

# Emerging Therapies for Acute Ischemic Stroke

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Stroke is a major public health problem in the United States and the development of novel therapeutic strategies is an important research priority. Advances in this field are proceeding on several fronts, including the use of next-generation plasminogen activators and glycoprotein IIb/ IIIa inhibitors, refined patient selection with advanced magnetic resonance imaging sequences, endovascular approaches to thrombolysis and thrombectomy, and adjuvant use of ultrasound. There remains no proven therapy for intracerebral hemorrhage, but early results with recombinant activated factor VII look very promising. It is hoped that in the near future, physicians managing patients with acute neurological events will have a robust armamentarium of therapies to bring to bear on both ischemic and hemorrhagic vascular disease.

*Keywords:* stroke, thrombolysis, embolectomy, ultrasound, neuroprotection, neuroimaging

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## INTRODUCTION

A stroke is an abrupt onset of clinically evident brain dysfunction due to vascular pathology. Approximately 80% of strokes are caused by cerebral ischemia,<sup>1</sup> which often results from embolism of thrombus from the heart or carotid bifurcation to an intracranial artery. In situ thrombosis of intracranial arteries also occurs, often in very small penetrating branches.

About 15% of strokes are caused by hemorrhage in the cerebral parenchyma. This usually results from rupture of a small parenchymal vessel and may be associated with hypertension. The remaining 5% are caused by subarachnoid hemorrhage, usually resulting from rupture of a saccular aneurysm in the circle of Willis.

In the United States, stroke is the third leading cause of death,<sup>2</sup> and a major cause of disability. This large public health burden will grow with the aging of our population, and thus the development of preventative and acute therapeutic strategies is an important research priority. This article will focus on emerging therapies for the treatment of acute ischemic stroke. Promising new treatments for intracerebral hemorrhage will also be discussed.

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## INTRAVENOUS THROMBOLYSIS

### Tissue plasminogen activator (alteplase)

Most strokes are caused by thrombotic occlusion of an intracranial artery,<sup>3,4</sup> and intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA, alteplase) is the only FDA-approved treatment. In two pivotal trials (published in an article), rt-PA was shown to increase the probability of complete recovery, as measured by a modified Rankin scale score of 0 to 1 in 90 days, from 26% to 39%.<sup>5</sup> This overall favorable response was seen despite a symptomatic intracerebral hemorrhage rate of 6.4%. It represents a 50% relative increase in favorable outcomes and a number-needed-to-treat of 8 to prevent a case of any disability.

### TNK (tenecteplase)

rt-PA administration is somewhat cumbersome, requiring reconstitution of 1 to 2 bottles of drug, withdrawal of a bolus dose, transfer of the remaining dose into an intravenous (IV) bag, and infusion of the remainder over 1 hour. TNK, a genetically modified form of rt-PA, has greater specificity for plasminogen that is bound to fibrin, reduced affinity for plasminogen activator inhibitor-1, and a longer plasma half-life.<sup>6</sup> These attributes allow for single bolus dosing. For acute myocardial infarction, TNK is associated with rates of mortality and cerebral hemorrhage equivalent to, and extracerebral hemorrhage lower than, rt-PA.<sup>7</sup> A pilot

dose-escalation study of TNK in acute stroke found no symptomatic intracerebral hemorrhages at doses of 0.1, 0.2, and 0.4 mg/kg.<sup>8</sup> Functional outcomes were similar to historical controls treated with rt-PA. A phase 2b/3 study is underway.

### Ancrod

Ancrod is a defibrinogenating agent derived from the Malaysian pit viper, *Calloselasma rhodostoma*. Cleavage of fibrinogen and formation of ancrod-fibrin complexes produces anticoagulation and thrombolysis, and 3 pilot studies<sup>9-11</sup> in acute ischemic stroke patients provided encouragement for further testing.

The stroke treatment with ancrod trial randomized 500 subjects to a 72 hour infusion of drug or placebo, with additional 1 hour infusions at 96 and 120 hours from symptom onset. The infusions were to be started within 3 hours of symptom onset, and the rates were adjusted to achieve fibrinogen levels between 1.18 and 2.03  $\mu\text{mol/L}$ . The primary outcome was functional independence as measured by a Barthel index of 95 to 100, or return to baseline functional status for those who had premonitory impairments. This was achieved in 41.1% of treated subjects versus 35.3% in the placebo arm. There were no statistically significant differences in mortality (25.4% vs. 23.0% at 90 days) or symptomatic intracerebral hemorrhage (5.2% vs. 2.0%).

Clinical application of these results was hampered by the fact that a subsequent European trial, enrolling subjects up to 6 hours from onset, was terminated early due to a failed futility assessment at a planned interim analysis.<sup>12</sup> Subjects (1222) had been enrolled at that time, and 90-day mortality was higher in the ancrod group than placebo. A new phase 3 study, also enrolling subjects within 6 hours, was stopped for futility.<sup>13</sup>

### Desmodus salivary plasminogen activator $\alpha$ -1 (desmoteplase)

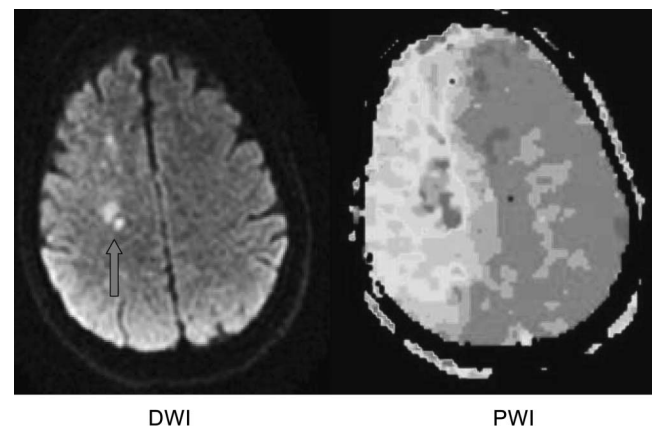
Desmoteplase is a recombinant plasminogen activator derived from the saliva of the vampire bat *Desmodus rotundus*. Like TNK, it exhibits very high fibrin specificity, has a long half-life, and can be administered as a bolus. In the desmoteplase in acute ischemic stroke trial, desmoteplase improved cerebral perfusion and vascular patency as measured by magnetic resonance imaging (MRI), and clinical outcome as measured by the National Institutes of Health stroke scale, the modified Rankin scale, and the Barthel Index.<sup>14</sup>

An important feature of this trial was the use of MRI for patient selection. It has been hypothesized that an MRI sequence called diffusion-weighted imaging identifies brain tissue that is irreversibly injured, whereas perfusion-weighted imaging identifies tissue

whose perfusion is compromised, but which may still be salvageable. The term diffusion-perfusion mismatch is applied when the area of compromised perfusion is larger than the area of restricted diffusion, implying that acute intervention might prevent further irreversible injury<sup>15</sup> (Fig. 1).

It should be noted that "diffusion-perfusion mismatch" is not synonymous with "ischemic penumbra",<sup>16</sup> a term originating in animal models of stroke and denoting tissue that is electrically silent, but with relatively normal ionic homeostasis<sup>17</sup> and histology.<sup>18</sup> Positron emission tomography (PET) provided a different surrogate for the ischemic penumbra in humans, identifying regions of reduced blood flow and increased oxygen extraction termed "miserable perfusion".<sup>19</sup> Using similar PET attributes as the reference standard, it has recently been shown in acute stroke patients that diffusion-weighted imaging tends to overestimate the volume of irreversibly injured tissue, and that diffusion-perfusion mismatch does not correspond well with the PET-defined ischemic penumbra.<sup>20</sup>

Thus, the new MRI sequences are not well validated, but the desmoteplase in acute ischemic stroke trial suggests that they may nonetheless be empirically useful in patient selection for future stroke therapies. Including subjects selected by MRI characteristics that may correlate with reversible cerebral ischemia allowed the time window for treatment to be widened to 9 hours. This is the first study ever to show a benefit of IV thrombolysis beyond 3 hours, but further verification of these results is necessary before they are applied in clinical practice. A phase 3 study is underway.



**FIGURE 1.** Diffusion-perfusion mismatch. The left panel shows small foci of restricted diffusion (red arrow). In the right panel, these foci exhibit severely reduced perfusion (orange), and are surrounded by a much larger territory of less severely compromised perfusion that represents the mismatch (yellow). DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging.

## GLYCOPROTEIN IIB/IIIA INHIBITORS

Glycoprotein IIb/IIIa receptors are found exclusively on the platelet membrane.<sup>21</sup> They bind fibrinogen and von Willebrand factor, and mediate platelet aggregation, which is one of the early steps in thrombus formation. Inhibitors of the glycoprotein IIb/IIIa receptor are approved by the US Food and Drug Administration for use after coronary stenting, for unstable angina, and in acute coronary syndromes where percutaneous coronary intervention is planned. These agents have recently been tested in acute ischemic stroke.

### Abciximab

Abciximab is an F<sub>ab</sub> fragment of a human/murine chimeric antibody that noncompetitively inhibits the glycoprotein IIb/IIIa receptor. A pilot study in rt-PA-ineligible subjects presenting within 24 hours of symptom onset,<sup>22</sup> and a phase 2 study in rt-PA-ineligible subjects presenting within 6 hours of symptom onset,<sup>23</sup> suggested that a 0.25 mg/kg bolus followed by a 12 hour infusion at 0.125 mcg/kg/min was safe. A phase 3 study was conducted to study this regimen in 2 populations: Subjects treated within 5 hours of onset, and subjects treated either within 6 hours of onset or 3 hours of awakening with a stroke. In October 2005, the trial was halted by the safety and efficacy monitoring committee due to "an observed safety concern."<sup>24</sup>

### Tirofiban

Tirofiban is a nonpeptide molecule that contains the arginine-glycine-aspartate sequence found in fibrinogen. Like abciximab, it is FDA approved for several coronary indications. Experience with this drug in stroke treatment is limited to a few promising pilot studies. A small study enrolled acute stroke subjects suffering from progressive neurologic deterioration; however, the drug caused no intracerebral hemorrhages.<sup>25</sup> Others showed benefit on the outcome measures of decreased infarct size<sup>26</sup> on MRI and vessel recanalization<sup>27</sup> on magnetic resonance angiography.

## ENDOVASCULAR PROCEDURES

Because of slow dissolution, IV thrombolysis is relatively ineffective when stroke is caused by a large thrombus occluding a proximal cerebral vessel segment. In an angiographic study, IV rt-PA treatment resulted in recanalization of only 38% of distal and 26% of proximal middle cerebral artery occlusions.<sup>4</sup> IV therapy also carries the risk of intracerebral and systemic bleeding complications, rendering treatment

more dangerous in the postoperative period, for example.

Endovascular treatment offers the advantage of better focusing therapy on the thrombus, which may offer a better chance of successful recanalization. Because lower thrombolytic doses are used, there may be a lower risk of systemic complication. Disadvantages are the need for an angiography suite, and trained interventional neuroradiologists, nurses, and technicians. Such resources are not widely available, and when they are, take time to mobilize. Accurate catheter placement requires yet additional time.

### Intra-arterial thrombolysis

Prolyse in acute cerebral thromboembolism II is the largest study of intra-arterial thrombolysis.<sup>28</sup> Included were 180 subjects presenting within 6 hours of symptom onset and demonstrating occlusion of the middle cerebral artery on catheter angiography. Subjects were randomized to receive the recombinant plasminogen activator pro-urokinase with a heparin infusion versus heparin alone in the control arm. Because baseline stroke severity is greater in a population with proximal middle cerebral artery occlusion compared to the stroke population as a whole, a favorable outcome in this study was defined by a modified Rankin scale score of 0–2, instead of 0–1 as in the pivotal IV rt-PA trials.

In the treatment arm, vascular recanalization was accomplished in 66% of the subjects, and 40% achieved a modified Rankin score of 0–2. In the control arm, only 18% of subjects had recanalization, and 25% achieved a modified Rankin score of 0–2. There was no difference in mortality (25% to 27%) but the treated group had a 10% rate of symptomatic intracerebral hemorrhage, versus 2% in the controls.

Although prourokinase was associated with significant benefit, these results were not accepted by the FDA for licensure without a confirmatory study, which has not been done. The drug is no longer available in the US, but the favorable results have provided additional encouragement to frequent intra-arterial use of other thrombolytics on an off-label basis.

### Combined IV and intra-arterial thrombolysis

The treatment delay imposed by mobilization of an interventional neuroradiology team and placement of the catheter suggest that a combined IV–intra-arterial approach could be of value. IV treatment can be started in most hospitals pending mobilization of the interventional team or transfer to a higher level of care. If cerebral angiography demonstrates persistent arterial occlusion, intra-arterial thrombolysis can then be attempted. Several pilot studies have demonstrated

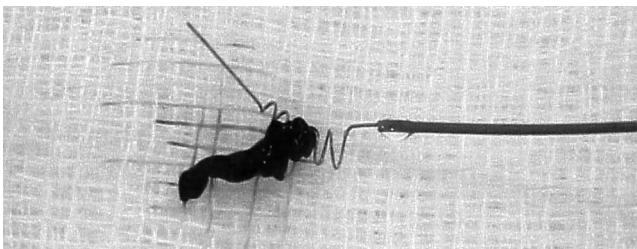
the feasibility of this approach,<sup>29-34</sup> but no trial to date has had sufficient power to demonstrate a significant effect on functional outcome. Further complicating decision making is that most studies have used a lower-than-standard initial IV dose of rt-PA, the rationale for which has not been well justified.

### Mechanical thrombectomy

Mechanical thrombus removal is an attractive new approach because it directly addresses the causative pathology while avoiding exposure to thrombolytic drugs. This may reduce the chances of systemic complications or intracerebral hemorrhage. On the other hand, hemorrhage may occur as a result of reperfusion into ischemic tissue irrespective of thrombolytic use,<sup>35</sup> and thus a superior safety profile should not be assumed.

The mechanical embolus removal in cerebral ischemia (MERCI) trial employed a corkscrewlike device inserted by arterial catheterization to remove thrombi from the intracranial vertebral, internal carotid, or middle cerebral arteries (Fig. 2). Subjects (151) ineligible for rt-PA, whose intervention could be accomplished within 8 hours of symptom onset, were enrolled in this open-label pilot study; the device was actually deployed in 141 subjects out of 151. Recanalization was produced in 46% of the subjects. Of the 141 subjects in whom the device was deployed, procedural complications (distal embolization, vascular dissection or perforation, etc.) occurred in 7.1%, and symptomatic intracerebral hemorrhage in 7.8%. At 90 days, a modified Rankin score of 0-2 was achieved in 27.7% and mortality was 43.5%.

Of importance is that there was no control arm in this study. The primary end point of vessel recanalization, seen in 46% of the subjects, was compared to historical controls from the placebo arm of prolyse in acute cerebral thromboembolism II, whose subjects achieved recanalization only 18% of the time. Secondary outcomes were similarly compared to historical controls from other trials, and thus the demonstration of clinical efficacy must await the results of a randomized controlled trial.



**FIGURE 2.** MERCI retrieval system with successfully removed thrombus (courtesy of Concentric Medical Inc).

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On the basis of this study, Concentric Medical Inc, was granted approval by the US Center for Devices and Radiologic Health to market the MERCI retrieval system "to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke".<sup>36</sup> The Center for Devices and Radiologic Health found that the device is "substantially equivalent...to legally marketed predicate devices..." In other words, the MERCI system is fundamentally similar to previous devices already approved for the removal of foreign bodies from the cerebral and other vascular beds. This approval, however, does not imply that the device has a salutary clinical benefit, the demonstration of which will require further testing in a properly controlled trial as noted above. At this time, the use of the MERCI retrieval system and other devices for mechanical embolectomy<sup>37,38</sup> should be considered experimental.

## SONOTHROMBOLYSIS

There is an extensive body of the preclinical literature showing that the application of ultrasound waves along with thrombolytic drugs enhances thrombolysis; this has been recently reviewed.<sup>39</sup> Translation to clinical practice has been slow, however, in part because of the great number of variables to be tested. The center frequency, pulse repetition frequency, duty cycle, intensity, and duration of ultrasound exposure may all affect the safety and efficacy of thrombolysis. Moreover, the ultrasound can be delivered transcranially or via an endovascular device.

### Transcranial sonothrombolysis

Despite the uncertainty regarding optimal ultrasound settings, a few clinical sonothrombolysis experiments have been done. A phase 2 randomized trial using 300 kHz transcranial ultrasound was terminated after only 26 subjects were enrolled. Ultrasound-treated subjects (13/14) developed MRI evidence of hemorrhage versus 5/12 control subjects.<sup>40</sup> Of note, some hemorrhages were subarachnoid and others were contralateral to the infarction; such complications are infrequent after cerebral infarction, whether treated with tPA or not.

Alexandrov et al randomized 126 tPA-treated subjects to 2 hours of 2 MHz transcranial ultrasound versus placebo.<sup>41</sup> A favorable effect was seen on the combined end point of vessel recanalization, early clinical recovery or dramatic clinical recovery: 49% in treated subjects versus 30% in control subjects. This result represents an important step toward the adoption of sonothrombolysis in clinical practice. Although

noninvasive and using relatively inexpensive equipment, this technique shares a limitation with endovascular therapies in that the ultrasound units employed require a specially trained operator.

### Endovascular sonothrombolysis

One limitation of transcranial ultrasound is attenuation of the ultrasound field by the cranium; endovascular ultrasound avoids this problem. Focusing the ultrasound energy directly on the thrombus may also avoid some of the safety issues associated with a more diffuse exposure of the brain parenchyma to the ultrasound field. Experience with this technique in acute ischemic stroke is limited, but a few pilot studies have shown it to be feasible.<sup>42,43</sup> It is subject to the same disadvantages of other intra-arterial procedures, requiring a skilled team, and the time to mobilize it and place the catheter.

## NEUROPROTECTION

The foregoing discussion has focused on ways to eliminate the thrombi responsible for cerebral ischemia, allowing the restoration of blood flow and hopefully, neurological function. However, cerebral ischemia secondarily produces an array of downstream effects, such as alterations in neurotransmission, calcium ion flux, free radical formation, and gene expression that may not be adequately reversed simply by restoring blood flow. Neuroprotective strategies seek to interrupt these deleterious processes and thus, limit the neurological dysfunction that results. Unfortunately, preclinical enthusiasm for a variety of putative neuroprotective compounds has been tempered by failure in clinical application.<sup>44</sup> However, a few clinically promising approaches have started to emerge.

### NX-Y-059

NXY-059 is a nitron compound with free radical trapping properties. In animal models of cerebral ischemia, it has been shown to reduce the infarct volume,<sup>45-47</sup> improve neurobehavioral outcome,<sup>47-49</sup> extend the time window for thrombolytic efficacy,<sup>50</sup> and reduce the probability of thrombolysis-associated intracerebral hemorrhage.<sup>51</sup> In a rat model of intracerebral hemorrhage, it improved behavioral outcomes and reduced peri-hematoma inflammation.<sup>52</sup> Interestingly, the compound does not readily cross the blood-brain barrier,<sup>46,53</sup> suggesting that it exerts its effects on the cerebral endothelium rather than the parenchyma.

A global phase 3 clinical trial in ischemic stroke was completed in 2005.<sup>54</sup> Subjects (1722) presenting within 6 hours of onset were randomized to a 72-hour infusion versus placebo. Those presenting within 3 hours

received rt-PA as well. The primary outcome was neurological function, as measured by the modified Rankin score, and this showed a statistically significant benefit in the NXY-059 arm ( $P = 0.038$  by the Cochran-Mantel-Haenszel test). A secondary efficacy outcome, change in NIH stroke scale score (a measure of neurologic impairment), was not significantly different between groups. Of potentially great importance is that the rate of symptomatic intracerebral hemorrhage in the rt-PA + NXY-059 subjects was only 2.5% versus 6.4% (identical to the NINDS trials) in the rt-PA + placebo arm. Another potentially confirmatory international phase 3 study is still underway, and a phase 2 study of the same drug for intracerebral hemorrhage has recently completed enrollment.

### Hypothermia

In contrast to NXY-059, which acts on a specific mediator of ischemia-related injury, hypothermia may have salutary effects on multiple pathways.<sup>55</sup> Several approaches have been reported, including surface cooling,<sup>56</sup> selective head cooling,<sup>57</sup> and endovascular cooling with a double lumen femoral venous catheter.<sup>58</sup> Surface cooling has been shown to reduce neurological morbidity in selected cases of cardiac arrest,<sup>59,60</sup> and in neonates with hypoxic-ischemic encephalopathy.<sup>61</sup> None of these approaches have demonstrated efficacy in ischemic stroke, although several pilot studies have yielded promising results.<sup>62,63</sup>

## INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage (ICH) is a devastating insult with 30-day mortality reported to be 35% to 52%.<sup>64</sup> When the initial head CT is obtained within 3 hours of symptom onset, the rates of hematoma expansion 1 and 20 hours later are 26% and 38%, respectively.<sup>65</sup> Thus, intervention to prevent such an expansion may limit neurological damage and improve functional outcome. As mentioned above, neuroprotectants such as NXY-059 may prove to be helpful, but unfortunately, there is no proven medical or surgical therapy for this condition yet.

### Surgical treatment

A randomized trial of 1033 subjects randomized to open surgical hematoma evacuation within 24 hours of randomization versus initial conservative therapy, showed no benefit from surgery.<sup>66</sup> Of importance is that patients, whose physicians believed a priori that emergency surgery was indicated, were not randomized in this trial. Thus, the trial does not disprove the

hypothesis that certain populations of ICH patients may benefit from an early surgery. Indeed, many physicians think that patients with posterior fossa hemorrhages do actually benefit from surgical evacuation, although there have been no well-designed trials testing this hypothesis.

### Recombinant activated factor VII (rFVIIa)

rFVIIa is FDA approved for the treatment of hemophilia patients with inhibitors rendering them resistant to factor VIII. The results of a phase II study testing this agent in ICH have recently been reported.<sup>67</sup> Subjects (399) were randomly assigned to placebo versus rFVIIa, at doses of 40, 80, or 160  $\mu\text{g}/\text{kg}$ . Drug was to be given within 4 hours of symptom onset. The primary efficacy end point was the change in hematoma volume at 24 hours as compared to baseline. In the placebo arm, hematoma growth was 29% (29  $\text{cm}^3$  at baseline, growing to 34  $\text{cm}^3$  at 24 h). There was a significant effect of the drug at the 160  $\mu\text{g}/\text{kg}$  dose (11% growth, from 22 to 24  $\text{cm}^3$ ), and in all doses combined (14% growth, from 24 to 27  $\text{cm}^3$ ).

Secondary outcome measures included poor functional outcome defined by a modified Rankin scale score of 4–6. Of placebo subjects, 66% fared poorly, whereas 53% of all treated subjects did so. Ninety-day mortality was 29% in the placebo group versus 18% in the combined treatment groups—a statistically significant relative reduction of 38%. Thromboembolic serious adverse events occurred in 2% of placebo subjects and 7% of all treated subjects.

This trial is the first ever to demonstrate benefit for ICH, although the primary outcome was a radiographic and not a clinical measure. Application in clinical practice should proceed cautiously, pending results of a phase III study.

## CONCLUSIONS

There is exactly 1 proven therapy for acute ischemic stroke—IV rt-PA given within 3 hours of symptom onset. Advances in this field are proceeding on several fronts, including the use of next generation plasminogen activators and glycoprotein IIb/IIIa inhibitors, refined patient selection with advanced MRI sequences, endovascular approaches to thrombolysis and thrombectomy, and adjuvant use of ultrasound. There remains no proven therapy for ICH, but early results with rFVIIa look very promising. It is hoped that, in the near future, physicians managing patients with acute neurological events will have a robust armamentarium of therapies to bring to bear on both ischemic and hemorrhagic vascular disease.

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