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## Acute Ischemic Stroke Treatment in 2007

Larry B. Goldstein, MD

A variety of interventions have proven effective in reducing the risk of a first stroke.<sup>1</sup> Nevertheless, each year, more than 700 000 Americans have strokes and more than 150 000 die, making stroke the country's third-leading cause of death.<sup>2</sup> More than 25% of stroke survivors older than age 65 years are disabled 6 months later.<sup>2</sup> On the basis of the results of prospective randomized clinical trials and other studies performed over the past decade, the general approach to the management of acute stroke has evolved from nihilism to active intervention.

### Principles of Management

A large volume of experimental studies delineates the various aspects of the ischemic cascade. The results of the single laboratory study shown in Figure 1 provide a conceptual framework that guides the current clinical approach to patients with acute ischemic stroke.<sup>3</sup> The experiment, performed in awake monkeys, shows that focal symptoms (in this case, paralysis) develop when local cerebral blood flow drops below a certain threshold (in this experiment,  $<23 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ). In Figure 1, the hatched area between the development of symptoms and infarction is a graphic representation of the so-called penumbra, an area of brain that is functionally inactive but structurally intact and potentially salvageable. Neurological function is completely recoverable if local cerebral blood flow is restored promptly. For a given level of reduced blood flow, the likelihood of sustaining irreversible injury (ie, ischemic stroke) increases as a function of time. This essential biology is the basis of the mantra, "Time lost is brain lost." Timely restoration of blood flow to ischemic brain offers the chance of reversing or limiting the injury.

### Management Algorithm

Figure 2 provides a basic algorithm that outlines a general approach to patients with acute ischemic stroke. It begins with establishing the diagnosis.<sup>4</sup> A variety of conditions can mimic stroke, including seizures, tumors, infection, hypoglycemia, and other metabolic abnormalities. Such stroke mimics are common. In one study, 13% of 821 consecutive patients initially diagnosed with stroke were eventually found to have other conditions.<sup>5</sup> In another series, 31% of 350 consecutive patients with suspected stroke who were being evaluated in an emergency department did not have strokes.<sup>6</sup>

Prehospital screening with any of several available diagnostic aids can increase the likelihood of a correct diagnosis in a patient being transported to a hospital because of suspected stroke.<sup>7-9</sup> A scale has also been developed to improve the accuracy of stroke diagnosis for patients being evaluated in an emergency department. The Recognition Of Stroke In the Emergency Room (ROSIER) scale includes 7 items.<sup>10</sup> Points are assigned depending on the characteristics of the event (loss of consciousness or syncope, -1; seizures, -1; acute onset of asymmetrical facial weakness, +1; asymmetrical arm weakness, +1; asymmetrical leg weakness, +1; speech disturbance, +1; or visual field defect, +1) in patients without hypoglycemia. Stroke is unlikely (but not completely excluded) if the total score is less than or equal to 0. An initial assessment of stroke by ambulance personnel using one of the validated screening instruments followed by use of the ROSIER scale by hospital personnel would be expected to lead to a large increase in the probability of stroke.<sup>11</sup> Diagnostic studies including neuroimaging are still required to exclude stroke mimics and, in patients in whom reperfusion therapy is being considered, to exclude the possibility of brain hemorrhage.<sup>4</sup>

### Reperfusion Therapy: Intravenous Recombinant Tissue Plasminogen Activator

Once stroke has been diagnosed, the next step is to determine whether the patient might be a candidate for reperfusion therapy (Figure 2). The US Food and Drug Administration approved intravenous recombinant tissue plasminogen activator (rtPA) as a treatment for acute ischemic stroke in 1996 (Table 1). It remains the only approved pharmacological treatment for this condition. Its use is largely based on the National Institute of Neurological Disorders and Stroke (NINDS) trial that showed treatment with intravenous rtPA 0.9 mg/kg (10% given as a bolus with the remainder given over 1 hour, maximum dose of 90 mg) within 3 hours of the onset of symptoms led to an overall 32% relative (12% absolute) increase in the proportion of patients with minimal or no disability after 3 months.<sup>12</sup> Those treated with rtPA were also more likely to have minimal or no disability after 1 year.<sup>13</sup> The widespread adoption of treatment with rtPA has not been without controversy, at least in part because other thrombolytic studies in stroke have been negative, because of concern that baseline imbalances might explain the benefit of

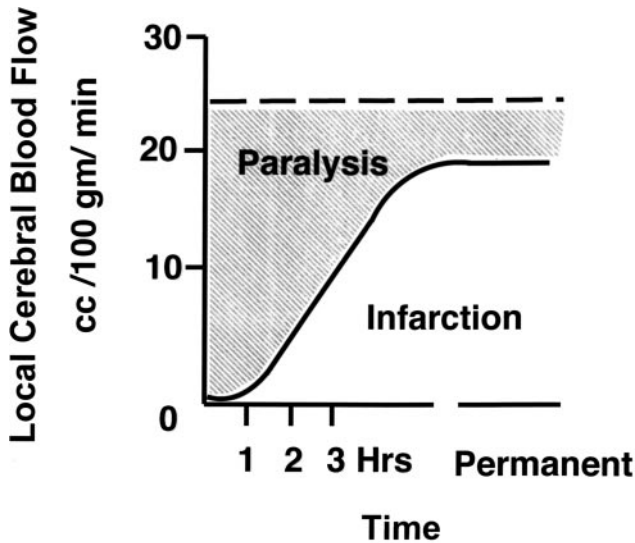
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**Figure 1.** Relationship between cerebral blood flow, time, functional impairment, and infarction. Even within 3 hours, ischemic tissue might go on to infarction or be viable if reperfused. Reproduced from Jones et al<sup>3</sup> with permission from the *Journal of Neurosurgery*. Copyright 1981, American Association of Neurological Surgeons.

treatment, and because the overall benefit in the NINDS trial included a 10-fold increase in the proportion of treated patients having symptomatic intracerebral hemorrhage (6.4% versus 0.6%), which could compromise the benefit when used outside a clinical trial setting.

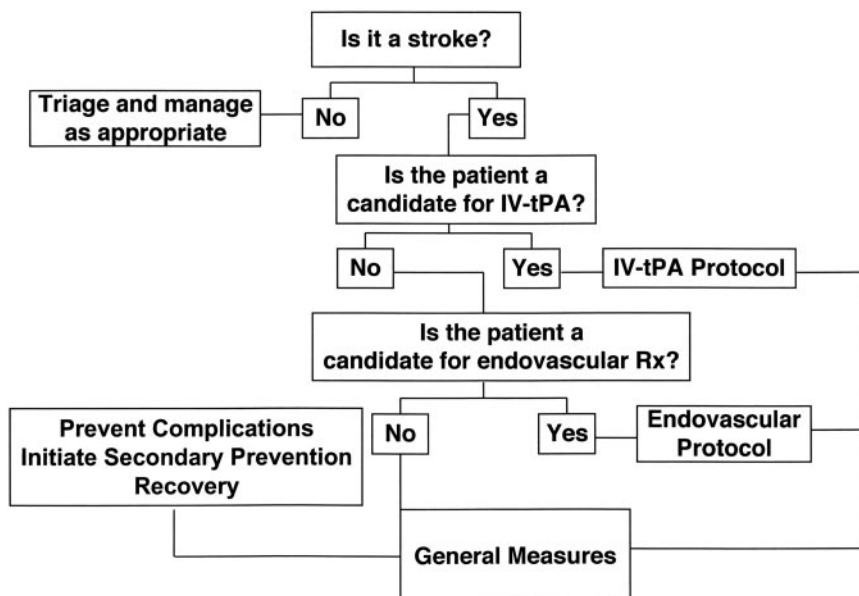
Negative thrombolytic studies differed from the NINDS trial in fundamental and important ways (eg, different thrombolytic drugs, different doses of rtPA, and longer intervals between symptom onset and treatment). Trials of another thrombolytic, streptokinase, included patients treated beyond 3 hours of symptom onset and generally incorporated the concomitant use of other antithrombotic drugs, which was prohibited in the NINDS trial.<sup>14-16</sup> Negative trials of intrave-

nous rtPA included the European Cooperative Acute Stroke Study (ECASS)-I, which used a higher dose of rtPA and randomized patients up to 6 hours after the onset of symptoms.<sup>17</sup> In the negative ECASS-II, the dose of tissue plasminogen activator was identical to that used in the NINDS trial, but there was a 6-hour treatment window, with most patients treated after 3 hours.<sup>18</sup> The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study used a treatment protocol identical to the NINDS trial but randomized patients 3 to 5 hours after stroke.<sup>19</sup>

Figure 3 gives the results of an intention-to-treat analysis of data pooled from randomized trials of rtPA for ischemic stroke (NINDS, ECASS-I, ECASS-II, and ATLANTIS) that included 2775 patients treated up to 6 hours after symptom onset at more than 300 hospitals located in 18 countries.<sup>20</sup> The analysis supports the primary finding of the NINDS trial in that treatment within 3 hours (and possibly up to 4.5 hours) of symptom onset is associated with a greater chance of a favorable outcome at 3 months. Moreover, as expected on the basis of the principles illustrated in Figure 1, the likelihood of benefit diminishes as time after symptom onset elapses (ie, the chances of benefit decrease as time to reperfusion increases).

A second concern was that a baseline imbalance in stroke severity between the rtPA- and placebo-treated groups in the NINDS trial might explain the observed benefit. An independent group reanalyzed the trial data and found a clinically important and statistically significant treatment benefit despite subgroup imbalances in baseline stroke severity.<sup>21</sup> Multiple exploratory analyses failed to identify any subgroup of ischemic stroke patients who would be more likely to either benefit from treatment or be harmed by it.

A third concern has been that the benefits of intravenous rtPA found in the NINDS trial would be not be generalizable to nonstudy settings. Several observational studies reinforced this fear, because higher rates of bleeding complications occurred more commonly when treatment protocols were



**Figure 2.** Algorithm for the management of patients with acute ischemic stroke. IV-tPA indicates intravenous tissue plasminogen activator; Rx, treatment.

**TABLE 1. Characteristics of Patients With Ischemic Stroke Who Could Be Treated With rtPA<sup>22</sup>**

Diagnosis of ischemic stroke causing measurable neurological deficit
The neurological signs should not be clearing spontaneously
The neurological signs should not be minor and isolated
Caution should be exercised in treating a patient with major deficits
The symptoms of stroke should not be suggestive of subarachnoid hemorrhage
Onset of symptoms <3 h before beginning treatment
No head trauma or prior stroke in previous 3 mo
No myocardial infarction in previous 3 mo
No gastrointestinal or urinary tract hemorrhage in previous 21 d
No major surgery in previous 14 d
No arterial puncture at a noncompressible site in previous 7 d
No history of previous intracranial hemorrhage
Blood pressure not elevated (systolic <185 mm Hg and diastolic <110 mm Hg)
No evidence of active bleeding or acute trauma (fracture) on examination
Not taking an oral anticoagulant, or if anticoagulant being taken, INR <1.7
If receiving heparin in previous 48 h, aPTT must be in normal range
Platelet count >100 000 mm <sup>3</sup>
Blood glucose concentration >50 mg/dL (2.7 mmol/L)
No seizure with postictal residual neurological impairments†
CT does not show a multilobar infarction (hypodensity >1/3 cerebral hemisphere)
The patient or family understands the potential risks and benefits of treatment

INR indicates international normalized ratio; aPTT, activated partial thromboplastin time.

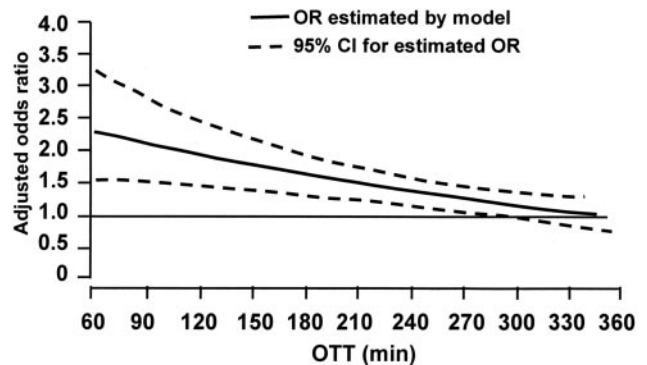
\*If greater than these levels, the patient can be given 1 or 2 doses of labetalol or a similar drug and treated if the blood pressure decreases to the indicated range, provided other criteria are met.

†A patient with a seizure at the time of onset of stroke might be eligible for treatment provided the clinician is convinced that the residual impairments are due to stroke and not to the seizure.

Adapted with permission from Adams et al.<sup>22</sup> Copyright 2005, American Heart Association.

violated. Other observational studies show that results similar to those found in the NINDS trial can be achieved in the “real world” if treatment protocols, as outlined in guideline statements,<sup>22</sup> are followed carefully.<sup>23</sup> Programs such as the designation of primary stroke centers have been developed in part to identify hospitals with the infrastructure and experience to use thrombolytic therapy safely.<sup>24</sup> Stroke center treatment is associated with increased use of intravenous rtPA, but whether this translates into the expected improvements in patient outcomes requires further study.<sup>25</sup>

Intravenous rtPA is given to only 1% to 2% of stroke patients in the United States. The commonest reason that patients are not treated is because they arrive at a hospital beyond the currently approved 3-hour treatment window.<sup>26</sup> Many patients who awaken with symptoms (the time of onset is taken from the last time they were known to be symptom free) are excluded, but numerous studies document that patient and bystander knowledge of stroke symptoms is poor, which results in delays in seeking emergency care. There can



**Figure 3.** Intention-to-treat analysis of data pooled from randomized trials of rtPA for ischemic stroke. OTT indicates onset to treatment time. Reproduced from Hacke et al<sup>20</sup> with permission from Elsevier. Copyright 2004.

also be delays in dispatch of emergency responders and in the diagnosis and transport of stroke patients by emergency medical services personnel. Because of the time dependency of reperfusion-related treatment benefits (ie, Figures 1 and 3), it is critical to expedite arrival at a hospital, which has led to the call for the development of systems of stroke care.<sup>27</sup> Comprehensive programs of patient and provider education and systematic organization of care are associated with more rapid arrival at hospitals after symptom onset and increases in the proportions of patients receiving treatment.<sup>28, 29</sup> The use of telemedicine is being explored as a way of extending stroke treatment expertise to patients arriving at community or rural hospitals where support and experience may be limited.

### Endovascular Therapy

There have been no direct comparative studies of intravenous thrombolysis and endovascular therapy to assess their relative effects on patient outcomes, and intravenous rtPA is viewed as first-line therapy for those who qualify for the treatment (Figure 2).<sup>22</sup> Endovascular treatment, however, offers the potential advantage of real-time visualization of a thrombus while recanalization therapies are administered. The approach requires a skilled neurointerventionalist and the necessary infrastructure support, is technically limited to more proximal occlusions, and logistically requires more time to initiate than intravenous thrombolysis.

A prospective randomized trial tested the efficacy and safety of intra-arterial prourokinase plus heparin versus heparin alone in patients with acute ischemic stroke and angiographically proven occlusion of the middle cerebral artery who could be treated within 6 hours of symptom onset (Prolyse in Acute Cerebral Thromboembolism Trial [PROACT-II]).<sup>30</sup> Although there was no effect on mortality, 40% of the intra-arterial prourokinase-treated patients had mild or no functional limitations (the study's primary end point) at 3 months compared with 25% of control subjects ( $P=0.04$ ). Intracranial hemorrhage with neurological deterioration occurred in 10% of patients treated with intra-arterial prourokinase and 2% of control patients ( $P=0.06$ ). There was no significant difference between the groups with regard to a variety of other secondary outcome measures, although trends

favored treatment. The Food and Drug Administration required a confirmatory study that was not pursued by the study's sponsor.

No placebo-controlled, randomized studies have evaluated the use of intra-arterial rtPA. It has been used in patients with middle cerebral artery–distribution strokes similar to those included in PROACT-II who do not fulfill the criteria for intravenous rtPA, in selected patients with catheter-associated stroke, and in patients with retinal artery occlusion. Another group of patients in whom intra-arterial rtPA is considered is those with basilar artery occlusion who do not meet criteria for intravenous rtPA because of time.

The effectiveness of intravenous rtPA may be poor in patients with a proximal occlusion. Recanalization occurs in only 10% of occluded internal carotid arteries and 25% of occluded middle cerebral arteries.<sup>31–33</sup> In addition, early reocclusion occurs in approximately one third of rtPA-treated patients.<sup>34</sup> The pilot Interventional Management of Stroke study investigated the feasibility and safety of sequential intravenous and intra-arterial treatment with rtPA using historical controls from the NINDS intravenous rtPA trial.<sup>35</sup> Of 80 enrolled patients, 77 had angiograms, and 62 received combination therapy with results that compared favorably with those of the NINDS intravenous rtPA trial. Further evaluation of this approach and of other means of improving recanalization rates with intravenous rtPA, such as the use of Doppler ultrasound, is in progress.<sup>36</sup>

Mechanical clot retrieval has the theoretical advantage of avoiding the systemic bleeding risk associated with thrombolytic drugs. The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) clot retriever was approved by the Food and Drug Administration as a tool for the removal of blood clots from brain blood vessels. This approval was based on the results of a noncontrolled case series that involved 151 enrolled patients (141 of whom could be treated) with proximal (internal carotid, middle cerebral, or vertebrobasilar) arterial occlusions treated within 6 hours of symptom onset (mean 4.3 hours to catheterization).<sup>37</sup> Adjuvant therapy with intra-arterial thrombolytics was permitted. Recanalization was achieved in 48% of those in whom the device was deployed, with 28% having asymptomatic intracerebral hemorrhages and 8% having symptomatic hemorrhages. Approximately 32% of those who were successfully recanalized died within 90 days, but 46% of those surviving at 90 days had little or no disability. Whether outcomes would be similar, better, or worse than with other reperfusion treatments is unknown because the study had no concurrent control subjects. The approach has the same logistic limitations as intra-arterial thrombolytic therapy but offers the possibility of treatment for selected patients who cannot be given a thrombolytic drug (eg, patients who have undergone a recent operation or invasive procedure).

### Neuroprotective Therapy

As depicted in Figure 1, a variable amount of brain tissue may be ischemic but structurally intact. Neuroprotective therapies are aimed at preserving this tissue until adequate blood supply can be reestablished, either through spontaneous or therapeutic recanalization or via collateral flow. There have

been published reports of >1000 experimental neuroprotective treatments for acute stroke targeting various portions of the ischemic cascade, with >100 coming to clinical trials.<sup>38</sup> To date, none has proved efficacious. The potential reasons for these failures are varied, and discussions of the problem have been the subject of numerous reviews, conferences, and commentaries.<sup>39</sup> Possible issues focus on limitations of pre-clinical testing and a host of concerns related to clinical trial design, including patient selection, drug dosing, treatment windows, outcome measures, and data analysis. Trials of neuroprotection, such as hyperacute administration of magnesium during transport to the hospital and the administration of albumin, continue.<sup>40,41</sup>

Experimental studies strongly support the potential of therapeutic hypothermia as a neuroprotective strategy.<sup>38</sup> A recent Cochrane review that included articles published between 1966 and 1998, however, could not identify any completed randomized trials of physical or chemical cooling in acute stroke.<sup>42</sup> Several small pilot studies of a variety of approaches for inducing hypothermia in patients with acute stroke, used either alone or in conjunction with surgical procedures for massive infarction, have since been published, but definitive studies have not been completed. Potential complications of induced hypothermia include pneumonia, sepsis, hypotension, cardiac arrhythmias, and coagulopathy, and the approach is still viewed as experimental.

### Radiological Identification of Neuroprotective and Reperfusion Candidates

As reflected in Figure 1, at any given time point, a patient's symptoms could result from involvement of infarcted or ischemic but potentially recoverable brain tissue. Although the likelihood of infarction increases with time, clinical features cannot be used to make this distinction. Infarction may already be completed in a subset of patients presenting soon after the onset of stroke symptoms, and others may have considerable areas of ischemic but noninfarcted tissue after the standard 3-hour treatment window has elapsed. Those with completed infarctions would not benefit from recanalization or neuroprotective therapy, whereas those with ischemic but uninfarcted tissue might be helped by treatment after the 3-hour period. The advent of advanced CT and magnetic resonance–based neuroradiological techniques offers the possibility of moving from a purely time-based to a more objective means of selecting patients for recanalization or other acute therapies. CT perfusion techniques use dynamic scanning to measure temporal changes in the density of the brain tissue that result from rapid changes in concentration of a contrast agent.<sup>43</sup> Diffusion-weighted MRI assesses water homeostasis, which enables the rapid detection of areas of ischemia, and it can be coupled with perfusion-weighted MRI, which provides a semiquantitative assessment of regional cerebral blood flow.<sup>44</sup> Despite experimental studies showing that areas of abnormality on diffusion-weighted MRI may be reversible, permanent tissue injury is generally present.<sup>45</sup> It is hypothesized that regions of brain with reduced perfusion that do not show abnormal diffusion may represent salvageable tissue (ie, the penumbra; Figure 1).<sup>46</sup> Longitudinal studies show that the area of diffusion abnormality can

expand to involve the area of perfusion abnormality over time. Although the concept of so-called diffusion-perfusion mismatch has limitations,<sup>47</sup> the technique has been used in clinical trials in an attempt to identify subgroups of patients who are more likely to benefit from both neuroprotective<sup>48,49</sup> and recanalization therapy,<sup>50,51</sup> including those presenting >3 hours after symptom onset.

MRI with T2\*-weighted sequences can identify remote microhemorrhages that were thought to be a marker of increased risk of hemorrhagic transformation in patients treated with thrombolytic therapy.<sup>52</sup> Prospective studies have not confirmed this risk,<sup>53-55</sup> which would also need to be balanced against the potential benefit of reperfusion in patients with acute ischemic stroke.

Perfusion CT and diffusion/perfusion MRI can be helpful diagnostically and are now commonly used in advanced centers to aid in the evaluation of patients with acute stroke. The techniques hold promise as means of identifying patients more or less likely to benefit from hyperacute interventions, but at present, the data are insufficient to support their widespread use for this purpose.<sup>56</sup>

### General Measures

A variety of general measures are relevant to the management of patients with acute ischemic stroke regardless of whether or not they are treated with intravenous rtPA or endovascular therapy (Figure 2).

### Blood Pressure

Cerebral blood flow (CBF) is determined by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR), where  $CBF = CPP/CVR$ .<sup>57</sup> Cerebral perfusion pressure is determined by the difference between the mean arterial pressure (MAP) and venous pressure, which is generally negligible (ie,  $CBF = MAP/CVR$ ; exceptions include venous obstruction). Cerebrovascular resistance depends on the degree of cerebral vasodilatation (decreasing cerebrovascular resistance) or vasoconstriction (increasing cerebrovascular resistance). Normally (ie, for mean arterial pressures ranging from approximately 60 to 150 mm Hg), decreases in cerebral perfusion pressure are matched by decreases in cerebrovascular resistance, and increases in cerebral perfusion pressure are matched by increases in cerebrovascular resistance (cerebral autoregulation).<sup>57</sup> The lower and upper limits of autoregulation are shifted to higher values in patients with chronic hypertension. As a result, cerebral blood flow decreases at a relatively higher mean arterial pressure in patients with chronic hypertension than in normotensive individuals.

The autoregulatory relationship is disrupted in the setting of acute ischemia, in part because ischemia-related local tissue acidosis leads to maximal vasodilation.<sup>58</sup> Therefore, changes in mean arterial pressure are directly reflected in changes in local cerebral blood flow. The potential consequences of reducing local cerebral blood flow in the setting of acute ischemia are apparent by referring to Figure 1. Nonischemic tissue immediately surrounding the zone of ischemia could become compromised, and further reductions in local cerebral blood flow in already ischemic tissue could lead to

infarction. In addition, an acute reduction in blood pressure could further compromise flow through a stenotic artery and collateral vessels.<sup>59</sup> Theoretical arguments favoring treatment include reduction in edema and decreasing the risk of hemorrhagic transformation.

Clinical data on the effect of blood pressure alterations on outcome after ischemic stroke come mainly from observational studies. Some show no clear relationship between acute elevations in blood pressure and neurological worsening or outcome after ischemic stroke; however, at least one observational study found that poor outcome 3 months after stroke was independently associated with the degree of systolic blood pressure reduction during the first 24 hours (OR=1.89 for poor outcome per 10% decrease in blood pressure [95% CI 1.02 to 1.87]).<sup>60</sup>

The calcium channel antagonist nimodipine was evaluated as a potential neuroprotective agent.<sup>61</sup> Nimodipine has anti-hypertensive properties, and given orally within 48 hours of ischemic stroke, it also reduced blood pressures and was associated with higher 1- and 3-month mortality rates. The Intravenous Nimodipine West European Stroke Trial (INWEST) tested intravenous nimodipine (1 or 2 mg/h) started within 24 hours of acute ischemic stroke.<sup>62</sup> Neurological outcomes were better in placebo-treated patients after both 3 weeks and 6 months. Exploratory analysis showed the odds of death or dependency at 21 days were 2.60 (95% CI 0.82 to 8.27) for those with a <10% early decrease in diastolic blood pressure, 2.97 (95% CI 1.16 to 7.63) for those with a 10% to 20% decrease, and 4.36 (95% CI 1.63 to 11.7) for those with a  $\geq 20\%$  decrease.<sup>63</sup> In contrast, the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) Study randomized 342 hypertensive patients with ischemic stroke to candesartan cilexetil over the first 7 days, targeting a 10% to 15% reduction in blood pressure in the first 24 hours, or placebo.<sup>64</sup> Both groups received candesartan cilexetil after 7 days. There were, however, no significant differences in blood pressures between the active-treatment and placebo-treated patients during the first week. There were no differences in outcome between the groups after 3 months, but there was a significant improvement in outcomes in acutely treated patients after 12 months. Because there were no differences in blood pressures between the groups, the study cannot address the relative benefits and risks of acute blood pressure treatment. The mechanism by which acute treatment led to a difference at 12 months is uncertain. A systematic review of studies assessing the effect of vasoactive drugs performed by the Cochrane Collaboration concluded that there was not enough evidence to reliably evaluate the effect of altering blood pressure on outcome in persons with acute stroke.<sup>65</sup>

Because of the lack of definitive data, current recommendations for the management of blood pressure in patients with acute ischemic stroke remain largely empirical (Table 2).<sup>22</sup> On the basis of the issues reviewed, acute treatment is not recommended unless hypertension is severe (ie, systolic blood pressure  $\geq 220$  mm Hg or diastolic blood pressure  $\geq 120$  mm Hg) or in those with hypertensive encephalopathy, aortic dissection, acute pulmonary edema, or acute myocardial infarction. Abrupt lowering of blood pressure should be avoided.

**TABLE 2. Approach to Elevated Blood Pressure in Acute Ischemic Stroke**

Clinical Situation	Recommendation
Systolic BP $\leq$ 220 mm Hg or diastolic BP $\leq$ 120 mm Hg	Observe BP unless other end-organ involvement (eg, aortic dissection, acute myocardial infarction, pulmonary edema, or hypertensive encephalopathy). Treat headache, pain, agitation, nausea, vomiting, and other stroke complications.
Systolic BP $>$ 220 mm Hg or diastolic BP 121–140 mm Hg	Labetalol 10–20 mg IV over 1 to 2 min. May repeat or double every 10 min (maximum dose of 300 mg) OR Nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing by 2.5 mg/h every 5 min to maximum of 15 mg/h (target 10% to 15% BP reduction)
Diastolic BP $>$ 140 mm Hg	Nitroprusside 0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ IV as initial dose with continuous BP monitoring (target 10% to 15% BP reduction)
Patient otherwise candidate for intravenous rtPA	If systolic BP $>$ 185 mm Hg or diastolic BP $>$ 110 mm Hg, labetalol 10–20 mg IV over 1 to 2 min; may repeat 1 time, or use 1 to 2 inches of nitropaste. If BP is not reduced and maintained at desired levels ( $<$ 185 mm Hg systolic and $<$ 110 mm Hg diastolic), <i>do not</i> administer rtPA.

BP indicates blood pressure.

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Another potential exception to the recommendation to avoid lowering blood pressure in patients with acute ischemic stroke is patients who are otherwise candidates for thrombolytic treatment in whom intravenous rtPA should be withheld unless blood pressures are  $<$ 185/110 mm Hg (Table 1). As shown in Table 1, an attempt can be made to gently lower blood pressure in these patients to below these levels. Postthrombolytic blood pressure management recommendations are given in Table 3. It must be recognized that these recommendations are based on the protocols used in the NINDS rtPA clinical trial, but an independent panel reviewing the trial data could not assess the effects of blood pressure or its management on outcome.<sup>21</sup>

### Fever

Although the benefit of therapeutic hypothermia is unproven, experimental studies show that even small temperature elevations increase the volume of infarcted brain tissue.<sup>66</sup> In patients with acute ischemic stroke, fever is associated with increases in both morbidity and mortality. It is reasonable to treat fevers aggressively, although no prospective randomized trials link treatment of fever with improved stroke outcomes.

### Anticoagulants and Antithrombotics

Potential reasons to provide anticoagulant therapy to patients with acute ischemic stroke include reducing the chances of both reembolization in those with a cardiogenic source of

embolism and neurological worsening related to clot propagation in those with stroke related to atheroembolism. These possible benefits need to be balanced against the risk of hemorrhagic complications. In 2000, a Cochrane systematic review based on 21 trials involving  $>$ 23 000 participants found no evidence that anticoagulant therapy reduced the risk of death, and on the basis of 5 trials that included nearly 22 000 patients, no evidence was found that anticoagulant therapy reduced the odds of death or dependency.<sup>67</sup> The International Stroke Trial (IST) contributed 19 435 patients to these analyses.<sup>68</sup> Using a factorial design, IST randomized patients to 1 of 2 fixed doses of subcutaneous heparin (5000 or 12 500 IU twice daily) or a strategy to avoid heparin, and aspirin 300 mg/d or a strategy to avoid aspirin. A small reduction in recurrent ischemic strokes was offset by a similar increase in hemorrhagic strokes in heparin-treated patients. The relevance of IST for clinical practice in the United States was questioned because only two thirds of patients had a CT scan before randomization, and as noted, the study did not evaluate dose-adjusted intravenous heparin.

Although the emergent use of anticoagulation in patients with acute ischemic stroke remains a source of some controversy, enthusiasm for treatment with these drugs is increasingly tempered by a lack of data showing that the approach is efficacious. Individual trial reviews published in 2002 (ie, after the Cochrane report) concluded that most patients with

**TABLE 3. Recommendations for Blood Pressure Management After Intravenous rtPA**

Measurement	Recommendation
Assessment frequency	Measure blood pressure every 15 min for the first 2 h, every 30 min for the next 6 h, and then every hour until 24 h from treatment
Diastolic BP $>$ 140 mm Hg	Sodium nitroprusside 0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ IV as initial dose and titrate to desired BP (systolic $<$ 180 mm Hg, diastolic $<$ 110 mm Hg)
Systolic BP $>$ 230 mm Hg or diastolic BP 121–140 mm Hg	Labetalol 10 mg IV over 1 to 2 min. May repeat or double labetalol every 10 min to a maximum dose of 300 mg, or give initial labetalol dose, then start labetalol drip at 2–8 mg/min OR Nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing by 2.5 mg/h every 5 min to maximum of 15 mg/h; if BP not controlled, consider sodium nitroprusside
Systolic BP 180–230 mm Hg or diastolic BP 105–120 mm Hg	Labetalol 10 mg IV over 1 to 2 min. May repeat or double labetalol every 10–20 min to a maximum dose of 300 mg, or give initial labetalol dose, then start labetalol drip at 2–8 mg/min

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**TABLE 4. Recommendations for the Use of Anticoagulants and Antiplatelet Agents in Patients With Acute Ischemic Stroke<sup>71</sup>**

1.	Patients with acute ischemic stroke presenting within 48 h of symptom onset should be given aspirin (160–325 mg/d) to reduce stroke mortality and decrease morbidity, provided contraindications such as allergy and gastrointestinal bleeding are absent and the patient has not been and will not be treated with rtPA. The data are insufficient at this time to recommend the use of any other platelet antiaggregant in the setting of acute ischemic stroke.
2.	Subcutaneous unfractionated heparin, LMW heparins, and heparinoids may be considered for DVT prophylaxis in at-risk patients with acute ischemic stroke, with the recognition that nonpharmacological treatments for DVT prevention also exist. A benefit in reducing the incidence of pulmonary embolism has not been demonstrated. The relative benefits of these agents must be weighed against the risk of systemic and intracerebral hemorrhage.
3.	Although there is some evidence that fixed-dose, subcutaneous, unfractionated heparin reduces early recurrent ischemic stroke, this benefit is negated by a concomitant increase in the occurrence of hemorrhage. Therefore, use of subcutaneous unfractionated heparin is not recommended for decreasing the risk of death or stroke-related morbidity or for preventing early stroke recurrence.
4A.	Dose-adjusted, unfractionated heparin is not recommended for reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke (ie, in the first 48 h) because the evidence indicates it is not efficacious and may be associated with increased bleeding complications.
4B.	High-dose LMW heparin/heparinoids have not been associated with either benefit or harm in reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke and are therefore not recommended for these goals.
5.	Intravenous, unfractionated heparin and high-dose LMW heparin/heparinoids are not recommended for any specific subgroup of patients with acute ischemic stroke that is based on any presumed stroke mechanism or location (eg, cardioembolic, large-vessel atherosclerotic, vertebrobasilar, or “progressing” stroke) because data are insufficient. Although the LMW heparin dalteparin at high doses may be efficacious in patients with atrial fibrillation, it is not more efficacious than aspirin in this setting. Because aspirin is easier to administer, it, rather than dalteparin, is recommended for the various stroke subgroups.

LMW indicates low molecular weight; DVT, deep vein thrombosis. Data derived from Coull et al.<sup>71</sup>

acute ischemic stroke should not be treated with unfractionated heparin or other rapidly acting anticoagulants and that there was no overall benefit of treatment with heparin in patients with acute ischemic stroke and atrial fibrillation.<sup>69,70</sup> A 2002 guideline statement jointly developed by the American Stroke Association and the American Academy of Neurology was based on a systematic literature review.<sup>71</sup> Recommendations are given in Table 4 and were reiterated in a subsequent guideline statement from the American Stroke Association.<sup>72</sup>

Despite the completion of several additional trials, little has changed since these guidelines were issued. The Rapid Anticoagulation Prevents Ischemic Damage in Acute Stroke (RAPID) study compared aspirin and dose-adjusted unfractionated heparin in patients with nonlacunar ischemic stroke started within 12 hours of symptom onset.<sup>73</sup> The study was halted after only 67 patients were randomized because of poor recruitment, with no effect on the primary end point (no significant disability at 90 days). A single-center trial randomized 418 patients with nonlacunar hemispheric ischemic stroke to dose-adjusted intravenous heparin or saline started within 3 hours of symptom onset and continued for 5 days.<sup>74</sup> There were more symptomatic intracerebral and systemic hemorrhages in the treated group, but there was an overall increase in the proportion of patients with favorable outcomes after 90 days (38.9% versus 28.6%,  $P=0.025$ ). Control subjects, however, were not given aspirin, and whether the results can be generalized to other settings is uncertain. The TOAST trial (Trial of Org 10172 in Acute Stroke Treatment) found no overall benefit of acute anticoagulation with a heparinoid (danaparoid) but a suggestion of benefit in the subgroup of subjects with large-artery-type stroke.<sup>75</sup> This finding has not yet been replicated in an independent study.

In contrast to acute anticoagulation, aspirin (160 to 325 mg/d) started within 48 hours of symptom onset is recommended for most patients with ischemic stroke (Table 4).<sup>22,71</sup>

This is largely based on a preplanned combined analysis of data from 40 000 patients who participated in IST and the Chinese Acute Stroke Trial (CAST), which found 9 fewer recurrent ischemic strokes or deaths during hospitalization per 1000 patients treated with aspirin.<sup>76</sup> Alternative oral antiplatelet drugs have not been evaluated in this setting.

Uncontrolled and phase 2 studies suggested that intravenous administration of platelet glycoprotein IIb/IIIa inhibitors might be safe and effective in the emergent treatment of patients with ischemic stroke. The Abciximab in Emergent Stroke Treatment Trial-II (AbESTT-II) trial was a phase 3 study that planned to randomize 1200 patients with ischemic stroke to double-blind treatment with abciximab versus placebo within 6 hours of symptom onset or 2.5 hours of awakening.<sup>77</sup> Reported in abstract form, the study was stopped prematurely because of safety concerns after 808 patients were enrolled.

Although the use of any therapeutic intervention needs to be individualized, there remain no data showing a net benefit of anticoagulants in most patients with acute ischemic stroke, although the possibility of benefit in some patient subgroups cannot be excluded, and there are only limited data for hyperacute administration. Although the benefits are small, aspirin should be given to most patients. Patients who are treated with intravenous rtPA should not receive any anticoagulants or antithrombotic drugs over the first 24 hours.<sup>22,71</sup>

### Preventing Complications

In addition to the general measures applicable to all stroke patients, prevention of complications, initiation of secondary prevention, and facilitation of functional recovery are integral to the management of patients with acute ischemic stroke (Figure 2). Several common complications of acute stroke are often preventable. One multicenter study found that medical complications were recorded in 85% of hospitalized stroke patients.<sup>78</sup> The commonest were pain (34%), falls (25%),

urinary tract infections (24%), pneumonia (22%), and pressure sores (21%). These complications can prolong hospitalization, interfere with the recovery process, and lead to further morbidity and mortality.

Indwelling urethral catheters in hospitalized patients are the major risk factor for the development of urinary tract infections.<sup>79</sup> The estimated rate of infection is 3% to 10% per day. Women are at greater risk than men. Avoidance of the use of indwelling catheters or their removal as soon as feasible can lessen the infection risk. Risk is also decreased with the use of condom catheters in men or through the use of intermittent or suprapubic catheterization.

Approximately one third of stroke patients have dysphagia, with 20% developing aspiration pneumonia.<sup>80</sup> Aspiration pneumonia also occurs in 10% of stroke patients without dysphagia.<sup>80</sup> Silent aspiration, without overt signs of dysphagia, can also occur.<sup>81</sup> Although having depression of the level of consciousness increases risk, dysphagia and aspiration also occur in patients with preserved consciousness.<sup>82</sup> Dysphagia has been associated with aspiration in 54% of patients with bilateral hemispheric strokes and 50% of those with brain stem strokes.<sup>83</sup> Aspiration occurs more commonly in patients with bilateral versus unilateral cranial nerve signs; however, it can complicate >40% of unilateral hemispheric strokes and can occur with strokes affecting various brain regions and with strokes of all sizes, including >20% of small-vessel-type strokes.

In addition to depressed consciousness, clinical identifiers of aspiration risk include the presence of dysarthria, dysphonia, a weak voluntary cough, and drooling.<sup>84</sup> Findings on clinical examination, however, have limited sensitivity for identifying patients at risk for aspiration. For example, an absent or diminished gag response is not helpful in discriminating aspirators from nonaspirators.<sup>85</sup> Having the patient attempt to swallow 3 oz of water is a sensitive screening tool for identifying patients at risk for clinically significant aspiration.<sup>86</sup> Patients with dysphagia and those suspected to be at risk for aspiration should be referred to a speech and language pathologist for further evaluation before the initiation of oral feeding.

Deep vein thrombosis (2% to 3%) and pulmonary embolism (1% to 5%) can be major complications in immobilized stroke patients.<sup>78,87</sup> A prospective study using MRI found 18% of patients with acute ischemic stroke had a proximal deep vein thrombosis after 21 days, with 12% having a pulmonary embolism.<sup>87</sup> The risk of deep vein thrombosis and pulmonary embolism in immobilized stroke patients can be decreased with subcutaneous unfractionated heparin; however, aspirin is not effective for this purpose (Table 4).<sup>71</sup> A Cochrane review based on studies reported through 2003 also found that treatment with either a heparinoid or a low-molecular-weight heparin is associated with a reduction in the risk of deep vein thrombosis.<sup>88</sup> The use of heparinoids but not low-molecular-weight heparin was associated with decreased deep vein thrombosis risk compared with unfractionated heparin.<sup>88</sup> There were too few events to determine whether heparinoids or low-molecular-weight heparins decrease the rate of pulmonary embolism in this setting (Table 4).<sup>71</sup> A trial comparing enoxaparin with subcutaneous heparin was com-

pleted recently.<sup>89</sup> The benefit of subcutaneous unfractionated heparin is enhanced by the concomitant use of pneumatic sequential compression devices.<sup>90</sup>

## Secondary Prevention and Recovery

Secondary prevention and integrated measures to facilitate and optimize poststroke recovery are separate topics but are integral to the care of patients with acute ischemic stroke. Guidelines were published recently that review the prevention of stroke in patients with prior stroke or transient ischemic attack.<sup>91</sup> Care in comprehensive stroke units incorporating multidisciplinary rehabilitation is associated with lower complication rates and improved functional outcomes after stroke.<sup>92</sup> Organized multidisciplinary rehabilitation is associated with reductions in stroke-related mortality, long-term institutionalization, and dependency such that 5 extra patients are returned home in an independent state for every 100 treated.<sup>93</sup> Functional outcome is improved with adherence to poststroke rehabilitation guidelines.<sup>94</sup>

## Conclusions

The management of patients with acute ischemic stroke has become complex. Optimization of care requires systematic organization that extends from primary prevention through poststroke rehabilitation.<sup>27</sup> Treatment will continue to be refined as ongoing clinical trials are completed.

## Disclosures

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