Experimental neuroprotection in ischemic stroke: a concise review

Gary B. Rajah, MD, and Yuchuan Ding, MD, PhD

Department of Neurosurgery, University Health Center, Wayne State University, Detroit Michigan

Acute ischemic stroke (AIS) is a leading cause of disability and death worldwide. To date, intravenous tissue plasminogen activator and mechanical thrombectomy have been standards of care for AIS. There have been many advances in diagnostic imaging and endovascular devices for AIS; however, most neuroprotective therapies seem to remain largely in the preclinical phase. While many neuroprotective therapies have been identified in experimental models, none are currently used routinely to treat stroke patients. This review seeks to summarize clinical studies pertaining to neuroprotection, as well as the different preclinical neuroprotective therapies, their presumed mechanisms of action, and their future applications in stroke patients.

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KEY WORDS neuroprotection; acute ischemic stroke; free radical; excitotoxicity; immune response

A CUTE ischemic stroke (AIS) resulted in 3.3 million deaths globally in 2013 according to Feigin et al. They estimated that there were close to 18 million ischemic stroke survivors worldwide in 2013. The global stroke burden continues to increase. Recent innovations in the clinical stroke arena include advanced imaging for stroke diagnosis and endovascular mechanical thrombectomy for reperfusion treatment of AIS due to large vessel occlusion, which has been validated in 7 randomized controlled trials. These new techniques, as well as intravenous tissue plasminogen activator, have transformed emergent stroke care. To date, however, there have been few successful adjuvant neuroprotective therapies to aid in the treatment of acute stroke. Such therapies would target reductions in secondary injury to penumbra tissue, minimizing damage before and after reperfusion while promoting neural recovery and plasticity. In this paper we review upcoming preclinical neuroprotective therapies as well as their proposed mechanisms of action. In addition, we evaluate the existing clinical data on neuroprotection in stroke.

Clinically Assessed Neuroprotective Therapies

In this review we first focus on therapies tested in patients in either a pilot study or a randomized controlled design. Despite the many preclinical studies suggesting clinical efficacy, there is a paucity of clinically proven therapies. We have created tables (Tables 1–3) recapping the clinically tested therapies and discuss the more relevant therapies below. Recently, randomized trials for acute stroke and neuroprotection have included growth factors, hypothermia, minocycline, natalizumab, fingolimod, and uric acid. Common pathways targeted for neuroprotection include free radical scavengers, excitotoxicity, immune modulation, and more.

Free Radical Scavengers

Free radicals are molecules with a free unpaired electron, making them highly reactive and capable of chain reactivity. They can react with and damage proteins, nucleic acids, and lipids. They are present in low levels via normal cellular respiration, but during acute ischemic episodes their levels can increase and have been postulated to contribute to cerebral edema. We summarize the studies on free radical scavenging therapies in Table 1.

Reduction of Excitotoxicity

Excitotoxicity is a type of neurotoxicity centered around glutamate. During acute ischemia, the extracellular concentration of glutamate rises quickly and stimulates N-methyl-D-aspartate receptor (NMDAR), which acts via calcium permeability. Excitotoxic cell death is triggered
via PTEN, cdk5, and DAPK1, among other downstream targets.\textsuperscript{42} We summarize the studies on excitotoxic blocking therapies for neuroprotection in Table 2.

**Immune Modulation**

The immune response after ischemic stroke is multifaceted and initiates a cascade leading to secondary brain injury following the initial ictus as well as after reperfusion therapies. Gelderblom et al.\textsuperscript{27} reported increased microglia activation and an influx of macrophages, lymphocytes, and dendritic cells with increased antigen-presenting capacity. The brain under normal conditions is able to maintain a relatively noninflammatory environment; however, once the brain is damaged, inflammation is left less regulated.\textsuperscript{2} We summarize studies on immune modulation therapies in Table 3.

**Other Therapies**

There are many ongoing clinical trials examining statins, imatinib, dapsone, interleukin-1 receptor antagonists, NA-1, hypothermia, lower limb tourniquet conditioning, insulin infusion, edaravone, and 3K3A-APC.\textsuperscript{11}

American Heart Association Stroke Guidelines Related to Early Management and Neuroprotection

There are no Level 1 recommendations for neuropro-

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**TABLE 1. Clinical free radical scavenging therapies for neuroprotection in AIS**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Trial Name</th>
<th>Agent</th>
<th>MOA</th>
<th>No. of Patients in Study</th>
<th>Benefit w/ Agent</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diener et al., 2008</td>
<td>SAINT</td>
<td>NXY-059</td>
<td>Free radical trapping</td>
<td>5028</td>
<td>No clinical benefit</td>
<td>Treated w/in 6 hrs of symptoms</td>
</tr>
<tr>
<td>Clark et al., 2001</td>
<td>Citicoline</td>
<td>Membrane stabilizer/free radical scavenger</td>
<td>899</td>
<td>No clinical benefit</td>
<td>Daily administration for 6 wks post-stroke</td>
<td></td>
</tr>
<tr>
<td>Yamaguchi et al., 1998</td>
<td>Ebselen</td>
<td>Seleno-organic compound w/ antioxidant properties</td>
<td>300</td>
<td>Better outcome at 1 mo but not 3 mos; improvements in mBI</td>
<td>Oral administration x 2 wks post-stroke</td>
<td></td>
</tr>
<tr>
<td>Chamorro et al., 2014</td>
<td>URICO-ICTUS</td>
<td>Uric acid</td>
<td>Antioxidant</td>
<td>411</td>
<td>No significant benefit, but 39% vs 33% (placebo) attained mRS score ≥2</td>
<td>Administered w/in 4.5 hrs w/ alteplase</td>
</tr>
</tbody>
</table>

mBI = modified Barthel Index; MOA = mechanism of action; mRS = modified Rankin Scale; SAINT = Stroke Acute Ischemic NXY Treatment; URICO-ICTUS = Efficacy Study of Combined Treatment with Uric Acid and t-TPA in Acute Ischemic Stroke.

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**TABLE 2. Clinical ion channel interaction/excitotoxicity blockade therapies for neuroprotection in AIS**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Trial Name</th>
<th>Agent</th>
<th>MOA</th>
<th>No. of Patients in Study</th>
<th>Benefit w/ Agent</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahlgren et al., 1999</td>
<td>CLASS</td>
<td>Clomethiazole</td>
<td>GABA A potentiator inducing membrane hyperpolarization</td>
<td>1360</td>
<td>No clinical benefit; in subgroup analysis, increased functional independence w/ large stroke</td>
<td>Administered w/in 12 hrs of stroke onset</td>
</tr>
<tr>
<td>Albers et al., 2001</td>
<td>Aptiganel hydrochloride</td>
<td>Selective ligand for NMDAR</td>
<td>628</td>
<td>No clinical benefit &amp; possibly harmful</td>
<td>Administered w/in 6 hrs of stroke onset</td>
<td></td>
</tr>
<tr>
<td>Davis et al., 2000</td>
<td>Selfotel</td>
<td>NMDAR antagonist</td>
<td>567</td>
<td>Stopped early given possible neurotoxic effects</td>
<td>Administered w/in 6 hrs of stroke onset</td>
<td></td>
</tr>
<tr>
<td>Horn et al., 2001</td>
<td>VENUS</td>
<td>Nimodipine</td>
<td>Ca(^{++}) channel blocker</td>
<td>454</td>
<td>No beneficial effect</td>
<td>Administered w/in 6 hrs</td>
</tr>
<tr>
<td>Liu et al., 2009</td>
<td></td>
<td>Ginsenoside</td>
<td>Ca(^{++}) channel blocker</td>
<td>199</td>
<td>Some benefit as determined by 15 day NIHSS</td>
<td>14-day infusion</td>
</tr>
<tr>
<td>Saver et al., 2015\textsuperscript{53}</td>
<td>FAST-MAG</td>
<td>Magnesium</td>
<td>Vasodilatory, neural &amp; glial protective</td>
<td>1700</td>
<td>No clinical benefit at 90 days</td>
<td>Administered w/in 2 hrs &amp; a 24-hr infusion</td>
</tr>
<tr>
<td>Hill et al., 2012</td>
<td>NA-1</td>
<td>Inhibitor of postsynaptic density protein-95\textsuperscript{*}</td>
<td>197</td>
<td>NA-1 group had fewer ischemic infarcts on DWI, FLAIR imaging 12–95 hrs postinfusion</td>
<td>Infusion at end of endovascular procedure</td>
<td></td>
</tr>
<tr>
<td>Ladurner et al., 2005</td>
<td>Cerebrolysin</td>
<td>Purified brain protein made from enzymatic degradation of brain protein w/ neurotrophic/pro- tective properties\textsuperscript{†}</td>
<td>146</td>
<td>Significant improvement in cognition as tested by Short Syndrome Test</td>
<td>Administered w/in 24 hrs, for 21 days</td>
<td></td>
</tr>
</tbody>
</table>

CLASS = Clomethiazole Acute Stroke Study; DWI = diffusion-weighted imaging; FAST-MAG = Field Administration of Stroke Therapy-Magnesium; GABA = \(\gamma\)-aminobutyric acid; NIHSS = National Institutes of Health Stroke Scale/Score; VENUS = Very Early Nimodipine Use in Stroke.

\textsuperscript{*} Postsynaptic density protein-95 is believed to regulate gating and surface expression of NMDA channels.\textsuperscript{45}

\textsuperscript{†} Orphan category added here for convenience.
tective agents in AIS. The 2013 American Heart Association stroke guidelines state the following: continuation of statin therapy is reasonable, the utility of induced hypothermia in AIS is not well established, transcranial near-infrared laser therapy for AIS is not well established, and the utility of hyperbaric oxygen therapy is inconclusive and may be harmful in AIS, unless due to air embolism. The guidelines also state that no neuroprotective pharmacological agents have demonstrated clinical efficacy and thus are not currently recommended.

Hypothermia

Hypothermia can target more than one aspect of secondary brain injury, including oxygen consumption and metabolic demand, enzymatic degradation, neurotransmitter uptake, membrane stabilization, and reduction in intracellular acidosis. In a small study, hypothermia post–middle cerebral artery (MCA) stroke has been shown to be tolerable, help control intracranial pressure, and possibly lead to better neurological outcomes. Post–cardiac arrest neural protection has also been demonstrated, with 55% of patients who underwent cooling having good outcomes versus 39% in the normothermia group.

Other neuroprotective strategies related to hypothermia in the clinical phase include an endovascular device inserted into the vena cava for cooling to 33°C for 24 hours, which was used in the Cooling for Acute Ischemic Brain Damage (COOL AID) study. This therapy was generally well tolerated, with trends toward less lesion growth on diffusion-weighted imaging. In a more recent pilot study, 26 patients underwent intraarterial endovascular cooling within 8 hours of intraarterial recanalization. This therapy did reduce brain temperature by at least 2°C with no obvious complications. The Intravascular Cooling in the Treatment of Stroke (ICTus) 2 trial results were recently published; however, only 120 patients of the intended 1600 were enrolled before the study was stopped. A femoral venous catheter was used for cooling. Mortality was 15.9% in the hypothermia group versus 8.8% in the normothermia group.

Kasner et al. performed a randomized controlled trial to determine if 3900 mg of acetaminophen administered daily to afibrile patients with acute stroke could reduce core body temperature, promote modest hypothermia, and prevent hyperthermia; however, these authors concluded that these effects are likely to have no robust impact on outcome. What has been shown is that fever in the first 24 hours of AIS leads to a doubling of the odds of death in 1 month post-stroke. Thus, despite the benefit of hypothermia on functional outcomes post–cardiac arrest, its use in AIS is still unproven.

Hyperbaric Oxygen

Since AIS occurs when the brain tissue oxygen supply does not meet the demand, many have investigated hyperbaric oxygen therapy as a way to boost brain oxygen levels. In a 2014 meta-analysis, Bennett et al. examined 11 randomized controlled trials assessing hyperbaric oxygen in AIS. These authors found no good evidence to suggest that hyperbaric oxygen improves clinical outcomes in AIS.

Near-Infrared Laser Therapy

Low-energy laser therapy has been used as a potential neuroprotective strategy in AIS. The theorized mechanism of action involves photostimulation of mitochondrial chromophores increasing enzymatic production of adenosine triphosphate, with resultant ischemic tissue preservation. A pooled analysis of the NeuroThera Effectiveness and Safety Trials (NEST) 1 and 2, involving 778 patients, supported the likelihood that transcranial laser therapy was effective when initiated within 24 hours of AIS.

Review of neuroprotection in ischemic stroke

### TABLE 3. Clinical immune modulation/antiinflammatory therapies for neuroprotection in AIS

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Trial</th>
<th>Agent</th>
<th>MOA</th>
<th>No. of Patients in Study</th>
<th>Benefit w/ Agent</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu et al., 2015</td>
<td></td>
<td>Fingolimod</td>
<td>Immune modulator*</td>
<td>47</td>
<td>Smaller lesion vol (10 vs 34 ml), less hemorrhage, better NIHSS; 90-day mRS Score 0–1 in 73% vs 32%</td>
<td>Administered w/ alteplase w/in 4.5 hrs, for 3 days</td>
</tr>
<tr>
<td>Elkins et al., 2016</td>
<td>ACTION</td>
<td>Natalizumab</td>
<td>Monoclonal antibody against α4 integrin</td>
<td>161</td>
<td>More patients had mRS Score 0–1 at 30 &amp; 90 days; however, no effect on infarct growth</td>
<td>Single dose 0–9 hrs from symptom onset</td>
</tr>
<tr>
<td>Kohler et al., 2013</td>
<td></td>
<td>Minocycline</td>
<td>Inhibit microglial &amp; T cell activation, decrease neural apoptosis, inhibit MMP-9</td>
<td>95</td>
<td>No clinical benefit</td>
<td>Infusion w/24 hrs &amp; every 12 hrs for total of 5 doses</td>
</tr>
<tr>
<td>Schäbitz et al., 2010</td>
<td>AXIS A</td>
<td>Filgrastim</td>
<td>Granulocyte colony-stimulating factor</td>
<td>44</td>
<td>No significant outcome difference, but exploratory analysis revealed some benefit for DWI lesions &gt;14 cm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>4 doses over 3 days w/in 12 hrs of symptoms</td>
</tr>
<tr>
<td>Emsley et al., 2005</td>
<td></td>
<td>Interleukin-1 receptor antagonist</td>
<td>Blocks interleukin-1–mediated cell death</td>
<td>34</td>
<td>Clinical outcomes at 3 mos better w/ antagonist, decreased C-reactive protein &amp; neutrophils</td>
<td>w/in 6 hrs of symptoms for 72 hrs</td>
</tr>
</tbody>
</table>

* Fingolimod acts via immune modulation and sequesters lymphocytes via sphingosine-phosphate receptor internalization, but also reportedly is a ceramide synthase inhibitor and cannabinoid receptor antagonist.

ACTION = Effect of Natalizumab on Infarct Volume in Acute Ischemic Stroke; AXIS = Treatment With AX200 for Acute Ischemic Stroke; MMP-9 = matrix metalloproteinase.
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threatening events and death. Death may provide some benefit. MultiStem treatment was identified, post hoc analysis did suggest early administration may provide some benefit. MultiStem treatment was associated with lower rates of infection and pulmonary events, shorter hospitalizations, and a reduction in life-threatening events and death.

Preclinically Assessed Neuroprotective Therapies

Despite the many promising therapies examined in clinical studies, none has yet gained guideline recommendation for the treatment of AIS. Many preclinical studies have been completed or are underway, and we review a few promising ones here.

Neuroprotection strategies have been traditionally divided into different mechanistic varieties including compounds or therapies that combat oxidative stress, the immune response, and excitotoxicity. Some therapies can target more than one aspect of the secondary brain injury following stroke.

Chlorpromazine/Promethazine

The phenothiazine class of drugs, which includes chlorpromazine and promethazine, have widely been used as neuroleptics but have also been shown to have depressive effects on the central nervous system through the inhibition of carbohydrate oxidation, as well as vasodilatory and anti-shivering properties. The drugs at high concentrations can induce hypothermia in rats. Liu et al. examined the combination of phenothiazine drugs with mild hypothermia in a rat intraluminal MCA filament model of stroke. Combination therapy reduced infarct volume and resulted in better long-term motor recovery than placebo, phenothiazine alone, or hypothermia alone. The authors concluded that phenothiazine drugs may enhance the neuroprotective effects of hypothermia by reinforcing depressive central nervous system effects and thus achieving goal hypothermia faster. These drugs can inhibit mitochondrial dysfunction and decrease free radical production.

Caffeinol (caffeine and ethanol)

Aronowski et al., utilizing a rat model of common carotid artery/left MCA infarct, treated different cohorts with combinations of ethanol, caffeine, and hypothermia. They concluded that low doses of caffeine, equivalent to 2–3 cups of coffee, and low doses of ethanol, equivalent to 1 cocktail, are highly neuroprotective and can reduce cortical infarct volumes and behavioral dysfunction after transient occlusion. However, daily exposure to ethanol eliminated the efficacy through tolerance, thought to be related to NMDA and γ-aminobutyric acid (GABA) receptor changes. The caffeinol treatment was further improved with mild hypothermia. Recently, Cai et al. suggested that the neuroprotection mediated through mild hypothermia and ethanol was PKC-Akt-NOX mediated. A pilot study in humans did demonstrate the feasibility of the administration of both agents in AIS patients.

Methylene Blue

Methylene blue (MB) is a drug used to treat malaria, methemoglobinemia, and cyanide poisoning. It is an FDA-grandfathered drug. Neuroprotective and memory-enhancing qualities have been demonstrated in neurodegenerative disease. Methylene blue is thought to act as a renewable auto-oxidizer, redirecting electrons in the mitochondrial transport chain promoting ATP production and cell survival. In hypoxic conditions, MB becomes the oxidizer and sustains ATP production while lowering oxidative stress. Furthermore, MB enhances cytochrome c oxidase activity while bypassing complexes 1–3. It is also thought to augment HIF-1α activation and stabilization, increase cerebral blood flow to mismatched areas, and promote autophagy via p53-AMPK-TSC2-mTOR, while downregulating apoptosis via the p53-Bax-Bcl2-caspase 3 pathway in perfusion-diffusion mismatched tissue. Shen et al. found that MB in a 60-minute rat MCA model of stroke had no effect on the initial MRI-demonstrated lesion volume; however, at 2 days after stroke, the final infarct volumes increased in the vehicle group but decreased in the MB group, yielding a 30% overall infarct difference. Pixel by pixel analysis showed that MB salvaged more core and penumbra pixels than the control treatment. Recently, the addition of normobaric hyperoxia to MB was found to further increase functional outcome and decrease infarct volume.

Rapamycin

Rapamycin is an immunosuppressant drug that targets mTOR and its downstream pathways. mTOR has been implicated in regulating cell survival, proliferation, growth, metabolism, and autophagy. Recently, rapamycin was found to extend lifespan in a variety of animal models. Chauhan et al. utilizing an MCA filament model in rats, found that rapamycin could significantly improve the infarct area and apparent diffusion coefficient and improve motor impairment as compared with controls. It also reversed the changes in malondialdehyde, glutathione, nitric oxide, and myeloperoxidase. When administered daily for 1 month before injury in diabetic rats, rapamycin was found to reduce ischemic brain damage via mTOR and ERK1/2 suppression. Not all rodent models of stroke have shown positive results with rapamycin; for example, the drug was found to increase infarct size and oxygen consumption in a rat model.

Inflammatory/ Stress Response and Immune Modulation

The inflammatory response in AIS has been called a double-edged sword with early inflammation causing harm, but late inflammatory changes contributing to regeneration. Hu et al. found that macrophage subtype
shifted from early beneficial M2 microglia to M1 microglia and suggested that new therapies should focus on adjusting the balance between good and bad subtypes. Recently, this shift from the M1 to the M2 phenotype in stroke was found to be mTOR mediated. Several antibodies targeting adhesion molecules designed to prevent leukotaxis have been produced in the last few years. Antibodies targeting anti-neutrophil markers have been shown to decrease myeloperoxidase injury, infarct volume, and edema post-reperfusion. Interleukin-6 expression and tumor necrosis factor-α expression while increasing the number of noninflammatory monocytes (CD43+/CD172a+) natural killer T cells. It induces interleukin-6 expression in cortical neurons also conferred neuroprotection and should be further investigated. This receptor is implicated in the stress response and hypoxic ischemic injury post-stroke.

Li et al. examined the therapeutic advantage of regulatory T cells (Tregs) in 2 rodent models of stroke and in vitro Treg-neutrophil cocultures. They found that systemic administration of Tregs out to 24 hours post-MCA occlusion resulted in a marked reduction in brain infarct and prolonged improvement in neurological function. This was achieved via decreased blood-brain barrier disruption and decreased cerebral inflammation. The Tregs also decreased levels of matrix metalloproteinase-9. Despite these promising results, however, many challenges remain, namely that Tregs constitute only 5%–10% of circulating T cells. Thus, they would need to be expanded either in vivo or in vitro and properly honed for cerebral post-reperfusion.

Doeppner et al. examined lithium in a rat MCA occlusion model. They noted that when lithium was administered within 6 hours of onset, reduced infarct volumes, edema, leukocyte infiltration, and microglia activation were present. They reported that lithium increased levels of miR-124, resulting in the degradation of RE1-silencing transcription factor and thus leading to postischemic neuroplasticity. This effect was independent of glycogen synthase kinase 3β (GSK3β).

**Finding New Ways to Use Old Therapies and Future Directions**

Lastly, it is important to remember older, previously studied neuroprotective agents. As technology changes, the ability to target previously nonspecific drugs or to change the pharmacokinetics of previously rapidly cleared compounds changes. For example, in 2014 Gaudin et al. reported that the conjugation of adenosine to the lipid squalene and the subsequent formation of nanoassemblies prolonged circulation and conferred neuroprotection in a rat stroke and spinal cord injury model. However, even though the delivery vehicle was improved, new data suggest a temporal effect of adenosine, namely that adenosine receptors support early excitotoxicity but then seem to attenuate the inflammatory response following. Regardless of this temporal finding, as technology finds new ways to deliver or improve therapies, we must be open to reassessing older agents.

In a landmark paper on experimental neuroprotection related to AIS, published in 2006, O’Collins et al. systematically reviewed 1026 experimental therapies in both focal and global ischemic animal models, with some studies dating back to the 1950s. These authors compared 114 drugs used clinically to 912 drugs used experimentally and found the clinical therapies to be no more efficacious experimentally than the therapies tested experimentally only. Overall, 64% of drugs tested in the focal ischemic animal models were effective, versus 70% of drugs tested in the global ischemic animal models. Interestingly, no specific drug mechanism distinguished itself by superior efficacy in the focal ischemic animal models. The authors suggested that this finding may reflect the multifaceted nature of stroke or perhaps an incorrect understanding of secondary stroke injury. Thus, they urged rigorous preclinical testing and reporting of data, so that only the most efficacious therapies move forward to clinical phases.

While many of the studies predating 2005, as compared with those from the last 10 years, and the studies reviewed in the current paper target similar pathways, many of the immune modulating and immunotherapy techniques discussed above have only recently been investigated. These studies, along with repeat validation of promising older drugs and therapies, will lay the foundation for stroke neuroprotection moving forward. Many promising therapies are available, including hibernation-like therapy, immune modulation therapy, and near-infrared laser therapy. The disconnect between the beneficial effects of hypothermia for post–cardiac arrest global neuronal ischemia and the lack of efficacy for focal ischemia due to AIS requires better understanding. As mentioned in the O’Collins et al. study, perhaps researchers and clinicians need to stop compartmentalizing AIS secondary injury and instead focus on the global picture. Targeting only one aspect of a multifaceted cascade will probably result in only mild benefits.

**Conclusions**

Many clinical and preclinical studies of neuroprotection in stroke have been completed; however, few studies have shown clinical benefit. It is imperative that relevant high-quality preclinical studies progress to randomized clinical trials. Neuroprotection in stroke remains very promising with many avenues for improvement and discovery, including trials of current and new therapies in combination. Given the benefits of hypothermia post–cardiac arrest, future studies should determine the exact role of therapeutic hypothermia in AIS, as well as the disconnect between current post–cardiac arrest data and AIS data. Stem cell therapy and immunomodulation also appear promising.
Acknowledgments

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Author Contributions
Conception and design: both authors. Analysis and interpretation of data: Ding. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Ding. Study supervision: Ding.

Correspondence
Yuchuan Ding, Department of Neurosurgery, Lande Building, #48, 550 East Canfield, Detroit, MI 48201. email: yding@med.wayne.edu.