

# Update on Intravenous Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke

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## Abstract

The controversial field of interventional stroke neurology has attracted considerable interest within the stroke community, but no endovascular interventional therapies have proved to be superior to intravenous (IV) recombinant tissue plasminogen activator (rtPA), the standard of care for patients with acute ischemic stroke. In this article, we review the evidence and background of IV thrombolysis for stroke, the clinical application of IV rtPA in practice, and the management of potential complications after thrombolysis. We conducted this review using a search of PubMed for articles published from January 1, 1995, to October 31, 2013, with the following terms: *ischemic stroke*, *tissue plasminogen activator*, *TPA*, *alteplase*, *thrombolysis*, and *intracranial hemorrhage*. Articles were also identified through searches of reference lists and the authors' files. In nearly 2 decades since the publication of the transformative National Institute of Neurological Disorders and Stroke trials, the efficacy and safety of IV rtPA has been consistently verified in international real-world clinical practice. Time from stroke symptom onset to thrombolysis is crucial and probably the most important determinant of success of IV therapy. Thus, optimal care of patients with acute stroke should include community education and standardized protocols to guide immediate patient assessment and triage to medical centers with capability for efficient neurologic assessment, brain imaging, drug administration, and specialized postthrombolysis care.

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The availability of intravenous (IV) recombinant tissue plasminogen activator (rtPA) has dramatically transformed the approach to acute ischemic stroke. As recently as just 2 decades ago, no emergent therapies for stroke were proven to be safe or effective in improving outcomes, and patient care was focused on supportive measures, rehabilitation, and secondary stroke prevention. Progress in preventive measures for cerebrovascular disease and in acute care have helped lower stroke from the third to the fourth leading cause of death in the United States, but it remains a major cause of long-term disability.<sup>1</sup> The cumulative poststroke disability burden is likely to become a growing problem for society as an increasing number of people survive their strokes because of developments in the medical field. Since the publication of the pivotal National Institute of Neurological Disorders and Stroke (NINDS) IV rtPA trials in 1995,<sup>2</sup> IV rtPA has become standard therapy for patients presenting within 3 hours of onset of acute ischemic stroke. Recent advances in the field center around interventional stroke neurology and direct intra-arterial therapies, which have captured considerable interest of

researchers, clinicians, and medical device companies. Yet despite a sound pathophysiologic rationale and promising results from non-randomized studies, treatment of patients with endovascular therapy has not proved to be superior in improving patient outcomes compared with IV rtPA.<sup>3,4</sup>

In this article, we review the evidence and background of IV thrombolysis for stroke, the clinical application of IV rtPA in practice, and the management of potential complications after thrombolysis. We conducted this review using a search of PubMed for articles published from January 1, 1995, to October 31, 2013, with the following terms: *ischemic stroke*, *tissue plasminogen activator*, *TPA*, *alteplase*, *thrombolysis*, and *intracranial hemorrhage*. Articles were also identified through searches of reference lists and the authors' files.

## REVIEWING THE EVIDENCE

Results of the NINDS rtPA Stroke Study<sup>2</sup>—a trial of 624 patients randomized to receive IV rtPA (0.9 mg/kg, maximum 90 mg) or placebo within 3 hours of ischemic stroke onset—revealed that IV rtPA increases the chance of achieving a

3-month complete or nearly complete neurologic recovery by at least 30%. The proportion of patients achieving 3-month favorable outcome (modified Rankin Scale score of  $\leq 1$ ) was 39% in the rtPA group and 26% in the placebo group ( $P=.019$ ). Intracranial hemorrhage (ICH) occurred more often in the rtPA-treated group (6.4% vs 0.6%), and the rate of severe systemic hemorrhage was less than 1%. Mortality rates were not significantly different between the groups (21% vs 17%). Absence of hemorrhage on noncontrast computed tomography (CT) was the only radiologic condition for proceeding with thrombolysis in this trial. However, on US Food and Drug Administration approval of IV rtPA for acute stroke, an additional radiologic exclusion criterion, the presence of multilobar low-attenuation changes on baseline CT, was added on the basis of exclusion criteria from the early European Cooperative Acute Stroke Study (ECASS) trials.<sup>5-7</sup> Intravenous rtPA is most effective when given shortly after symptom onset. In the NINDS study sample, after adjustment for stroke severity, patients treated within 90 minutes had significantly increased odds of improvement at 24 hours and favorable 3-month outcome compared with patients treated beyond 90 minutes (odds ratio [OR], 2.11 vs 1.69).<sup>8</sup> This result has been consistently found in subsequent studies. In a recent analysis of 58,353 IV rtPA-treated patients from the national Get With The Guidelines—Stroke registry, faster onset to treatment time, in 15-minute increments, was associated with reduced mortality (OR, 0.96; 95% CI, 0.95-0.98), reduced symptomatic ICH (OR, 0.96; 95% CI, 0.95-0.98), and increased rate of independent ambulation at hospital discharge (OR, 1.04; 95% CI, 1.03-1.05).<sup>9</sup>

Following approval of IV rtPA for the treatment of acute ischemic stroke by the US Food and Drug Administration in 1996, rtPA gained international acceptance, and its effectiveness and safety have been repeatedly confirmed by several postmarketing observational studies of real-world clinical practice. One of the largest was SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study), which included 6483 patients from nearly 300 centers in 14 European countries.<sup>10</sup> The rate of symptomatic ICH (sICH) in this population at 24 hours was only 1.7%, and the 3-month mortality rate was 11.3%. These unfavorable events

#### ARTICLE HIGHLIGHTS

- Intravenous (IV) recombinant tissue plasminogen activator (rtPA) remains the only proven therapy for acute ischemic stroke and is most effective when given early.
- There is evidence that the “therapeutic window” for IV rtPA can be extended to 4.5 hours for most patients with stroke who are less than 80 years old, but efficacy and safety are greatest when thrombolytic therapy is administered within the first 3 hours.
- Factors most predictive of prognosis include onset to treatment time, stroke severity (National Institutes of Health Stroke Scale score), age, and blood glucose levels.
- The most feared complication of IV rtPA is symptomatic intracranial hemorrhage, which occurs in 2% to 6% of patients.
- Postthrombolysis intracranial hemorrhage should prompt neurosurgical evaluation, strict blood pressure control, and consideration of antifibrinolytic agents, cryoprecipitate, and platelet transfusion.

occurred at lower rates than those reported in the pooled analysis of earlier randomized trials of IV thrombolysis for stroke, and even centers with very limited IV thrombolysis experience achieved good results. The lower rate of sICH is likely due to a different definition of sICH in this study (parenchymal hemorrhage in  $>30\%$  of infarcted area with substantial mass effect combined with neurologic deterioration of  $\geq 4$  points on the National Institutes of Health Stroke Scale [NIHSS] or leading to death).<sup>10</sup> Although treatment with IV rtPA has become standard of care for patients with acute ischemic stroke, only 3% to 5% actually receive the therapy.<sup>11-13</sup> Utilization is increased in academic teaching medical centers—particularly those with neurology training programs—but still is generally less than 5%.<sup>14</sup> The main reason for this low rate is that many patients present for medical attention beyond 3 hours after symptom onset. This delay has led to interest in expanding the therapeutic window for IV rtPA. In 2004, a pooled analysis of 6 trials of IV rtPA administered up to 6 hours after symptom onset suggested that a clinical benefit may exist even when rtPA was administered beyond 3 hours.<sup>15</sup> This analysis confirmed that efficacy is greatest when IV rtPA is given within 90 minutes of symptom onset but showed similar efficacy between time to treatment of 91 to 180 and 181

to 270 minutes. Subsequently, results of the ECASS III trial, a European multicenter randomized trial that evaluated rtPA vs placebo administered between 3 and 4.5 hours after stroke symptom onset, was published.<sup>7</sup> In this study of 821 patients, the odds of regaining full independence were 28% higher among rtPA-treated patients, and these results led to international recommendations to expand the time window for thrombolysis to 4.5 hours. The mortality rate was slightly higher in the placebo arm, but there was not a statistically significant difference between the groups. Symptomatic ICH—as defined by NINDS criteria—occurred in 7.9% in the rtPA group but caused neurologic worsening in only 2.4%. It should be noted that additional exclusion criteria were used in ECASS III, including age greater than 80 years, the combination of previous stroke and diabetes mellitus, anticoagulation regardless of international normalized ratio, and NIHSS score greater than 25. Thus, when recommending treatment with IV rtPA for this extended time window it is prudent to consider these factors as possible contraindications.

The large European observational study SITS-ISTR (Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register) confirmed that IV rtPA is effective when administered 3 to 4.5 hours after ischemic stroke symptom onset.<sup>16</sup> An analysis of 29,618 patients with acute ischemic stroke from SITS-ISTR during 2002-2011 revealed that patients treated within 3 to 4.5 hours had rates of functional independence of 63%, sICH of 1.8%, and mortality of 11%.<sup>17</sup> There was no significant difference in these rates compared with those treated with IV thrombolysis within 3 hours, although this comparison was not controlled for initial stroke severity. Furthermore, in this registry, patients treated within 4.5 to 6 hours had outcomes comparable to those of patients treated within 3 hours.<sup>17</sup> However, when onset to treatment time was analyzed as a continuous variable, it was significantly associated with higher sICH rates and unfavorable 3-month outcomes, again highlighting the well-established value of early treatment. Treatment between 3 and 4.5 hours after symptom onset has been supported and recommended by many international regulatory agencies, but the US Food and Drug Administration did not approve its use in this time frame. The basis for that decision was kept confidential,

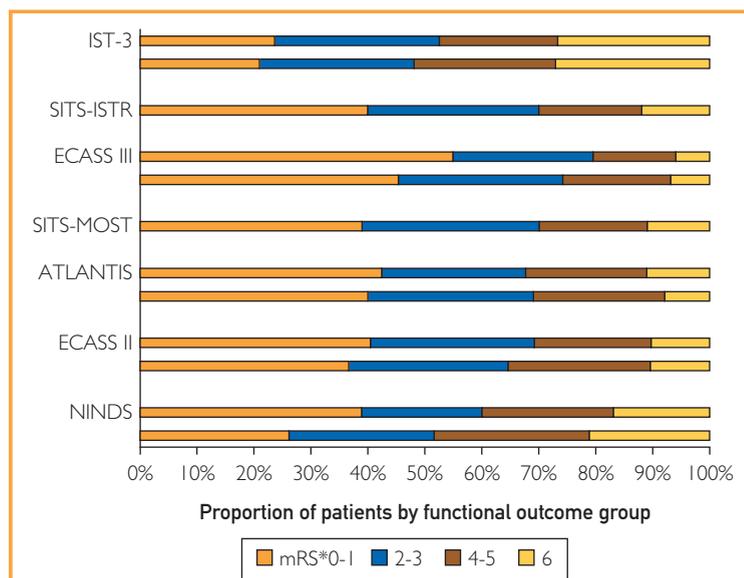
but it is thought that they believed the evidence supporting rtPA efficacy within this window was inconclusive. Conversely, the American Heart Association (AHA) has recommended treatment with IV rtPA to eligible patients within 3 and 4.5 hours after symptom onset with the additional exclusion criteria listed in ECASS III.<sup>18</sup> At Mayo Clinic in Rochester, Minnesota, we typically adhere to these additional exclusion criteria as well and offer off-label rtPA to eligible patients who present within this extended time window.

The third International Stroke Trial (IST-3) was a multicenter randomized trial from 12 countries that tested the efficacy and safety of IV rtPA only in patients in whom there was clinical uncertainty about its usefulness.<sup>19</sup> Thus, if patients with acute stroke had clear indications or contraindications for treatment with IV thrombolysis, they were not included. If the clinician was convinced that the patient should or should not be treated with IV rtPA, then the patient was not randomized. Randomization occurred only if the patient met eligibility criteria and the clinician was truly uncertain about the risks and benefits of rtPA for that individual. Patients undergoing thrombolysis were treated relatively late in this study, with a median time from symptom onset to treatment of 4.2 hours (3.2-5.2 hours). The study enrolled 3035 patients but was underpowered to detect a difference between groups for its primary outcome (6000 patients were needed by estimated sample size). This was a primarily negative trial because at 6 months, 37% of rtPA-treated patients were alive and independent vs 35% of the control group ( $P=.18$ ). There was a favorable shift in 6-month functional outcomes for those receiving thrombolysis (OR, 1.27 for outcome ranging from no disability to moderate disability for rtPA group vs control group), but the shift analysis was not planned at the beginning of the trial. Subgroup analysis suggested benefit in elderly patients (age >80 years) and in patients treated between 4.5 and 6 hours.<sup>19</sup> However, the lower benefit observed in younger patients and the lack of significant benefit in patients treated within the 3- to 4.5-hour time window incited questions over the reliability of these subgroup analyses. Functional outcomes of patients in major thrombolysis stroke studies are shown in [Figure 1](#).

Our knowledge about safe candidates and how to optimize the effect of IV rtPA continues

to grow and will be enhanced by results of ongoing trials. A large area of ongoing research involves the possible extension of IV lysis to patients historically excluded, such as patients who wake up from sleep with stroke symptoms. Two trials are currently recruiting patients to study this population: one is studying the effect and safety of giving IV rtPA to patients within 3 hours of waking,<sup>21</sup> and the other, the WAKE-UP trial, will treat patients with a mismatch in visibility of an acute ischemic lesion between diffusion-weighted magnetic resonance imaging and fluid-attenuated inversion recovery magnetic resonance imaging (“DWI-FLAIR mismatch”) performed within 4.5 hours of awakening.<sup>22</sup> Additionally, sonothrombolysis, the use of transcranial Doppler ultrasonography to enhance clot dissolution following administration of IV lysis, has had promising results. Meta-analyses of sonothrombolysis studies have revealed safety, improved recanalization rates, and better clinical outcomes compared with IV rtPA alone, but with wide confidence intervals.<sup>23,24</sup> Results of the CLOBUST-ER trial (Combined Lysis of Thrombus With Ultrasound and Systemic tPA for Emergent Revascularization in Acute Ischemic Stroke), a phase 3 randomized trial that is currently recruiting, will shed light on the usefulness of this adjunct.<sup>25</sup> Eptifibatide, a glycoprotein IIb/IIIa antagonist, is also under investigation as an adjunctive treatment to IV rtPA. In a multicenter double-blind safety study (CLEAR-ER [Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke—Enhanced Regimen]), patients with stroke were randomized to a lower dose of rtPA (0.6 mg/kg) in combination with eptifibatide (bolus and 2-hour infusion) compared with treatment with standard IV rtPA (0.9 mg/kg).<sup>26</sup> Symptomatic ICH occurred in 2 of 101 patients (2%) in the combined treatment group compared with 3 of 25 patients (12%) in the standard rtPA group (OR, 0.15; 95% CI, 0.01-1.40). However, an earlier phase 3 trial of abciximab—another glycoprotein IIb/IIIa antagonist—was prematurely terminated because of an unfavorable benefit-risk profile (5.5% of abciximab-treated and 0.5% of placebo-treated patients had sICH).<sup>27</sup> Recruitment is ongoing for another trial randomizing patients to full-dose IV rtPA in combination with eptifibatide or standard IV rtPA alone.<sup>28</sup>

One of the biggest barriers to more widespread use of rtPA is that a substantial proportion of the population does not live near a hospital with rtPA capability. The delay caused by the need to transfer patients from these areas to another hospital often shifts these patients outside the therapeutic window. As a result, there has been recent interest in developing and expanding practices using audiovisual telemedicine so that thrombolysis can be administered to more patients in their community with real-time interaction between local practitioners, patients, and stroke experts.<sup>29,30</sup> One randomized trial of 234 patients with acute stroke found that the decision to administer rtPA was “correct” more often in those evaluated by telemedicine than by telephone (98% vs 82%;  $P < .001$ ) consultation.<sup>31</sup> There were no



**FIGURE 1.** Outcomes were assessed at 90 days after stroke. \*Modified Rankin Scale was used for all studies except the third International Stroke Trial (IST-3),<sup>19</sup> which used the Oxford Handicap Scale. In studies with 2 bars, the top bar indicates those who were treated with intravenous recombinant tissue plasminogen activator (IV rtPA), and the bottom bar represents patients in the placebo or control arm. The Safe Implementation of Treatments in Stroke (SITS) studies were observational without control groups. The IV rtPA was given within 0 to 3 hours of symptom onset for the National Institute of Neurological Disorders and Stroke rtPA Stroke Study (NINDS),<sup>2</sup> the SITS-Monitoring Study (SITS-MOST),<sup>10</sup> and the SITS-International Stroke Thrombolysis Register (SITS-ISTR)<sup>16</sup>; 0 to 6 hours for the European Cooperative Acute Stroke Study (ECASS) II<sup>6</sup> and IST-3<sup>19</sup>; 3 to 5 hours for the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study<sup>20</sup>; and 3 to 4.5 hours for ECASS III.<sup>7</sup> Note that IST-3 included only patients in whom clinicians were uncertain whether IV rtPA would be beneficial.

statistically significant differences in rates of good functional outcome, mortality, or rates of ICH between the groups.

Intravenous thrombolysis is not only effective in clinical trials and in real-world practice but also produces economic benefits by reducing societal and health care costs.<sup>32-34</sup> Although rtPA use results in extra costs in the acute care setting (cost of rtPA itself, stay in an intensive care unit, additional brain imaging, and increased overall length of stay), these costs are more than offset by the ultimate reduction in long-term disability costs.<sup>32</sup> One analysis of expected cost savings from rtPA use in the United States estimated that \$7.4 million can be saved for every 2% increase in rtPA-treated patients.<sup>33</sup> Another model derived from a systematic review found that rtPA use in the United States is associated with \$60 million in direct savings to society and an additional 7510 quality-adjusted life-years, for a total benefit of \$363 million.<sup>32</sup>

### PATIENT SELECTION

Patients with acute ischemic stroke require emergent medical evaluation because brain cells die rapidly without adequate blood flow,

and IV rtPA is most effective for acute stroke when given early. Hospitals need to implement protocols to triage patients quickly to medical centers with the capability of rapid neurologic assessment and treatment of acute stroke. Within very efficient systems, it is possible to reduce the time to IV thrombolysis to as short as 20 minutes on average.<sup>35</sup> Methods that reduce delays to treatment include premixing rtPA before patient arrival and taking the patient directly to the CT suite, where the brief neurologic examination takes place, blood is withdrawn, and rtPA bolus is given.<sup>35</sup> Furthermore, treatment can be accelerated by enhancing prehospital care through education of dispatchers, direct communication between paramedics and stroke specialists,<sup>35</sup> and even transporting CT scanners and neurologists to the field in ambulances.<sup>36</sup> Many of the contraindications to IV thrombolysis (Table 1) are derived from exclusion criteria of early major randomized trials. The rationale underlying many of the criteria is based on data from small observational studies or expert opinion, and the contraindications for IV rtPA vary slightly among the AHA guidelines, the European Stroke Initiative recommendations, and the alteplase package insert.<sup>37</sup> For example, rapidly improving or minor symptoms are considered a relative contraindication in the alteplase package insert and the AHA guidelines but are not listed as contraindications in the European guidelines.<sup>18,38</sup> Recent myocardial infarction is a contraindication in the AHA guidelines but not in the European guidelines or the alteplase package insert.

The single most important part of the acute stroke history is determination of the time of symptom onset. Current AHA guidelines define symptom onset as the last time that the patient was at his or her previous baseline or in a symptom-free state.<sup>18</sup> Neurologic examination should be brief, timely, and focused. The use of a standardized examination such as the NIHSS (Supplemental Table, available online at <http://www.mayoclinicproceedings.org>) allows rapid quantification of deficits and facilitates communication among health care professionals in addition to providing early information about prognosis.<sup>18</sup>

Only a few diagnostic tests are absolutely necessary before administering IV rtPA for acute stroke. Required tests include noncontrast head

**TABLE 1. Contraindications to Administration of IV rtPA for Acute Ischemic Stroke Within 3 Hours of Symptom Onset**

Clinical contraindications
Major head trauma or stroke within the previous 3 mo
Sustained hypertension >185 mm Hg systolic or >110 mm Hg diastolic
Active internal bleeding
Blood glucose level <50 mg/dL (2.7 mmol/L) and symptoms resolve with administration of dextrose
History of intracranial hemorrhage
Major surgery or serious trauma within the previous 14 d
Acute bleeding diathesis
Platelet count <100 × 10 <sup>9</sup> /L
Heparin received within 48 h resulting in elevated apTT
Anticoagulation resulting in INR >1.7
Current use of direct thrombin inhibitors or factor Xa inhibitors with elevated laboratory test results (eg, apTT, TT, ECT, or factor Xa activity assays)
Pregnancy
Gastrointestinal or urinary tract hemorrhage within the previous 21 d
Acute myocardial infarction within the previous 3 mo
Radiographic contraindications
Multilobar infarction (hypodensity of more than one-third of the MCA territory)
Intracranial hemorrhage

apTT = activated partial thromboplastin time; ECT = ecarin clotting time; INR = international normalized ratio; IV rtPA = intravenous recombinant tissue plasminogen activator; MCA = middle cerebral artery; TT = thrombin time.

CT (to exclude ICH and large established infarction) and blood glucose measurement. For most acute ischemic stroke evaluations, clinicians do not need to await the results of laboratory tests—except for blood glucose concentration—before administering IV rtPA.<sup>18</sup> If patients are currently taking or have recently taken anticoagulants or if they have a history of thrombocytopenia, end-stage liver disease, or hematologic disorders, then the activated partial thromboplastin time and prothrombin time/international normalized ratio need to be checked before administration. The increasing use of direct thrombin inhibitors and factor Xa inhibitors adds complexity to the assessment of patients because routine coagulation parameters are not reliable indicators of the anticoagulation effect of these agents. The AHA guidelines recommend against treating patients currently taking these novel oral anticoagulants if more sensitive laboratory values are elevated (eg, thrombin time, ecarin clotting time, factor Xa activity assays).<sup>18</sup> This is an area of current uncertainty that demands research. Other tests such as electrocardiography, chest radiography, and measurement of serum electrolytes and hemoglobin level are reasonable to obtain in the emergency setting, but thrombolysis should not be delayed while awaiting results of these tests.<sup>18</sup>

Fear of misdiagnosis of a possible “stroke mimic” such as seizure, migraine, or functional disorder should not prevent the administration of IV rtPA if there is reasonable concern for acute ischemic stroke. The risk of sICH in patients with these disorders is exceedingly low,<sup>39-43</sup> and the consequences of missing the opportunity to treat acute ischemic stroke could be devastating. In fact, some of the traditional contraindications such as seizure at onset of symptoms or minor or resolving stroke symptoms are no longer considered absolute contraindications.<sup>18,44</sup> Observational studies have found that approximately 25% to 30% of patients who do not undergo thrombolysis because of mild or improving symptoms have unfavorable outcomes, including permanent disability.<sup>45,46</sup>

#### **PRACTICALITIES: ADMINISTRATION AND POSTTHROMBOLYSIS CARE**

Intravenous rtPA should be administered as quickly as possible once a patient with a

potentially disabling deficit has been deemed eligible. The dose is 0.9 mg/kg (maximum, 90 mg) with 10% given as a bolus over 1 minute and the remainder infused over 1 hour. The patient should be admitted to a specialized stroke unit or neurocritical care intensive care unit for postthrombolysis care. Protocol-guided care may be useful to standardize and optimize care and to avoid risks. Patients should be monitored with cardiac telemetry for at least 24 hours. Neurologic examinations should be performed and vital signs should be monitored every 15 minutes for the first 2 hours, followed by every 30 minutes for the next 6 hours and then hourly until 24 hours following treatment. Optimal management of arterial blood pressure (ABP) after acute ischemic stroke is complex, particularly if the recanalization status of an occluded artery is unknown. Although exact blood pressure goals are not derived from rigorous data, marked hypertension in IV rtPA-treated patients has been associated with sICH.<sup>47</sup> Intravenous labetalol or nicardipine infusions are effective agents for most patients. Guidelines recommend smoothly lowering ABP to less than 185/110 mm Hg before thrombolysis and maintaining ABP at less than 180/105 mm Hg thereafter.<sup>18</sup> Intravenous labetalol (10- to 20-mg bolus doses) and/or a continuous IV nicardipine infusion (5-15 mg/h) are sufficient for most hypertensive stroke patients. If hypertension is severe and/or resistant to these measures, an infusion of sodium nitroprusside can be considered. It has been deemed prudent to avoid invasive procedures during the first 24 hours after rtPA administration. This includes the placement of nasogastric feeding tubes or urinary catheters, but we consider it reasonable to place these devices if necessary after several hours given that the initial half-life of alteplase is less than 5 minutes. The optimal timing of mobilizing patients after rtPA administration is not clear, but it is often avoided for 24 hours. A small pilot study mobilized 10 patients between 12 and 24 hours after administration of rtPA and found that only 1 patient had an adverse event (orthostatic hypotension).<sup>48</sup> A difficult circumstance arises when a patient requires decompressive hemicraniectomy for treatment of malignant edema from large middle cerebral artery infarcts. One

study compared 20 patients undergoing decompressive hemicraniectomy who had received IV rtPA with 20 patients who had not been treated with rtPA and underwent the procedure.<sup>49</sup> Craniectomy was performed an average of 44 hours after stroke onset, and 2 patients in each group experienced new ICH or worsening of preexisting ICH. The optimal interval to wait before a major procedure such as this is performed is uncertain, and risks and benefits must be assessed on an individual basis. It may be reasonable to wait at least 24 hours after rtPA administration if possible.

The most feared complication after IV thrombolysis for acute stroke is ICH. This potentially devastating development occurs most commonly in older patients with severe deficits and large areas of ischemia at presentation.<sup>50,51</sup> Reperfusion injury is broadly considered to be the most common pathophysiologic mechanism causing sICH. Thus, patients who are at greatest risk of this complication already have a poor prognosis with high likelihood of disability. As a consequence, few patients are actually harmed by IV rtPA (number needed to harm has been estimated to be 126 for disabled or fatal outcome).<sup>51</sup>

Other complications of IV rtPA are much less frequent. Angioedema occurs in about 1.3% to 5% of cases, is more common in patients taking angiotensin-converting enzyme inhibitors, and often involves the orolingual regions ipsilateral to the side of hemiparesis.<sup>52</sup> The mainstays of treatment are antihistamines and corticosteroids. Although evidence-based recommendations regarding the dose and duration of these treatments are not available, we consider it reasonable to administer diphenhydramine at 25 to 50 mg IV, ranitidine at 50 mg IV, and dexamethasone at 6 to 10 mg IV and monitor the clinical response. Treatments can be continued for 24 to 72 hours as dictated by the severity and resolution or persistence of symptoms. Airway safety must be carefully monitored because the angioedema can occasionally involve the posterior laryngeal structures and lead to airway obstruction. Rarely, other life-threatening complications such as myocardial wall rupture or aortic dissection have occurred.

Prompt initiation of measures to prevent early recurrent stroke are important, and

antiplatelet agents and anticoagulants can be administered (or resumed) 24 hours after the administration of IV rtPA. It is generally safe to begin treatment with antiplatelet agents at 24 hours, but anticoagulation may need to be withheld longer depending on the risk of hemorrhage, which depends largely on the ultimate size of brain infarction. Notably, urgent anticoagulation, or “bridging” with full therapeutic doses of unfractionated heparin or low-molecular-weight heparin, is not recommended for patients with acute ischemic stroke who require anticoagulation (eg, patients with atrial fibrillation).<sup>18</sup> In our experience, most patients who require anticoagulation can begin treatment with vitamin K antagonists within days of the stroke, targeting therapeutic anticoagulation within 1 to 2 weeks from the event. However, early anticoagulation should be avoided when the infarction is large or in the presence of uncontrolled hypertension or bleeding diatheses. Direct thrombin inhibitors and factor Xa antagonists are alternatives to vitamin K antagonists, but reliable data regarding their efficacy and safety in very early secondary stroke prevention, particularly after the administration of IV rtPA, are currently unavailable.

## OUTCOME PREDICTION

The fundamental clinical predictors of poor outcomes in patients with acute ischemic stroke are advanced age, worse neurologic deficits (higher NIHSS score), disturbed consciousness at onset, and hyperglycemia.<sup>16,53,54</sup> More recently, renal function has also been identified as a predictor of outcome after acute stroke. Low estimated glomerular filtration rate is independently associated with poor outcomes, death, and sICH.<sup>55</sup> Radiographic predictors of poor outcome include early ischemic changes and hyperdense middle cerebral artery sign on baseline noncontrast CT.<sup>56</sup> As previously discussed, the time from symptom onset to administration of IV rtPA is strongly associated with outcomes, with earlier time to treatment predicting better clinical outcomes.<sup>9</sup> Over the past few years, several scales have been developed to quantify risk and assist with outcome prediction in patients with stroke (Table 2).<sup>57-60</sup> The DRAGON score<sup>57</sup> was designed to predict outcome for patients treated with IV thrombolysis and ranges from 0 to 10 points. The higher the score, the higher the likelihood a patient will have a poor

**TABLE 2. Scales to Predict Functional Outcome After Acute Ischemic Stroke<sup>a</sup>**

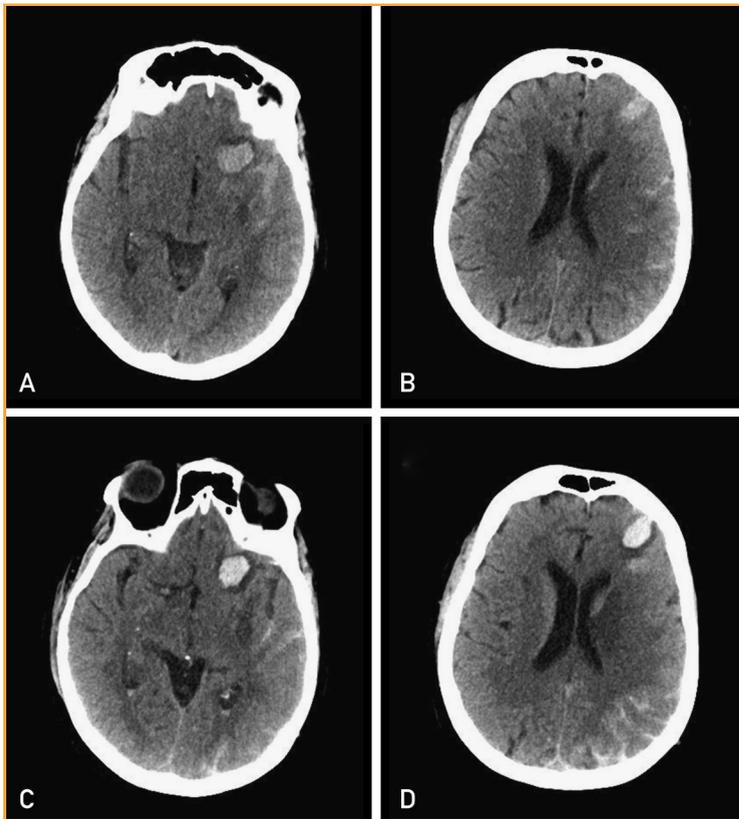
Scale or score	Variables	Derivation cohort	Scoring paradigms	Favorable outcome	AUC
DRAGON <sup>57</sup>	Hyperdense MCA or CT signs of early infarct, prestroke mRS score, age, glucose level, onset to treatment time, NIHSS score	1319 Stroke patients treated with IV lysis in Helsinki, Finland	2 Points: 88% favorable outcome 8 Points: 70% "miserable outcome" <sup>b</sup>	mRS score 0-2 at 3 mo	0.84
ASTRAL <sup>58</sup>	Age, severity of stroke (NIHSS score), time from stroke onset to admission, range of visual fields, glucose level, level of consciousness	1645 Stroke patients from the Acute Stroke Registry in Lausanne, Switzerland	Score $\leq$ 23: 80% favorable outcome Score $\geq$ 38: 20% favorable outcome	mRS score 0-2 at 3 mo	0.85
SPAN-100 <sup>59</sup>	Age, NIHSS score	624 Stroke patients from NINDS tPA trials	Score $<$ 100: 55% favorable outcome Score $\geq$ 100: 6% favorable outcome	Composite: mRS score 0-1, NIHSS score $\leq$ 1, Barthel index score $\geq$ 95, and GOS score 1 at 3 mo	0.64
THRIVE <sup>60</sup>	Age, NIHSS score, hypertension, diabetes mellitus, atrial fibrillation	5724 Stroke patients from VISTA	Score 0-2: ~70% good outcome Score 6-9: ~10% good outcome	mRS score 0-2 at 3 mo	0.76

<sup>a</sup>AUC = area under the receiver operating characteristic curve; CT = computed tomography; GOS = Glasgow Outcome Scale; IV = intravenous; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; tPA = tissue plasminogen activator; VISTA = Virtual International Stroke Trials Archive.  
<sup>b</sup>mRS score 5-6.

**TABLE 3. Scales to Predict Postthrombolysis ICH<sup>a</sup>**

Scale or score	Variables	Derivation cohort	Scoring paradigms	Findings
SPAN-100 <sup>59</sup>	Age, NIHSS score	624 Stroke patients from NINDS trials (312 received IV rtPA)	Score $<$ 100: 12% ICH Score $\geq$ 100: 42% ICH	OR <sup>b</sup> (95% CI) Any ICH: 4.93 (2.64-9.6) sICH: 3.5 (1.45-8.46) Fatal ICH: 5.0 (1.4-17.8)
THRIVE <sup>60</sup>	Age, NIHSS score, hypertension, diabetes mellitus, atrial fibrillation	5724 Stroke patients from VISTA	Score 0-2: ~3% ICH Score 6-9: ~10% ICH	Each 1-point increase in score was associated with an OR (95% CI) of 1.29 (1.16-1.43) for hemorrhage
HAT <sup>61</sup>	NIHSS score, diabetes mellitus or blood glucose $<$ 200 mg/dL, hypodensity on initial head CT	302 rtPA-treated patients from NINDS trials	ICH rate: Score 0, 6% Score 1, 16% Score 2, 23% Score 3, 36% Score $>$ 3, 78%	C statistic (95% CI): Any ICH, 0.70 (0.61-0.79) sICH, 0.68 (0.56-0.81) Fatal ICH, 0.75 (0.63-0.87)
SITS <sup>62</sup>	NIHSS score, blood glucose, age, body weight, time from stroke onset to treatment, antiplatelet agents, hypertension	13,908 patients treated with rtPA from SITS-ISTR	sICH rate: Score 0-2, 0.4% Score 3-5, 1.5% Score 6-8, 3.6% Score $\geq$ 9, 9.2%	C statistic: sICH, 0.67

<sup>a</sup>CT = computed tomography; ICH = intracerebral hemorrhage; IV = intravenous; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; OR = odds ratio; rtPA = recombinant tissue plasminogen activator; sICH = symptomatic ICH; SITS-ISTR = Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register; VISTA = Virtual International Stroke Trials Archive.  
<sup>b</sup>For patients with a positive SPAN-100 (score  $\geq$ 100) vs a negative SPAN-100 score.

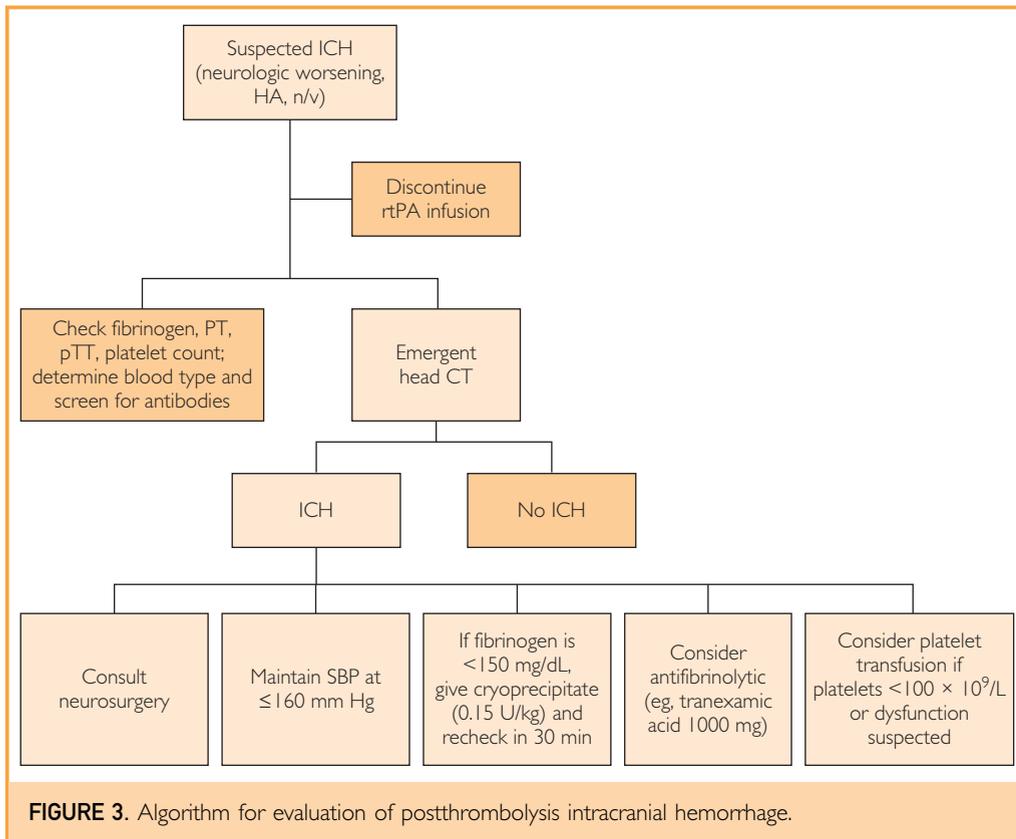


**FIGURE 2.** Example of postthrombolysis intracranial hemorrhage. Non-contrast computed tomography (CT) of the head shortly after infusion of recombinant tissue plasminogen activator shows intraparenchymal hemorrhage in the left inferior frontal lobe (A) and diffuse subarachnoid hemorrhage over the left cerebral hemisphere (B). Tranexamic acid (1000 mg intravenously), cryoprecipitate (2 U), and fresh frozen plasma (2 U) were administered. Repeated CT the following day showed minimal evolution of hemorrhage and hypodensity in the left middle cerebral artery territory consistent with ischemic infarction (C, D).

outcome. In the initial cohort, the proportions of patients with good outcome (modified Rankin Scale score of 0-2 at 3 months) were 96%, 88%, 74%, and 0% for scores of 0 to 1, 2, 3, and 8 to 10, respectively. The ASTRAL score<sup>58</sup> incorporates 6 variables: age, NIHSS score, time from stroke onset to admission, visual fields, glucose level, and level of consciousness. This score did not take thrombolysis into consideration but was validated in external populations. The Stroke Prognostication using Age and NIH Stroke Scale (SPAN)-100 index<sup>59</sup> is a simple method to estimate the clinical response of patients with stroke who are treated with thrombolysis. The index, calculated by combining age and NIHSS score, is considered

positive if the total is 100 or higher.<sup>59</sup> The Total Health Risks in Vascular Events (THRIVE) score<sup>60</sup> incorporates age, NIHSS score, and medical comorbidities of hypertension, diabetes mellitus, or atrial fibrillation. It predicts clinical outcomes, mortality, and risk of ICH.

Many of the same features that predict clinical outcomes also predict the occurrence of sICH: higher NIHSS score at presentation, larger areas of ischemia, and higher blood glucose levels (Table 3).<sup>59-62</sup> Additional factors include longer time to thrombolysis and higher systolic blood pressure at presentation.<sup>15,16,50,63</sup> It is notable that although elderly patients with acute stroke have favorable outcomes less frequently than younger patients (regardless of whether IV rtPA is given), the rates of sICH after IV thrombolysis are comparable, and the best available evidence indicates that the benefit from IV rtPA is not diminished in elderly patients.<sup>19,64,65</sup> The SPAN-100<sup>59</sup> and THRIVE<sup>60</sup> scores predict not only functional outcome but also risk of ICH after thrombolysis. Among patients receiving rtPA in the NINDS trial, ICH rates were higher for SPAN-100-positive patients vs SPAN-100-negative patients (42% vs 12%;  $P < .001$ ).<sup>59</sup> Each 1-point increase in THRIVE score is associated with a 29% increased chance of hemorrhage after rtPA (OR, 1.29; 95% CI, 1.16-1.43).<sup>60</sup> Other scores have been developed specifically to predict ICH after IV rtPA. The hemorrhage after thrombolysis (HAT) score is a 5-point scale based on the NIHSS score, hypodensity on CT, baseline glucose level, and history of diabetes. The proportion of patients in whom ICH develops after rtPA increases with higher HAT scores (C statistic, 0.70).<sup>61</sup> A larger cohort of 31,627 patients treated with IV rtPA from the SITS Registry formed the basis of the development of the SITS symptomatic intracerebral hemorrhage risk score.<sup>62</sup> In this database, 9 independent risk factors for sICH were identified: NIHSS score, glucose level, systolic blood pressure, age, body weight, stroke onset to treatment time, aspirin or combined aspirin and clopidogrel, and history of hypertension. The score ranges from 0 to 12 points, and there was a more than 70-fold increase in the rate of sICH for those with a score of 10 or more points compared with patients with no points. Although these prediction scales are useful to stratify those patients at highest risk of



**FIGURE 3.** Algorithm for evaluation of postthrombolysis intracranial hemorrhage.

hemorrhagic complications and poor outcome, they should not be used to make therapeutic decisions because patients with high scores who are eligible for rtPA should still be treated.<sup>66</sup>

**MANAGING HEMORRHAGIC COMPLICATIONS**

Most sICHs after IV thrombolysis for stroke occur in the first 24 hours. If a patient experiences neurologic deterioration after thrombolysis, emergency CT should be performed to exclude ICH. If it is still being administered, the infusion of rtPA should be discontinued and a complete blood cell count, fibrinogen levels, coagulation parameters, and blood type and antibody screen should be obtained. Depending on the size and extent of hemorrhage, there may be reason to consider reversing the fibrinolytic effect of rtPA. Generally, small petechial hemorrhages—particularly when found incidentally—or microhemorrhages on gradient echo sequences should be monitored but do not require active intervention. Larger parenchymal hematomas, subarachnoid hemorrhage, and the presence of mass effect or intraventricular

hemorrhage are factors that may prompt reversal. There is no universally accepted standardized guideline for reversal of thrombolysis-associated hemorrhages, but many protocols advise administering cryoprecipitate if fibrinogen levels are low (<150 mg/dL). Antifibrinolytics, such as tranexamic acid or aminocaproic acid, have not been well studied, but their use is backed by solid pathophysiologic rationale. Tranexamic acid competitively inhibits the activation of plasminogen and may stabilize hemorrhage expansion.<sup>67</sup> Figure 2 depicts an example of a patient with postthrombolysis ICH who was treated with tranexamic acid, fresh frozen plasma, and cryoprecipitate and had no further hemorrhage expansion or deterioration. Surgical evacuation of hematomas can be considered on the basis of the size and location of the ICH and the patient’s overall medical condition and capacity for rehabilitation. A suggested algorithm for management of sICH after IV thrombolysis for acute ischemic stroke is shown in Figure 3, but it is empirical rather than data based. Further studies are warranted to determine the optimal management strategy.

## FUTURE DIRECTIONS

The introduction of IV rtPA nearly 2 decades ago marked the end of one era, in which ischemic stroke was generally considered untreatable, and the beginning of another, in which we are only beginning to recognize the impact that treatments can have in improving stroke outcomes. It is likely that as we continue to gain experience, the inclusion and exclusion criteria for IV rtPA will be relaxed, and this change—in combination with the increasing use of telemedicine—will allow more patients with ischemic stroke to be considered for treatment. Some fibrinolytic alternatives, such as tenecteplase, show promise<sup>68</sup> and may be even more effective than alteplase. The use of advanced brain imaging techniques (CT perfusion, magnetic resonance imaging perfusion, arterial spin-labeled perfusion) may assist in refining our selection of the optimal candidates for emergent revascularization therapies. The organization of prehospital care systems in which neuroprotectants can be studied and administered opens up myriad opportunities. The future of acute stroke treatment appears bright with abundant opportunities to improve our ability to salvage ischemic brain tissue and improve patient outcomes.

## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>.

**Abbreviations and Acronyms:** **ABP** = arterial blood pressure; **AHA** = American Heart Association; **CT** = computed tomography; **ECASS** = European Cooperative Acute Stroke Study; **ICH** = intracranial hemorrhage; **IV** = intravenous; **NIHSS** = National Institutes of Health Stroke Scale; **NINDS** = National Institute of Neurological Disorders and Stroke; **OR** = odds ratio; **rtPA** = recombinant tissue plasminogen activator; **sICH** = symptomatic ICH; **SPAN-100** = Stroke Prognostication using Age and NIH Stroke Scale; **THRIVE** = Total Health Risks in Vascular Events

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