

## Emerging Therapies in Ischemic Stroke Management

a report by

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### Pharmaceutical Recanalization Therapies

When given within three hours of stroke onset in well-selected eligible patients, intravenous (IV) thrombolysis with realtime plasminogen activator (rt-PA) has become the cornerstone of hyperacute stroke therapy. This follows approvals by the US Food and Drug Administration (FDA) in 1996 and the European Medicines Agency (EMA) in 2002. Although effective, the therapy has several limitations, including certain contraindications, a short application time window, fear of hemorrhagic complications, which may lead to physicians refraining from using rt-PA, the lack of the necessary health service infrastructure in many developed countries, and the fact that not all patients benefit from IV thrombolysis. Recanalization rates with IV thrombolysis range between 20 and 66% (average 46% for all occlusions) depending on the occlusion site, size and consistency of the thromboembolic material, and several other factors.<sup>1</sup> Even if recanalization is achieved, reocclusion associated with clinical deterioration may occur.

Only 4–5% of all ischemic stroke patients in the developed world receive IV thrombolysis. According to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) registry, in Finland more ischemic stroke patients receive thrombolysis per million inhabitants than in any other EU country, and the emergency room of Helsinki University Central Hospital provides more thrombolysis than any other European hospital. However, even in Finland stroke patients do not have equal opportunities for thrombolysis. For benefits to be achieved, a number needed to treat

(NNTT) of seven<sup>2</sup> was determined, and for hazards to occur a number needed to harm (NNTH) of one in 100<sup>3</sup> has been calculated.

The earlier thrombolysis is given, the better the outcome; however, not all stroke patients arrive early enough and thus the current three-hour time window is often too short. In addition to making thrombolysis available for more patients, several other treatments need to be developed. A recent analysis suggested that the benefit of IV thrombolysis continues up to 4.5 hours.<sup>4</sup> The European Co-operative Acute Stroke Study III (ECASS III) is a multinational, controlled, randomized study in which patients are randomized to placebo or standard IV rt-PA in a time-frame of three to 4.5 hours from stroke onset. ECASS III will bring more certainty to the question of whether patients benefit from IV thrombolysis between three and 4.5 hours after stroke. Attempts have been made to further extend the time window for IV thrombolysis with the use of modern brain imaging modalities such as diffusion–perfusion magnetic resonance imaging (MRI) and perfusion computed tomography, with promising success. These modalities may help patient selection for thrombolysis after three hours after the onset of symptoms.

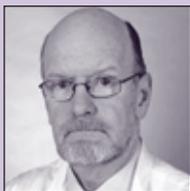
Intra-arterial (IA) thrombolysis may be more effective than IV thrombolysis, especially in cases of large artery occlusions such as internal carotid, basilar, or proximal middle cerebral artery occlusions with extensive thrombus. IA thrombolysis leads more often to recanalization compared with IV thrombolysis (63 versus 46% for all vessels) and is associated with a similar rate of intracranial hemorrhages to IV thrombolysis.<sup>1</sup> IA thrombolysis with pro-urokinase was beneficial even up to six hours after stroke onset in one study,<sup>5</sup> but it was not approved by the FDA. A combined approach of IV and IA thrombolysis in open trials has been found to be better than IV thrombolysis, with a similar hemorrhagic complication rate to IV thrombolysis alone.<sup>6,7</sup> A large randomized trial is warranted.

Novel thrombolytic agents including desmoteplase, tenecteplase, and reteplase have longer half-lives, higher fibrin specificity, and a higher resistance to PA inhibitor-1. Originally isolated from vampire bat saliva, IV desmoteplase was given in randomized trials three to nine hours after stroke onset to patients with a substantial region of penumbra. The first two trials delivered promising results,<sup>8,9</sup> but the most recent efficacy trial could not confirm their results. A mutant form of rt-PA, tenecteplase, was found to be safe in a small study when given IV at 0.1–0.5mg/kg within three hours of stroke onset.<sup>10</sup> A randomized phase IIb trial comparing three different doses of tenecteplase with standard IV rt-PA within three hours of the time window is under way. Reteplase can be administered as a bolus, and was superior to standard rt-PA in myocardial infarction. Experience with reteplase in stroke patients remains limited.



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### Mechanical Recanalization

Mechanical thrombus retraction has been used as a rescue therapy for patients who do not respond to thrombolytics, or as a primary treatment for those with contraindications to thrombolytics, and may lead to higher rates of vessel patency. Thromboemboli that are especially platelet-poor may be more amenable to mechanical thrombectomy and remain intact during the procedure. Mechanical thrombectomy can be combined with IA thrombolytic agents when appropriate, although it may increase the intracranial hemorrhage rate. A catheter can be used to aspirate clots, in a procedure in which a capable interventional radiologist is needed. This process requires large-bore catheters to allow adequate suction and therefore is limited to most proximal arterial occlusions. Among many emerging devices, the Mechanical Embolus Removal in Cerebral Ischemia device (MERCI, Concentric Medical, Mountain View, California) has received the most attention. A microcatheter is inserted through the embolus to the distal side of the occlusion in a similar way to a corkscrew, and stabilizes the thrombus in a nitinol-made wire basket. During thrombus extraction, the balloon in the distal tip of the main catheter is inflated to cease forward blood flow, thus preventing thrombus fragments lodging into distal arteries. The thrombus is then aspirated into the catheter and subsequently removed with the catheter from the arterial tree. A series of clinical trials<sup>11–13</sup> demonstrated high recanalization rates in a time window of three to eight hours post-stroke with reasonable hemorrhagic complication rates, and led to FDA approval for endovascular recanalization of cerebral arteries in patients for whom IV rt-PA is contraindicated or has failed. Angioplasty (with or without stenting) has been used for acute stroke in anecdotal cases with success, but experience is limited.

Ultrasonic energy has been internally delivered to the clot through a catheter (the EKOS MicroLysUS infusion catheter, EKOS Corp, Seattle), causing microscopic cavitations within the thrombus and augmenting the effect of following thrombolytic drug by facilitating its penetration deep in the clot;<sup>14</sup> studies in this area are ongoing. Similarly, laser energy has been applied locally and internally to the clot material with the Endovascular PhotoAcoustic Recanalization (EPAR) device (Endovasix, Belmont, California). A small study showed not only high recanalization rates, but also high mortality.<sup>15</sup> Ultrasonic energy was combined with IV rt-PA in the Combined Lysis of Thrombus in Brain Ischaemia Using Transcranial Ultrasound and Systemic Tissue Plasminogen Activator (CLOTBUST) trial,<sup>16</sup> which demonstrated significantly higher recanalization rates in patients who received the combination of IV thrombolysis and transcranial ultrasound for middle cerebral artery occlusions. However, the clinical outcome was not significantly better in the combination-treated group. A variety of microbubbles have been developed to improve recanalization rates. They can be applied intravenously, and incorporate themselves to the thromboembolus and explode within the clot when predisposed to external ultrasound energy, leading to fragmentation of the clot material. These therapies are under intense investigation.

### Hypothermia

Hypothermia has been proved to be neuroprotective in numerous experimental studies and hyperthermia is associated with poor outcome in clinical studies. Two randomized trials<sup>17,18</sup> have shown that reducing body temperature to 32°C from 34°C for 12–24 hours in comatose survivors of cardiac arrest leads to better neurological outcomes and reduced mortality. Moderate hypothermia in stroke patients has been tried in a small patient series;<sup>19</sup> however, a well-controlled randomized trial is required. Deep hypothermia necessitates anesthesia and respiratory care with intubation and therefore has many severe

complications and requires extensive resources, which are not always available. In contrast, mild hypothermia with invasive or non-invasive systems may be accomplished in awake patients and can easily be given in stroke units. Pilot studies have shown a feasibility of mild (34–36°C) and moderate (32–34°C) hypothermia in stroke. Randomized studies are ongoing to prove whether mild or moderate hypothermia is beneficial in acute stroke patients.

### Craniectomy

Following a number of experimental and non-randomized pilot clinical studies, three large, randomized, controlled clinical trials—Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts (DECIMAL), Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY), and the Hemicraniectomy After Middle Cerebral Artery Infarction with Life-Threatening Edema Trial (HAMLET)—were initiated to test the safety and efficacy of decompressive craniectomy in malignant middle cerebral artery infarction in relatively young ischemic stroke patients (18–60 years of age) even up to 48 hours after stroke onset. When the results of these three studies were pooled, they revealed a reduced death rate and improved functional recovery without increasing the proportion of severely disabled patients.<sup>20</sup> Decompressive craniectomy is already in use in comprehensive stroke centers.

### Blood-pressure-increasing/-decreasing Treatments

Induced hypertension may increase cerebral perfusion in penumbral regions and alleviate ischemic injury. Induced hypertension by means of drugs (phenylephrine) or invasive devices such as the NeuroFlo (CoAxia, Maple Grove, Minnesota) is under evaluation. A reduction of 10mmHg in arterial systolic blood pressure was associated with an 18% increase in mortality in a *post hoc* analysis of the International Stroke Trial,<sup>21</sup> but in the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) Study the treatment to reduce blood pressure had a positive effect on the outcome.<sup>22</sup> Further trials in which blood pressure is reduced to improve the outcome of patients are under way.

### Neuroprotective Treatments

Neuroprotective therapy is appealing because neuroprotective agents can be safely started without a brain scan even in an ambulance and can be combined with various other therapies, and therefore may help to extend the time window for thrombolysis. A plethora of agents have been tested in randomized clinical trials. So far not one has been proved effective. Recent success with NYX-059 in the first Stroke Acute Ischemic NXY-059 Trial (SAINT) was encouraging,<sup>23</sup> but the second trial had negative results,<sup>24</sup> reducing the enthusiasm raised by the first trial. Among many molecules, we can list albumin, statins, citicoline, caffeineol, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and N-methyl D-aspartate (NMDA) receptor antagonists, free radical scavengers, anti-inflammatory agents, and a number of growth factors and several hematopoietic agents that are already in or about to undergo clinical testing. A comprehensive list of ongoing clinical stroke trials can be seen at [www.strokecenter.org/trials/](http://www.strokecenter.org/trials/)

### Brain Plasticity and Stem Cell Therapy

In experimental stroke, it has been known for a while that a brain damaged by stroke has the capacity to recover using its own or transplanted neural stem cells. This is one of the most exciting frontiers in stroke research, if not the most interesting emerging therapy for stroke.<sup>25,26</sup> Bone marrow stem cells and drugs such as statins and phosphodiesterase inhibitors can induce neurogenesis from endogenous stem cells and promote functional recovery after experimental stroke.<sup>27–29</sup> It is hard to predict when stem cell therapies will become part of the

recovery-enhancing therapy armory for stroke patients because much time-intensive basic and clinical research is needed. However, two small clinical trials in human stroke patients have been undertaken with FDA approval,<sup>30,31</sup> and new ones are imminent. The research field is promising and will probably be included in the next scientific strategy of the European Commission (EC), as the European experts included it in their priority list to the EC.<sup>32</sup>

## Combination Therapies

Combination therapies are becoming more popular. Combined IV and IA thrombolysis, thrombolysis with hypothermia, ultrasound, mechanical clot extraction, antiplatelet agents, neuroprotective agents, and other combinations are all feasible and some are already under evaluation. ■

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## Key Associations Back STOP Stroke Bill

The American Stroke Association is leading the effort to campaign to enact legislation that could ensure current and future stroke patients receive high-quality, appropriate stroke care.

The Stroke Treatment and Ongoing Prevention Act (STOP Stroke Act) seeks to ensure that stroke is more widely recognized and treated via the initiation of key actions:

- a grant program to help states ensure that patients have access to quality stroke prevention, treatment, and rehabilitation services;
- a national public awareness campaign to educate the public about stroke warning signs and how stroke can be prevented;
- the Coverdell Stroke Registry and Clearinghouse to collect data and share best practices; and
- a grant program to educate medical professionals in newly developed diagnostic approaches, technologies, and therapies.

Source: American Stroke Association.

The STOP Stroke Act (S.999) was approved by the Senate Health, Education, Labor, and Pensions Committee by voice vote on March 13, 2008. ■

### Prevalence of Stroke by Age and Sex

