

# Advances in thrombolytics for treatment of acute ischemic stroke

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## ABSTRACT

Over the past 50 years, thrombolytic agents have been devised with the aim of recanalizing occluded coronary vessels, and later on, applied in the setting of acute ischemic stroke. Pharmacologic agents have generally targeted the plasminogen-plasmin transformation, facilitating the natural process of fibrinolysis. Newer agents with varying degrees of fibrin selectivity and pharmacologic half-life have influenced both recanalization rates and hemorrhagic complications, inside and outside the CNS. Intra-arterial (IA) administration of fibrinolytic agents increases delivery of the drug to the thrombus at a higher concentration with smaller quantities and therefore lowers systemic exposure. Mechanical thrombus disruption or extraction allows for drug delivery to a greater surface area of the thrombus. Delays associated with IA therapy may worsen the risk/benefit ratio of thrombolysis; therefore, combinations of IA-IV treatments have been studied. To date, there are no direct comparative trials to show that endovascular administration is more efficacious or carries a lower risk of hemorrhagic complications than IV tissue plasminogen activator. *Neurology*® 2012;79 (Suppl 1):S119-S125

## GLOSSARY

**AIS** = acute ischemic stroke; **DIAS** = Desmoteplase in Acute Ischemic Stroke Trial; **ECASS** = European Cooperative Acute Stroke Studies; **FDA** = US Food and Drug Administration; **IA** = intra-arterial; **ICH** = intracerebral hemorrhage; **MCA** = middle cerebral artery; **MMPs** = matrix metalloproteinases; **MRA** = magnetic resonance angiography; **NIHSS** = NIH Stroke Scale; **NINDS** = National Institute of Neurological Disorders and Stroke; **PROACT** = Prolyse in Acute Cerebral Thromboembolism; **rtPA** = recombinant tissue plasminogen activator; **TIMI** = thrombolysis in myocardial ischemia; **tPA** = tissue plasminogen activator.

Stroke is the fourth leading cause of death in the United States and is a major cause of disability worldwide.<sup>1-3</sup> Over the past 20 years, many advances in the treatment of stroke have been directed at better prevention and acute intervention in an effort to improve clinical outcomes and decrease associated mortality. Most of the acute interventions target the salvageable ischemic penumbra. This is best achieved by IV or intra-arterial (IA) thrombolysis. Ongoing development of thrombolytic agents has produced 4 generations of drugs based on fibrin specificity and pharmacologic half-life. In addition, interventional mechanical devices can enhance the performance of thrombolytic agents.

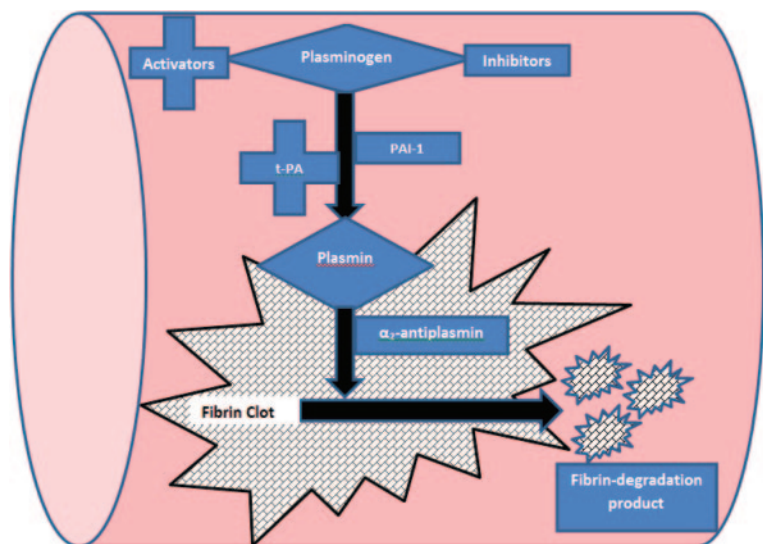
**THROMBOLYTICS** Vessel occlusion, caused by a blood clot, interrupts cerebral blood flow and results in an acute ischemic stroke (AIS). Most commonly, the clot comprises a mesh of fibrin and platelets. The resultant cerebral infarct has a core lesion containing dead tissue and a surrounding viable ischemic penumbra. The ischemic penumbra is a region of hypoperfused and dysfunctional cerebral tissue, which may be salvageable. The stability and size of the penumbra are dependent mainly on the collateral blood supply.<sup>4</sup> Rapid restoration of blood flow through dissolution of the obstructing clot allows recovery of the penumbra.

Thrombolytic agents aim at disrupting the fibrin-rich clot that is created in response to injury of the endothelium.<sup>5</sup> By activating plasminogen, the administration of thrombolytics leads to an increased production of plasmin, which dissolves the fibrin bonds in the clot (figure 1). When IV thrombolysis occurs, rapid local and systemic complications may be minimized. However, this time constraint is one of the major limitations of thrombolytic use, and penumbral imaging becomes of paramount significance in triaging AIS

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**Figure 1** The specificity for bound plasmin increases and systemic effects decrease as thrombolytics progress from first generation to fourth



First, streptokinase and urokinase; second, alteplase and prourokinase; third/fourth, reteplase, tenecteplase, monteplase, desmoteplase, and lanoteplase (t-PA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor 1).

patients for thrombolytic therapy, which is addressed elsewhere in the supplement.

**First generation.** Streptokinase and urokinase are the first generation of thrombolytics. Although they are effective in clot lysis, they are not fibrin-specific.

Streptokinase is the oldest thrombolytic agent. It is naturally produced by bacteria and was isolated and manufactured in the 1950s.<sup>6</sup> Streptokinase is known to have immunogenic properties that may reduce its effectiveness or induce an allergic reaction.<sup>7</sup> Early trials of streptokinase as a treatment for AIS had poor outcomes and were all terminated early because of increased mortality related to the development of intracerebral hemorrhage (ICH) after treatment.<sup>8</sup> During these early trials, investigators were unable to recruit patients within the first few hours of symptom onset, and many patients were enrolled days later. This delay, among other factors, contributed to the increased incidence of hemorrhages.<sup>8</sup>

More trials using streptokinase were conducted in the late 1980s and early 1990s. These included the Australian Streptokinase Trial (AST), the Multicenter Acute Stroke Trial (MAST), and the Multicenter Acute Stroke Trial in Italy (MAST-I).<sup>7,9</sup> In these trials, IV streptokinase was administered within 4 to 6 hours of symptom onset. The results failed to show clear benefit and led to abandonment of its use in the treatment of AIS.

Urokinase was developed and studied in the 1970s. In the early 1980s, 3 trials tested IV urokinase in AIS. Again, these trials recruited patients up to

several days after stroke onset and, as a result, had high rates of ICH. In 1980, the NIH consensus recommended that thrombolysis of acute cerebrovascular disorders be contraindicated,<sup>10</sup> thus limiting its use in treatment of AIS.

**Second generation.** Alteplase is a protease that is thought to exert a neurotoxic effect on the brain parenchyma when it crosses the blood–brain barrier. It also amplifies calcium currents through the NMDA receptor leading to neuroexcitotoxicity and cell death.<sup>11,12</sup> Alteplase directly activates matrix metalloproteinases (MMPs), which have been found to play a role in blood–brain barrier breakdown and neuronal injury in a stroke. Because these proteases may increase the risk of ICH and cerebral edema, early administration of the drug prior to natural MMP activation is ideal.

The second-generation thrombolytics include recombinant tissue plasminogen activator (rtPA), also known as alteplase, and prourokinase. These agents are more fibrin-selective and have been studied extensively in ischemic stroke.<sup>13–16</sup> The National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trial was the first study to demonstrate efficacy of alteplase in patients with AIS. The efficacy was based on administering tPA, 0.9 mg/kg IV, given within 3 hours of symptom onset.<sup>16</sup> On the basis of the results of this study, the US Food and Drug Administration (FDA) approved IV alteplase for treatment of AIS. Patients who received treatment within the first 90 minutes had a more favorable outcome at 3 months than patients who were treated after 90 minutes.<sup>17</sup>

The European Cooperative Acute Stroke Studies (ECASS I, II, and III) looked at the efficacy of IV alteplase within 6 hours of symptom onset. These studies did not show significant improvement in neurologic outcomes at 3 months in comparison with placebo. ECASS I used a dose of 1.1 mg/kg, a higher dose than the NINDS rtPA study, which led to a higher incidence of ICH (19.8%).<sup>13</sup> A lower dose of 0.9 mg/kg was used in ECASS II, and a lower ICH rate (8%) was observed, as well as a trend toward better outcome.<sup>14</sup> The ATLANTIS study began as an investigation of alteplase used within 6 hours of symptom onset. Because of safety concerns, the time window was shortened to 5 hours.<sup>15</sup> A pooled analysis of the ATLANTIS, ECASS, and NINDS trials showed beneficial effects of IV alteplase up to 4.5 hours after symptom onset. There was no significant benefit when it was given between 4.5 to 6 hours.<sup>18</sup> ECASS III showed that although overall symptomatic ICH was higher in treated patients, the rate was not higher in patients treated within the approved 3-hour window and was not associated with in-

creased mortality. The results were significant across multiple endpoints and showed efficacy of treatment despite an increased rate of hemorrhage within 3 to 4.5 hours of symptom onset.<sup>19</sup> There is evidence from MRI protocols and several studies that IV thrombolysis beyond 3 hours in selected patients can be effective.<sup>20,21</sup>

Prourokinase is a proenzyme precursor of urokinase. When activated by fibrin-associated plasmin, 2 single-chain prourokinase units bind at the surface of the thrombus to form an active 2-chain urokinase molecule.<sup>22</sup> The thrombolytic effect is enhanced by heparin, possibly through neutralization of thrombin or by stimulating tPA from the endothelium.<sup>23,24</sup> Prourokinase was utilized for IA thrombolysis studies in the mid-1990s. The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial evaluated IA infusion of prourokinase (6 mg) vs placebo for treatment of middle cerebral artery (MCA) occlusion in patients who presented within 6 hours of symptom onset.<sup>25</sup> At 90 days, there was a 10% to 12% absolute increase in excellent neurologic outcome, defined as a modified Rankin Scale score of 2 or less, in the patients who received prourokinase compared with placebo. Symptomatic hemorrhages within the first 24 hours occurred in 15.4% of patients who received prourokinase, vs 7.1% in the placebo group. The PROACT II trial compared patients who received an IA infusion of prourokinase (9 mg) and low-dose heparin vs low-dose heparin alone within 6 hours of symptom onset for treatment of angiographically proven MCA occlusion.<sup>26</sup> Although early symptomatic hemorrhage occurred in 10% of the IA prourokinase group vs 2% in the control group, there was a 15% absolute increase in favorable outcome with IA prourokinase. However, despite these results, prourokinase did not gain FDA approval for use in AIS.

Although these second-generation agents may be beneficial, there are still a significant number of patients who did not respond to treatment, had low recanalization rates, or had high rates of reocclusion.<sup>5</sup> In addition, hemorrhagic complications occurred frequently when these agents were used. Due to the potentially poor clinical outcome, the need for newer thrombolytic agents with lower adverse profiles and possibly longer therapeutic windows remained.

**Third/fourth generation.** Several third- and fourth-generation thrombolytics are being developed, including mutants of scuPA and tPA; chimeric plasminogen activators of these 2 molecules (amediplase); conjugates of plasminogen activators with monoclonal antibodies against fibrin, platelets, or thrombomodulin; and plasminogen activators of animal (vampire bat) or bacterial (*Staphylococcus aureus*) origin.<sup>27</sup> These agents have longer half-lives in

plasma, allowing for single or repeated bolus injections, as opposed to the continuous infusion required with the first- and second-generation thrombolytics. They have higher fibrin specificity and lower or no neurotoxicity, which may in turn lead to lower hemorrhagic complications.<sup>5,12</sup>

Staphylokinase is a highly fibrin-selective agent. It has a low affinity for plasminogen that is free or bound to intact fibrin, but it binds strongly to plasmin and to plasminogen that is bound to partially degraded fibrin.<sup>28</sup> This feature enables it to concentrate on the surface of a lysing thrombus. The staphylokinase-plasmin complex is rapidly inhibited by  $\alpha_2$ -antiplasmin in the absence of circulating fibrin. When bound to fibrin, the complex is protected from inhibition. Thus, staphylokinase acts as an indirect activator of plasminogen within a thrombus.<sup>12,28</sup> Nevertheless, this agent has not been extensively studied for use in AIS.

Tenecteplase is another third-generation agent that is more fibrin-specific than alteplase and may reduce the risk of systemic complications.<sup>29,30</sup> It has a longer half-life (15 to 19 minutes) and greater resistance to plasminogen-activator inhibitor.<sup>5</sup> The “plasminogen steal” effect that is seen with alteplase is not seen with tenecteplase, thus making it more effective.<sup>30</sup> This phenomenon occurs when high levels of alteplase lower systemic plasminogen levels, which leads to a paradoxical diffusion of plasminogen out of the clot, thereby reducing clot lysis.<sup>12,31</sup>

Tenecteplase has been tested in AIS patients in phase II trials.<sup>32,33</sup> At this point, the most beneficial dose of tenecteplase is unclear. A small pilot study using magnetic resonance angiography (MRA) and MRI perfusion-weighted imaging showed improved recanalization and reperfusion rates in 15 patients receiving 0.1 mg/kg tenecteplase and 35 patients receiving standard doses of tPA.<sup>32</sup> There were no cerebral hemorrhages in the tenecteplase group, but 4 were seen in the tPA group. A recent phase IIB/III trial comparing 0.1 mg/kg, 0.25 mg/kg, and 0.4 mg/kg tenecteplase with tPA was ended prematurely because of poor enrollment.<sup>34</sup> A total of 112 patients were randomized, and the 0.4-mg/kg dose was discarded early because of inferiority and a higher rate of ICH. Optimal dose selection could not be made between the 0.1 mg/kg and 0.25 mg/kg doses because of the termination of the study.<sup>34</sup>

Retepase is a deletion mutant of tPA<sup>5</sup> that lacks the terminal domains of alteplase, including the terminal finger, epidermal growth factor, and kringle 1 domains.<sup>27</sup> As a result, reteplase does not bind strongly to fibrin, allowing unbound reteplase to penetrate the thrombus and promote lysis. It has a reduced affinity for binding to endothelial cells and

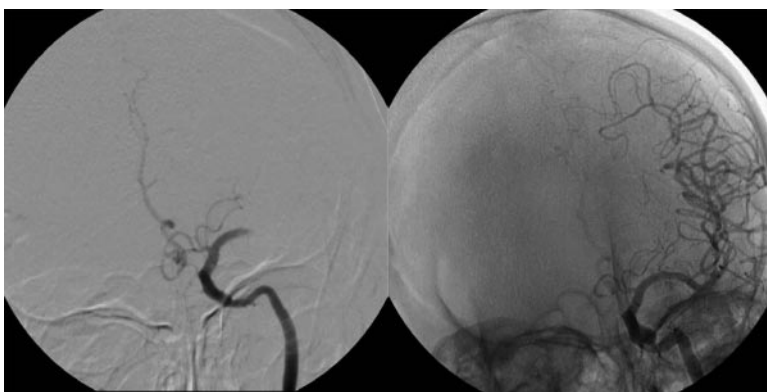
monocytes, which in turn leads to higher levels in the bloodstream. Reteplase has a longer half-life (15 to 18 minutes) than alteplase and may be given as a bolus.<sup>5</sup> It is used for IA thrombolysis in AIS. The first human clinical trial using this agent intra-arterially was reported in 2001.<sup>35</sup> Sixteen patients who were poor candidates for IV alteplase were selected for therapy. Selection criteria included a time interval of 3 hours or longer from symptom onset or severe neurologic deficit on presentation (NIH Stroke Scale [NIHSS] scores ranged from 10 to 26). This was primarily a dose escalation safety trial. Of the 16 treated patients, 1 had symptomatic ICH. A modified thrombolysis in myocardial infarction (TIMI) grading system was used, and the authors reported TIMI 3 or 4 (equivalent to the original TIMI grade 3) recanalization rates in 88% of patients. This high rate of recanalization was achieved even though 8 of 16 patients presented with occlusion of either the cervical (n = 4) or intracranial (n = 4) internal carotid artery. Forty-four percent of patients had early neurologic improvement (defined as a decrease of 4 or more points in the NIHSS score at 24 hours). However, further studies are necessary to evaluate the proper dosage and durability of reteplase for IA thrombolysis in AIS.

Desmoteplase is a serine protease that naturally occurs in the saliva of the bat *Desmodus rotundus*.<sup>12</sup> It has pharmacologic and toxicologic properties superior to human tPA, including a higher fibrin selectivity, lower hemorrhagic transformation profile, longer half-life, and lack of NMDA-mediated neurotoxicity, in comparison with alteplase.<sup>12,35,36</sup> The Desmoteplase in Acute Ischemic Stroke Trial (DIAS) was an MRI-based phase II study. DIAS was conducted to explore the safety and efficacy of various

doses of IV desmoteplase in patients with AIS and evidence of perfusion/diffusion mismatch with symptom onset between 3 and 9 hours.<sup>37</sup> Results showed a higher rate of reperfusion (71.4%) and a favorable 90-day clinical outcome (60.0%) compared to placebo (19.2% and 22.2%, respectively), and a low rate of symptomatic intracranial hemorrhage using doses up to 125  $\mu\text{g}/\text{kg}$ .<sup>37</sup> The phase III DIAS-2 study failed to show the same benefits. This was believed to be related to the inclusion of a large number of patients with mild strokes at baseline and no vessel occlusion, as well as a high response rate among placebo-treated patients.<sup>38</sup> However, post hoc analysis showed a positive response in patients who had a proximal cerebral vessel occlusion or high-grade stenosis on baseline angiography.<sup>39</sup> DIAS-3 and DIAS-4 phase III trials are currently underway to evaluate patients with AIS related to occlusion or high-grade stenosis of proximal arteries, as assessed by MRA or CT angiogram.<sup>40</sup>

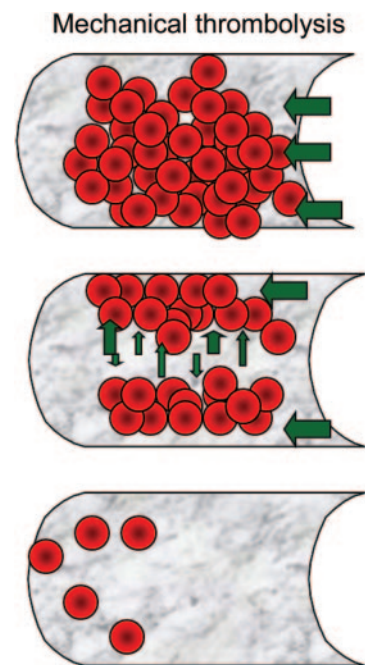
Ancrod is a biological agent extracted from the venom of the Malayan pit viper that reduces blood fibrinogen levels.<sup>41</sup> It induces defibrinogenation in humans by cleaving fibrinopeptide A from fibrinogen, thus depleting the substrate needed for thrombus formation. This substrate depletion indirectly

**Figure 2** An example of intra-arterial treatment only: a 42-year-old man with sudden onset of global aphasia and right-sided hemiplegia pericardiac catheterization presenting within 2 hours of symptoms to the neuro-angio suite



The left internal carotid injection demonstrated complete occlusion of the middle cerebral artery M1 segment (thrombolysis in cerebral ischemia score [TICI] 0), treated with intra-arterial recombinant tissue plasminogen activator for a total of 22 mg, with complete recanalization (TICI 3) and near-complete clinical improvement to an NIH Stroke Scale score of 2.

**Figure 3** Surface area for clot penetration may be increased with use of mechanical devices for thrombolysis to be more effective



The middle illustration depicts a disrupted clot with a greater surface area. A longer half-life may further enhance clot lysis, as is the case with newer-generation thrombolytics.

leads to anticoagulation and decreased blood viscosity, which later helps with improving circulation to affected areas.<sup>12,42-45</sup> Products of defibrinogenation may also enhance local clot-specific thrombolysis by stimulating endogenous plasminogen activators.<sup>46</sup> Two small trials of ancred for AIS in the 1980s suggested that it was safe and beneficial in stroke patients.<sup>47,48</sup> On the basis of these promising results, the Stroke Treatment with Ancrod Trial (STAT) was conducted.<sup>44</sup> In this study, 500 patients who presented within 3 hours of symptom onset were randomized to receive ancrod or placebo as a continuous infusion over 72 hours and 1-hour infusions at 96 and 120 hours. Patients in the ancrod group had a more favorable functional outcome (42.2%) than the placebo group (34.4%) ( $p = 0.04$ ). There appeared to be more symptomatic intracranial hemorrhages in the ancrod group (5.2%) vs placebo recipients (2.0%) ( $p = 0.06$ ), but the difference was not statistically significant. A follow-up clinical trial, in which 500 subjects with AIS were randomized within 6 hours of symptoms to ancrod at 0.167 IU/kg IV per hour vs placebo for 2 to 3 hours, showed no difference in clinical outcome between the 2 groups.<sup>49</sup> A favorable functional outcome at 39.6% in the treatment arm vs 37.2% ( $p = 0.47$ ) was found.<sup>49</sup>

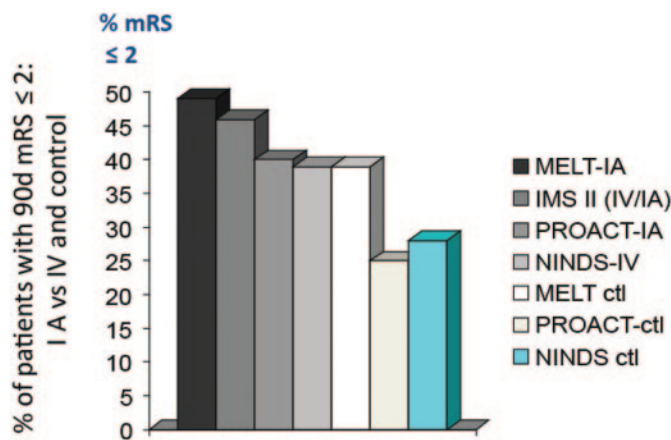
**Intra-arterial delivery.** Despite the improvement in functional outcome in stroke patients who receive IV rtPA, a large number of patients (57% to 58%) die or become dependent despite treatment.<sup>13,16,50,51</sup> This has prompted a search for better drugs and modalities of delivery that will achieve higher and quicker rates of recanalization with minimal risk to the pa-

tient. IA thrombolysis involves administration of high concentrations of thrombolytic agents near the thrombus, utilizing lower doses than systemic administration. This may result in lower systemic complications, including extracranial hemorrhages (figure 2), and minimizing local neurotoxic effects of these agents.<sup>5</sup> This approach also allows the simultaneous use of mechanical devices to facilitate thrombolysis (figure 3).<sup>5,52,53</sup> Combining the IA delivery with mechanical thrombectomy increases the surface area exposed to the thrombolytic agents (figure 2). The disadvantages of the IA modality include the potential delay required to obtain initial cerebral angiography and position of the microcatheter for administration of the thrombolytic agent. These concerns led to the initiative of delivering the IA thrombolysis following IV thrombolysis. The Emergency Management of Stroke (EMS) bridging trial, which had a randomized, double-blind, placebo-control design, demonstrated higher recanalization rates (53%) in the combined IV/IA alteplase treatment group than in the IA alteplase group (28%).<sup>54</sup> There was no difference in clinical outcomes between the 2 groups and no significant difference in the rate of symptomatic ICH. This suggested the feasibility of the combined treatment. Although in some centers the IA approach is favored in a subset of patients who are expected to have limited response to IV treatment, including those with severe neurologic deficits, those presenting between 3 and 6 hours of symptom onset, those who have a history of major surgery within the previous 2 weeks, and those with occlusion of major cervical or intracranial vessels, this has yet to be proven in controlled trials.<sup>51</sup>

Another combined approach involves using IA treatment initially to maximize the rate of recanalization, followed by IV infusion to increase the efficacy of the treatment.<sup>55</sup> This approach was studied but the results were inconclusive.<sup>12</sup>

Thrombolytics are also known to activate thrombin, which promotes platelet adhesion and potentially reocclusion of patent vessels.<sup>56</sup> No conclusive data on combining the IA thrombolysis delivery with a glycoprotein IIb/IIIa platelet receptor inhibitor via an IA or IV route exist. However, a glycoprotein IIb/IIIa receptor inhibitor, abciximab, was evaluated for safety and efficacy in AIS. The Abciximab in Ischemic Stroke pilot study was a randomized, double-blind, placebo-controlled, dose-escalation trial, where 4 escalated doses of IV abciximab were administered up to 24 hours after stroke onset.<sup>57</sup> It showed a relatively low risk of ICH (7%) and a trend toward improved outcome after 30 days. It was concluded that abciximab was safe to use within 24 hours after stroke onset. However, the trial failed to

**Figure 4** Histogram summary of the clinical outcome in the pivotal chemical thrombolysis IA trial, in comparison with the IV tissue plasminogen activator and control groups



Ctl = control; IA = intra-arterial; IMS = Interventional Management of Stroke; MELT = Middle cerebral artery Embolism Local fibrinolytic intervention Trial; mRS = modified Rankin Scale score; NINDS = National Institute of Neurological Disorders and Stroke; PROACT = Prolyse in Acute Cerebral Thromboembolism.

demonstrate safety or efficacy of IV abciximab; in fact, there was an increased rate of symptomatic or fatal hemorrhage.<sup>58</sup>

**DISCUSSION** IA fibrinolysis is an effective AIS therapy within 6 hours of symptom onset, in comparison with placebo. A meta-analysis of IA thrombolysis studies showed that this approach substantially increases recanalization rates and good clinical outcomes in AIS.<sup>59</sup> A higher rate of ICH was not associated with any increase in mortality (figure 4).<sup>59</sup>

**Future directions.** The best way of delivering IA fibrinolysis—alone, in combination with mechanical thrombectomy, as systemic thrombolysis, or followed by antiplatelet therapy—remains to be determined after further study.

The development of newer-generation thrombolytic agents, safer and more effective for treating AIS, is needed. This may be accomplished by increased fibrin specificity, rapid onset of action, and shorter half-life to improve on safety.

#### AUTHOR CONTRIBUTIONS

Dr. Kirmani: study concept or design, study supervision. Dr. Alkawi: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Panezai: drafting/revising the manuscript. Dr. Gizzi: drafting/ revising the manuscript, study supervision.

#### DISCLOSURE

Dr. Kirmani has served on the Editorial Board of *Frontiers in Endovascular and Interventional Neurology*. Dr. Alkawi, Dr. Panezai, and Dr. Gizzi report no disclosures. **Go to [Neurology.org](#) for full disclosures.**

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