–2924.
45. Merino JG, Silver B, Wong E, Foell B, Demaerschalk B, Tamayo A, Poncha F, Hachinski V. Extending tissue plasminogen activator use to community and rural stroke patients. *Stroke*. 2002;33:141–146.
46. Riopelle RJ, Howse DC, Bolton C, Elson S, Groll DL, Holtom D, Brunet DG, Jackson AC, Melanson M, Weaver DF. Regional access to acute ischemic stroke intervention. *Stroke*. 2001;32:652–655.
47. Cross DT III, Tirschwell DL, Clark MA, Tuden D, Derdeyn CP, Moran CJ, Dacey RG Jr. Mortality rates after subarachnoid hemorrhage: variations according to hospital case volume in 18 states. *J Neurosurg*. 2003;99:810–817.
48. Domeier R, Scott P, Wagner C. From research to the road: the development of EMS specialty triage. *Air Med J*. 2004;23:28–31.
49. Pepe PE, Zachariah BS, Sayre MR, Floccare D. Ensuring the chain of recovery for stroke in your community. *Acad Emerg Med*. 1998;5:352–358.
50. Wojner AW, Alexandrov AV, Rodriguez D, Persse D, Grotta JC. The Houston Paramedic and Emergency Stroke Treatment and Outcomes Study (HoPSTO). *Stroke*. In press.
51. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. Stroke Unit Trialists' Collaboration. *BMJ*. 1997;314:1151–1159.
52. How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. Stroke Unit Trialists Collaboration. *Stroke*. 1997;28:2139–2144.
53. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2002;CD000197.
54. Ma RH, Wang YJ, Zhao XQ, Wang CX, Yang ZH, Qu H. [The impact of stroke unit on early outcome of cerebral infarction patients]. *Zhonghua Nei Ke Za Zhi*. 2004;43:183–185.
55. Oppenheimer SM, Cechetto DF, Hachinski VC. Cerebrogenic cardiac arrhythmias: cerebral electrocardiographic influences and their role in sudden death. *Arch Neurol*. 1990;47:513–519.
56. LaMonte MP, Bahouth MN, Hu P, Pathan MY, Yarbrough KL, Gunawardane R, Crarey P, Page W. Telemedicine for acute stroke: triumphs and pitfalls. *Stroke*. 2003;34:725–728.
57. Rymer MM, Thurtchley D, Summers D. Expanded modes of tissue plasminogen activator delivery in a comprehensive stroke center increases regional acute stroke interventions. *Stroke*. 2003;34:e58–e60.
58. Audebert HJ, Kukla C, Clarmann von Claranau S, Kuhn J, Vatakhah B, Schenkel J, Ickenstein GW, Haberl RL, Horn M. Telemedicine for safe and extended use of thrombolysis in stroke: the Telemed Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria. *Stroke*. 2005;36:287–291.
59. Connors JJ III, Sacks D, Furlan AJ, Selman WR, Russell EJ, Stieg PE, Hadley MN. Training, competency, and credentialing standards for diagnostic cervicocerebral angiography, carotid stenting, and cerebrovascular intervention: a joint statement from the American Academy of Neurology, American Association of Neurological Surgeons, American Society of Interventional and Therapeutic Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, AANS/CNS Cerebrovascular Section, and Society of Interventional Radiology. *Radiology*. 2005;234:26–34.
60. Schriger DL, Kalafut M, Starkman S, Krueger M, Saver JL. Cranial computed tomography interpretation in acute stroke: physician accuracy in determining eligibility for thrombolytic therapy. *JAMA*. 1998;279:1293–1297.
61. Hill MD, Buchan AM. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. *CMAJ*. 2005;172:1307–1312.
62. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. *Stroke*. 2003;34:2847–2850.
63. Heuschmann PU, Berger K, Misselwitz B, Hermanek P, Leffmann C, Adelman M, Buecker-Nott HJ, Rother J, Neundoerfer B, Kolominsky-Rabas PL. Frequency of thrombolytic therapy in patients with acute ischemic stroke and the risk of in-hospital mortality: the German Stroke Registers Study Group. *Stroke*. 2003;34:1106–1113.
64. Kwiatkowski TG, Libman RB, Frankel M, Tilley BC, Morgenstern LB, Lu M, Broderick JP, Lewandowski CA, Marler JR, Levine SR, Brott T. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med*. 1999;340:1781–1787.
65. Ingall TJ, O'Fallon WM, Asplund K, Goldfrank LR, Hertzberg VS, Louis TA, Christianson TJ. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke*. 2004;35:2418–2424.
66. Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2003;CD000213.
67. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, Broderick JP, Levine SR, Frankel MP, Horowitz SH, Haley EC Jr, Lewandowski CA, Kwiatkowski TP. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology*. 2000;55:1649–1655.
68. Mann J. Truths about the NINDS study: setting the record straight. *West J Med*. 2002;176:192–194.
69. Lindley RI. Further randomized controlled trials of tissue plasminogen activator within 3 hours are required. *Stroke*. 2001;32:2708–2709.
70. Kwiatkowski T, Libman R, Tilley BC, Lewandowski C, Grotta JC, Lyden P, Levine SR, Brott T. The impact of imbalances in baseline stroke severity on outcome in the National Institute of Neurological Disorders and Stroke

- Recombinant Tissue Plasminogen Activator Stroke Study. *Ann Emerg Med*. 2005;45:377–384.
71. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, Hammel JP, Qu A, Sila CA. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA*. 2000;283:1151–1158.
  72. Bravata DM, Kim N, Concato J, Krumholz HM, Brass LM. Thrombolysis for acute stroke in routine clinical practice. *Arch Intern Med*. 2002;162:1994–2001.
  73. Lopez-Yunez AM, Bruno A, Williams LS, Yilmaz E, Zurru C, Biller J. Protocol violations in community-based rTPA stroke treatment are associated with symptomatic intracerebral hemorrhage. *Stroke*. 2001;32:12–16.
  74. Asimos AW, Norton HJ, Price MF, Cheek WM. Therapeutic yield and outcomes of a community teaching hospital code stroke protocol. *Acad Emerg Med*. 2004;11:361–370.
  75. Katzan IL, Hammer MD, Furlan AJ, Hixson ED, Nadzam DM. Quality improvement and tissue-type plasminogen activator for acute ischemic stroke: a Cleveland update. *Stroke*. 2003;34:799–800.
  76. Lattimore SU, Chalela J, Davis L, DeGraba T, Ezzeddine M, Haymore J, Nyquist P, Baird AE, Hallenbeck J, Warach S. Impact of establishing a primary stroke center at a community hospital on the use of thrombolytic therapy: the NINDS Suburban Hospital Stroke Center experience. *Stroke*. 2003;34:e55–e57.
  77. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. Intra-arterial prourokinase for acute ischemic stroke: the PROACT II study: a randomized controlled trial. *Prolyse in Acute Cerebral Thromboembolism*. *JAMA*. 1999;282:2003–2011.
  78. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke*. 2004;35:904–911.
  79. Suarez JJ, Sunshine JL, Tarr R, Zaidat O, Selman WR, Kernich C, Landis DM. Predictors of clinical improvement, angiographic recanalization, and intracranial hemorrhage after intra-arterial thrombolysis for acute ischemic stroke. *Stroke*. 1999;30:2094–2100.
  80. Gonner F, Remonda L, Mattle H, Sturzenegger M, Ozdoba C, Lovblad KO, Baumgartner R, Bassetti C, Schroth G. Local intra-arterial thrombolysis in acute ischemic stroke. *Stroke*. 1998;29:1894–1900.
  81. Suarez JJ, Zaidat OO, Sunshine JL, Tarr R, Selman WR, Landis DM. Endovascular administration after intravenous infusion of thrombolytic agents for the treatment of patients with acute ischemic strokes. *Neurosurgery*. 2002;50:251–259; discussion 259–260.
  82. Ernst R, Pancioli A, Tomsick T, Kissela B, Wood D, Kanter D, Jauch E, Carrozella J, Spilker J, Broderick J. Combined intravenous and intra-arterial recombinant tissue plasminogen activator in acute ischemic stroke. *Stroke*. 2000;31:2552–2557.
  83. Bourekas EC, Slivka AP, Shah R, Sunshine J, Suarez JJ. Intra-arterial thrombolytic therapy within 3 hours of the onset of stroke. *Neurosurgery*. 2004;54:39–44; discussion 44–46.
  84. Keris V, Rudnicka S, Vorona V, Enina G, Tilgale B, Fricbergs J. Combined intra-arterial/intravenous thrombolysis for acute ischemic stroke. *AJNR Am J Neuroradiol*. 2001;22:352–358.
  85. Ueda T, Sakaki S, Kumon Y, Ohta S. Multivariable analysis of predictive factors related to outcome at 6 months after intra-arterial thrombolysis for acute ischemic stroke. *Stroke*. 1999;30:2360–2365.
  86. Jahan R, Duckwiler GR, Kidwell CS, Sayre JW, Gobin YP, Villablanca JP, Saver J, Starkman S, Martin N, Vinuela F. Intra-arterial thrombolysis for treatment of acute stroke: experience in 26 patients with long-term follow-up. *AJNR Am J Neuroradiol*. 1999;20:1291–1299.
  87. Alvarez-Sabin J, Molina CA, Montaner J, Arenillas JF, Huertas R, Ribo M, Codina A, Quintana M. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. *Stroke*. 2003;34:1235–1241.
  88. Baird TA, Parsons MW, Phan T, Butcher KS, Desmond PM, Tress BM, Colman PG, Chambers BR, Davis SM. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 2003;34:2208–2214.
  89. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol*. 2002;52:20–28.
  90. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426–2432.
  91. Bhalla A, Sankaralingam S, Tilling K, Swaminathan R, Wolfe C, Rudd A. Effect of acute glycaemic index on clinical outcome after acute stroke. *Cerebrovasc Dis*. 2002;13:95–101.
  92. Bruno A, Biller J, Adams HP Jr, Clarke WR, Woolson RF, Williams LS, Hansen MD. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *Neurology*. 1999;52:280–284.
  93. Celik Y, Utku U, Asil T, Balci K. Factors affecting haemorrhagic transformation in middle cerebral artery infarctions. *J Clin Neurosci*. 2004;11:656–658.
  94. Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, Fineberg SE, Tierney WR. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology*. 2002;59:67–71.
  95. Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: the Glucose Insulin in Stroke Trial (GIST). *Stroke*. 1999;30:793–799.
  96. Gray CS, Hildreth AJ, Alberti GK, O'Connell JE. Poststroke hyperglycemia: natural history and immediate management. *Stroke*. 2004;35:122–126.
  97. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359–1367.
  98. Adams HJ, Brott T, Crowell R, Furlan A, Gomez C, Grotta J, Helgason C, Marler J, Woolson R, Zivin J, Feinberg W, Mayberg M. Guidelines for the management of patients with acute ischemic stroke: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 1994;25:1901–1914.
  99. Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome: a meta-analysis of studies in patients. *Stroke*. 2000;31:410–414.
  100. Azzimondi G, Bassein L, Nonino F, Fiorani L, Vignatelli L, Re G, D'Alessandro R. Fever in acute stroke worsens prognosis: a prospective study. *Stroke*. 1995;26:2040–2043.
  101. Reith J, Jorgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, Olsen TS. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. *Lancet*. 1996;347:422–425.
  102. Boyson G, Christenson H. Stroke severity determines body temperature in acute stroke. *Stroke*. 2001;32:413–417.
  103. De Georgia MA, Krieger DW, Abou-Chebl A, Devlin TG, Jauss M, Davis SM, Koroshetz WJ, Rordorf G, Warach S. Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. *Neurology*. 2004;63:312–317.
  104. Georgiades D, Schwarz S, Aschoff A, Schwab S. Hemicraniectomy and moderate hypothermia in patients with severe ischemic stroke. *Stroke*. 2002;33:1584–1588.
  105. Georgiades D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. *Stroke*. 2001;32:2550–2553.
  106. Wang H, Olivero W, Lanzino G, Elkins W, Rose J, Honings D, Rodde M, Burnham J, Wang D. Rapid and selective cerebral hypothermia achieved using a cooling helmet. *J Neurosurg*. 2004;100:272–277.
  107. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke*. 1998;29:2461–2466.
  108. Schwab S, Georgiades D, Berrouschot J, Schellinger PD, Graffagnino C, Mayer SA. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke*. 2001;32:2033–2035.
  109. Kammersgaard LP, Rasmussen BH, Jorgensen HS, Reith J, Weber U, Olsen TS. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: a case-control study: the Copenhagen Stroke Study. *Stroke*. 2000;31:2251–2256.
  110. Knoll T, Wimmer ML, Gumpinger F, Haberl RL. The low normothermia concept—maintaining a core body temperature between 36 and 37 degrees C in acute stroke unit patients. *J Neurosurg Anesthesiol*. 2002;14:304–308.
  111. Krieger DW, De Georgia MA, Abou-Chebl A, Andrefsky JC, Sila CA, Katzan IL, Mayberg MR, Furlan AJ. Cooling for acute ischemic brain damage (COOL AID): an open pilot study of induced hypothermia in acute ischemic stroke. *Stroke*. 2001;32:1847–1854.
  112. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549–556.
  113. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.