Neuroprotective delivery platforms as an adjunct to mechanical thrombectomy

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Despite the success of numerous neuroprotective strategies in animal and preclinical stroke models, none have effectively translated to clinical medicine. A multitude of influences are likely responsible. Two such factors are inefficient recanalization strategies for large vessel occlusions and suboptimal delivery methods/platforms for neuroprotective agents. The recent endovascular stroke trials have established a new paradigm for large vessel stroke treatment. The associated advent of advanced mechanical revascularization devices and new stroke technologies help address each of these existing gaps. A strategy combining effective endovascular revascularization with administration of neuroprotective therapies is now practical and could have additive, if not synergistic, effects. This review outlines past and current neuroprotective strategies assessed in acute stroke trials. The discussion focuses on delivery platforms and their potential applicability to endovascular stroke treatment.

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To date, few effective therapies exist for treatment of acute ischemic stroke (AIS).^{2,3,45,74,75} In select individuals, intravenous tissue plasminogen activator (tPA) improves outcomes when administered within 4.5 hours of symptom onset.³⁷ Limitations of intravenous thrombolysis have led to the development of alternative revascularization and reperfusion strategies.^{11,77,78} The 2015 endovascular stroke trials demonstrate that the prompt use of new-generation mechanical thrombectomy devices, particularly stent retrievers, significantly improves functional independence in the setting of large-vessel stroke compared with best medical management alone.^{14,17,33,48,81,92} These trials marshaled a new treatment paradigm that has revolutionized acute stroke care. A greater number of stroke patients are now eligible for established therapies with potential for substantially improved functional outcomes. However, significant limitations exist with regard to prehospital management, timely selection for intravenous tPA or endovascular therapy, and multidisciplinary

coordination of posttreatment stroke and ICU care.^{4,6} Perhaps most importantly, both intravenous thrombolysis and mechanical revascularization target vessel recanalization rather than tissue reperfusion and are highly dependent on time.

Despite recent advances, the rates of functional independence (14%–58%) following mechanical thrombectomy are poor compared with the efficient rates of recanalization (60%–90%).^{7,34} The mechanism underlying this paradox remains elusive. One hypothesis, first proposed in the cardiology literature, is the “no-reflow phenomenon.” Supporters advance the concept of minimal capillary reperfusion despite adequate recanalization.²⁸ Restoration of blood flow is thought to alter the microvascular milieu, creating a proinflammatory state that renders affected microvascular beds incompetent.^{21,72,98} While blood flows through the large vessels, there is resistance at the capillary level. A lack of functional reperfusion causes marginally viable penumbral tissue to be recruited into the ische-

ABBREVIATIONS AIS = acute ischemic stroke; APC = activated protein C; BM-MNC = bone marrow mononuclear cell; DWI = diffusion-weighted imaging; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; rPerC = remote ischemic preconditioning (preconditioning); tPA = tissue plasminogen activator.

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mic core. The discrepancy between recanalization rates and functional outcome underscores the need for further advancements in stroke therapy.

Endovascular treatment is recommended in appropriately selected patients who have symptom onset within 6 hours of presentation.⁴⁶ However, The International Management of Stroke (IMS III) trial found that for every 30-minute delay in the time to reperfusion, there was a 12%–15% relative reduction in the likelihood of good clinical outcome.⁵² Not only is the time window for revascularization short, there is a bias toward better outcome earlier in the treatment period. As thrombectomy devices and recanalization rates have improved significantly, alternative points along the stroke treatment pathway must now be engaged to improve outcomes. Extension of the treatment window by preserving “at-risk” brain tissue is a logical target.

Adjunct neuroprotective administration in the setting of mechanical revascularization could address these 2 therapeutic gaps. Neuroprotective agents may promote reperfusion at the capillary level in the region of the target tissue and could potentially increase the time window for effective recanalization (by preserving brain tissue and decreasing hemorrhage rates). New-generation mechanical thrombectomy delivery systems provide a unique opportunity to effectively administer neuroprotectants in the treatment of AIS. This review focuses on neuroprotective strategies and their potential ability to “freeze time” by limiting ischemic damage while a patient proceeds through the acute stroke pathway.^{27,50,56,96} The *Discussion* introduces novel platforms for delivery of neuroprotective therapies and specifically highlights the potential utility of neuroprotection as an adjunct before, during, and after mechanical thrombectomy.

Barriers to Implementation of Neuroprotective Strategies

Thousands of preclinical animal studies have demonstrated benefits of neuroprotective therapies in the setting of experimental acute stroke.⁹³ However, none of these treatment strategies have been widely translated to human patients.³² Species-specific differences in brain structure and function, lack of sex heterogeneity, and a shortage of trials in the setting of relevant comorbidities are potential reasons for translational failures.⁴⁷ The Stroke Treatment Academic Industry Roundtable (STAIR) recommendations were created in an effort to develop a rigorous standard in the transition of preclinical neuroprotectant studies to clinical trials.²⁵

Factors that limit the potential for treatment agents to reach target territories (ischemic penumbra) can prevent significant changes in clinical stroke outcomes even if neuroprotective therapies could otherwise salvage ischemic tissue. Such factors include lack of perfusion due to thrombus burden, inefficient delivery methods, and poor collateral vessels.³¹ In the past, neuroprotectant delivery platforms were tailored and optimized to supplement definitive revascularization strategies, such as endovascular therapy. Mechanical revascularization presents a now-proven procedure with no potential drug-drug interactions

that can be administered in series or parallel with neuroprotective agents. This combined, and potentially synergistic, therapeutic strategy holds great promise.

The sections below outline the various time points, with respect to mechanical thrombectomy treatment, at which putative neuroprotective agents may be administered.

Prehospital Delivery Methods

In AIS, the volume of the ischemic core expands into previously salvageable penumbral tissue as time progresses.^{10,42,49,71} A slower rate of early diffusion-weighted imaging (DWI) growth is associated with greater penumbral salvage following tissue reperfusion.⁹⁵ Neuroprotective strategies could slow the rate of ischemic growth prior to endovascular AIS treatment (Table 1). Successful application would broaden eligibility for endovascular therapy and ultimately improve functional outcomes for each patient by shifting the time-to-reperfusion/functional outcome curve. The Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial was the first to deliver a neuroprotective agent during the hyperacute period, the “golden hour” after stroke onset.⁸² Although FAST-MAG did not achieve its primary efficacy end point (that prehospital administration of magnesium sulfate during the hyperacute phase of AIS would reduce disability at 90 days), it established safety and feasibility of a novel prehospital delivery platform.^{83,84} The investigators demonstrated that a study agent could be effectively delivered to patients during the first 60 minutes after stroke onset by ambulance paramedics and established methods and protocols that can be used in future trials. An under-recognized, yet important aspect of the trial was the implementation of a 2-stage screening process that paramedics used to identify potential study patients. The first stage consisted of assessment via the Los Angeles Prehospital Stroke Screen (LAPSS).⁵³ This is a diagnostic inventory that takes minutes to perform, exhibits high sensitivity and specificity, and is widely used among ambulance personnel worldwide. The second stage incorporated physician assessment over the telephone. These streamlined steps allow neuroprotective agents to be safely administered while patients were delivered to the hospital (parallel processing). In a subset analysis, investigators studied patients who received prehospital treatment with magnesium or placebo initiated less than 2 hours from symptom onset and underwent endovascular treatment. Magnesium therapy still showed no effect; however, the investigators calculated that the strategy exposed patients to 3 hours and 28 minutes of potential neuroprotective exposure prior to endovascular treatment.

An in-depth discussion of novel neuroprotective agents amenable to this type of delivery mechanism is beyond the scope of this paper. However, there are a number of promising therapies, such as NA-1, glyburide, activated protein C, and uric acid, that have recently passed Phase 2 clinical trials.^{19,40,64,85}

It is hypothesized that the failure of many neuroprotective strategies is due to the fact that agents only target 1 point in a mechanistic pathway. Hypothermia, however, is a promising therapy that exhibits a wide range of cel-

TABLE 1. Prehospital delivery methods

Reference/ Registration No.	Study Name	Study Type	Neuroprotectant/ Neuroprotective Mode	Treatment Method	Primary Outcome	Results
Saver et al., 2015	FAST-MAG	RCT	Magnesium sulfate	IV w/in 45 mins of stroke symptoms	mRS score at 90 days	Prehospital infusion of magnesium sulfate was safe w/in 2 hours of stroke symptoms but did not improve disability outcome at 90 days
Krieger et al., 2001	COOL AID	Open pilot study	Hypothermia (32°C)	Systemic hypothermia w/in 6.2 ± 1.3 hrs	Safety & feasibility of moderate hypothermia	Induced hypothermia found to be safe w/ mRS score of 3.1 ± 2.3 at 3 mos
van der Worp et al., 2014	EuroHYP-1	RCT	Hypothermia (34°C–35°C)	Intravenous infusion of 20 ml/kg refriger- ated normal saline (4°C) over 30–60 mins or a surface cooling method	mRS score at 90 days	Ongoing
NCT01584167	iCOOL2	RCT	Hypothermia	EMCOOLS Flex.Pads	Change in brain tempera- ture during 1 hr after start of cooling	Ongoing
Meng et al., 2012	Upper-limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis	Prospect- ive random- ized study	Repetitive bilateral-arm ischemic pre- conditioning	5 brief cycles of bilateral upper-limb ischemia, twice daily for 300 con- secutive days	Time point of the 1st stroke recurrence event	Incidence of recurrent stroke was reduced to 5% & 7.9% at 90 & 300 days, respectively
Hougaard et al., 2014	Remote Ischemic Perconditioning as an Adjunct Therapy to Thrombolysis in Patients With Acute Ischemic Stroke	Open-label blinded outcome proof-of- concept study	rPerC	Prehospital rPerC as an adjunct to treat- ment w/ intrave- nous alteplase.	Penumbra salvage as defined by the vol of the perfusion-diffusion mismatch not pro- gressing to infarction after 1 mo	rPerC reduced tissue risk of infarction using voxel- wise analysis after adjustment for baseline perfusion & diffusion lesion severity
Pico et al., 2016	RESCUE BRAIN	RCT	rPerC	rPerC w/in 6 hrs of stroke onset	Absolute difference in brain infarct volume measured by DWI MRI from baseline to 24 hrs	Ongoing

IV = intravenous; RCT = randomized clinical trial.

lular mechanisms.⁹⁷ Systemic cooling to a temperatures of 32°C and 34°C for 24 hours has been shown to increase survival and improve neurological outcome in patients with spontaneous circulation restoration after cardiac arrest due to ventricular fibrillation.¹ Induced hypothermia was first found feasible and safe in acute ischemic stroke in the Cooling for Acute Ischemic Brain Damage (COOL AID) open pilot study.⁵⁴ EuroHYP-1 is an ongoing Phase 3 clinical trial that employs systemic cooling to decrease body temperature to a target between 34°C and 35°C. Hypothermia is initiated within 6 hours of stroke onset and maintained for 24 hours. The primary outcome is the modified Rankin Scale (mRS) score at 90 days. Patients in this study are either cooled with an intravenous infusion of 20 ml/kg refrigerated normal saline (4°C) over 30–60 minutes or a surface cooling method, depending on local practice.⁹¹ Although patients in this study begin the cold infusions when they enter the hospital, intrave-

nous cooling can easily be administered in the prehospital setting. The appeal of a cold infusion is that it is easy to deliver, widely accessible (i.e., refrigerator in ambulance), and portable. Further methods of cooling and their effects on brain temperature are also being studied. The iCOOL2 clinical trial is testing a novel, noninvasive, surface cooling system called the EMCOOLS Flex.Pads (Emergency Medical Cooling Systems AG) (clinical trial registration no. NCT01584167 [clinicaltrials.gov]).

Remote ischemic preconditioning (preconditioning) (rPerC) has been shown to be neuroprotective in animal models of cerebral ischemia.³⁸ rPerC occurs when ischemia induced in one organ leads to ischemic tolerance in others, with the protective effect attributed to the activation of multiple endogenous defense mechanisms.⁷⁶ The safety of rPerC was tested in a randomized single-center study in patients with myocardial infarction. The treatment was found to be safe and effective in myocardial salvage.¹⁵

TABLE 2. Neuroprotectant administration coupled with mechanical thrombectomy

Reference/ Registration No.	Study Name	Study Type	Neuroprotectant/ Neuroprotective Mode	Treatment Method	Primary Outcome	Results
NCT02222714; Lyden et al., 2016	Safety Evaluation of 3K3A-APC in Ischemic Stroke (RHAPSODY)	RCT	APC	Safety & efficacy of multiple increasing intravenous doses of 3K3A-APC in combination w/ tPA, mechanical thrombectomy or both	Adverse events that meet dose-limiting toxicity criteria	Ongoing
Hill et al., 2012	The Safety and Efficacy of NA-1 in Patients with Iatrogenic Stroke after Endovascular Aneu- rysm Repair (ENACT)	RCT	NA-1	IV infusion of NA-1 after endovascular aneurysm repair	Safety as well as no. & vol of new ischemic strokes defined by MRI at 12–95 hrs after infusion	NA-1 group sustained fewer ischemic in- farcts than placebo group as measured by DWI & FLAIR
NCT02930018	The Safety and Efficacy of NA-1 in Subjects Un- dergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1)	RCT	NA-1	NA-1 use coupled w/ endo- vascular revascularization in patients w/ small es- tablished infarct core & w/ good collateral circulation	mRS score at 90 days	Ongoing

Bilateral-arm rPerC was first found to be neuroprotective in reducing the incidence of stroke and transient ischemic attack in patients with symptomatic intracranial arterial stenosis.⁶¹ rPerC was then tested as an adjunct to thrombolysis in patients with acute ischemic stroke in an open-label, prehospital, paramedic-administered study.⁴⁴ This study used MRI lesion volumes (as opposed to functional outcomes) to determine effect size. Upper-arm rPerC was performed for a total of 4 cycles by ambulance staff and was discontinued on arrival to the stroke unit. The study showed no overall benefit. However, when the findings were adjusted for baseline severity of hypoperfusion, a voxel-by-voxel analysis showed increased tissue survival after 1 month in the treatment group. This suggests that prehospital rPerC may have neuroprotective capacity. Currently, the Remote Ischemic Conditioning in Acute Brain Infarction (RESCUE BRAIN) trial is underway. This study examines whether rPerC during ischemic stroke (< 6 hours) reduces brain infarct size at 24 hours.⁷³ The primary end point is the absolute difference in brain infarct volume measured by DWI MRI from baseline to 24 hours, in the intervention versus control groups. The authors state that if RESCUE BRAIN shows effect on infarct volume, they would conduct a larger trial using a clinical primary end point. In the setting of acute stroke, rPerC is a promising prehospital neuroprotective adjunct to mechanical thrombectomy. The treatment is easy to administer and has already demonstrated positive results in patients with myocardial infarction and those with symptomatic intracranial stenosis.

Neuroprotectant Administration Coupled With Mechanical Thrombectomy

Activated protein C (APC) is a promising neuroprotectant agent. APC is an endogenous serine protease that is generated in multiple cell types within the neurovascular unit during the response to cerebral ischemia.^{35,99} Like hy-

pothemia, APC targets several pathological mechanisms of the ischemic cascade. The Safety Evaluation of 3K3A-APC in Ischemic Stroke (RHAPSODY) Phase 2 clinical trial is assessing the safety, pharmacokinetics, and preliminary efficacy of multiple increasing intravenous doses of 3K3A-APC (recombinant variant of human APC) in combination with tPA, mechanical thrombectomy or both (registration no. NCT02222714). Although the neuroprotectant delivery route is intravenous, this is the first trial of its kind to incorporate mechanical thrombectomy with the use of a putative neuroprotectant. Just as the FAST-MAG trial set the stage for prehospital delivery of neuroprotectants, the RHAPSODY trial has established the use of mechanical thrombectomy with the concurrent administration of neuroprotective agents.⁵⁸ The study authors needed to develop criteria that ensured patients are treated with current evidence-based standards for mechanical thrombectomy while, at the same time, allowing for assessment of efficacy for a neuroprotective agent. The door-to-needle times, imaging criteria, and National Institutes of Health Stroke Scale (NIHSS) scores established for inclusion in this study will set the standard for future investigations for combined neuroprotective agents and mechanical thrombectomy procedures (Table 2).

The Safety and Efficacy of NA-1 in Patients With Iatrogenic Stroke After Endovascular Aneurysm Repair (ENACT) study established safety and feasibility of neuroprotective strategies in the setting of endovascular procedures.⁴⁰ ENACT was a double-blind, randomized, controlled trial that found that NA-1 could be safely administered to patients undergoing endovascular repair of ruptured and unruptured intracranial aneurysms. Investigators assessed whether NA-1 reduced the volume and number of iatrogenic ischemic strokes (detection via MRI). NA-1 was administered at the conclusion of the procedures and was found to reduce the number of iatrogenic embolic strokes but not the overall volumes of

TABLE 3. Intraarterial neuroprotectant delivery

Reference/ Registration No.	Study Name	Study Type	Neuroprotectant/ Neuroprotective Mode	Treatment Method	Primary Outcome	Results
NCT01502761	Intra-arterial Magnesium Administration for Acute Stroke	RCT	Magnesium	Intraarterial high-concentration magnesium administration	Magnesium concentration in region of cerebral ischemia	Ongoing
NCT02235558	Superselective Administration of Verapamil During Recanalization in Acute Ischemic Stroke (SAVER-I)	RCT	Magnesium	Intraarterial verapamil administered immediately following intraarterial thrombolysis (either tPA or mechanical thrombectomy)	Presence or absence of intracranial hemorrhage	Ongoing
NCT02912663	Magnesium and Verapamil After Recanalization in Ischemia of the Cerebrum: a Clinical and Translational Study (MAVARIC)	RCT	Magnesium & verapamil	Selective intraarterial administration of verapamil & magnesium immediately after mechanical thrombectomy	Presence or absence of intracranial hemorrhage	Ongoing

lesions. This study establishes feasibility of intravenous delivery of a putative neuroprotective agent during neuroendovascular procedures. The investigators have leveraged their delivery platform to test the same agent in AIS. The Safety and Efficacy of NA-1 in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1) Phase 3 clinical trial expands the use of NA-1 to patients with major AIS (registration no. NCT02930018). AIS patients with a small, established infarct core and favorable collateral circulation are treated with a single 2.6-mg intravenous dose of NA-1 or placebo once selected for mechanical thrombectomy. The primary study outcome is global disability, with secondary measures of functional dependence, neurological outcome, activities of daily living, and mortality rate.

Intraarterial Neuroprotectant Delivery

Inadequate delivery of neuroprotective therapies to target tissue has been a concern in the setting of emergent large vessel occlusion. A large thrombus prevents the direct passage of blood, oxygen, nutrients, and any systemically administered agents. It is posited that potential neuroprotectants reach the penumbral tissue through collateral circulation.^{31,87} New-generation endovascular techniques allow for selective intraarterial drug delivery, a concept first described as endovascular restorative neurosurgery.⁷ Neuroprotective agents can be administered regionally through guide catheters positioned in the carotid or vertebral artery. Alternatively, treatments can be administered directly through microcatheters positioned at the face of, or beyond, the occlusive lesion. The benefits of intraarterial delivery of neuroprotectants are numerous. A high concentration/dose ratio can be achieved in a small, targeted volume of the brain, ultimately leading to lower systemic toxicity. Delivery can be executed rapidly and accessed repeatedly, while limiting perturbations of neural tissue inherent to traditional surgical routes of access.^{5,57}

The neuroendovascular community has a significant experience with intraarterial delivery platforms outside of stroke treatment. Lessons from these endeavors can be translated directly to mechanical thrombectomy pro-

cedures. Isolated or daily intraarterial infusion of spasmolytic agents (papaverine, verapamil, nitroglycerine) is common practice in the setting of cerebral vasospasm.^{8,24} Continuous intraarterial infusion of nimodipine has recently been reported. Safety of active infusion over the duration of 2 weeks was documented.^{12,41,65} The safety of continuous intraarterial infusion of nimodipine has implications for the delivery of neuroprotectants. Current trials (see below) use short-term, intraoperative, administration of neuroprotective agents. However, with the advent of continuous intraarterial treatment, the delivery of neuroprotectants can, theoretically, be administered safely for longer durations after stroke.

Intraarterial delivery of chemotherapeutics for brain tumors was first described in the 1950s.²⁹ With the advancement of endovascular techniques, the concept of superselective intraarterial cerebral infusion was established. This allows for the selective targeting of afferent tumor vessels, enabling the infusion of a chemotherapeutic agent to a localized area. Selective microcatheter delivery of a targeted agent to brain tumors was first described in 2009.⁷⁹ To date, superselective intraarterial cerebral infusion has been successfully leveraged for the treatment of high-grade gliomas and retinoblastomas.^{3,67,86}

In large-vessel stroke, intraarterial delivery of neuroprotectants can occur prior to, or following, clot extraction. If an agent is delivered distal to a thrombus prior to recanalization, it will likely remain in the tissue bed until flow is restored. This has implications on both efficacy and toxicity. However, if the neuroprotectant therapy is delivered after recanalization, the agent will be subject to the same first-pass effects that might be seen in other tissue beds. Stent retriever catheters allow for distal delivery once a thrombus is traversed, while aspiration with distal catheters would only allow local/regional administration, as they do not typically cross the face of the clot. Several ongoing trials are examining intraarterial delivery platforms in the setting of acute stroke (Table 3). The Intra-arterial Magnesium Administration for Acute Stroke trial examines the effect of intraarterial high concentration magnesium administration in patients with AIS (registration no.

TABLE 4. Alternate endovascular delivery methods

Reference	Study Name	Study Type	Neuroprotectant/ Neuroprotective Mode	Treatment Method	Primary Outcome	Results
De Georgia et al., 2004	Cooling for Acute Ischemic Brain Damage (COOL AID)	Feasibility trial	Intravascular cooling	Triple-looped, helically wound, heat-exchange balloon catheters placed in the inferior vena cava via femoral vein access	Safety & feasibility	Endovascular cooling is safe & well tolerated
Lyden et al., 2016	Intravascular Cooling in the Treatment of Stroke 2 (ICTuS 2)	RCT	Intravascular cooling	Femoral venous intravascular cooling w/ the use of a catheter after IV tPA for 24 hrs followed by a 12-hr rewarm	Whether pneumonia rate was lowered compared w/ previous ICTuS study & whether the cold saline bolus was safe and effective	Endovascular cooling is safe & feasible; however, protocol changes implemented to reduce pneumonia risk failed due to small sample size

NCT01502761). This safety and feasibility study is the first to directly quantify levels of neuroprotectants in the region of ischemia. Similarly, Superselective Administration of Verapamil During Recanalization in Acute Ischemic Stroke (SAVER-I) examines the safety of verapamil as a neuroprotective agent administered intraarterially immediately following intraarterial thrombolysis (either tPA or mechanical thrombectomy) (registration no. NCT02235558). This study uses newer generation mechanical thrombectomy devices, and it uses a guide in the region previously burdened by a clot, administering 10 mg verapamil/20 ml normal saline over 20 minutes. By assessing 2 neuroprotective agents with relatively benign safety profiles, these 2 studies have established a paradigm for administering other intraarterially delivered neuroprotectants.

The Magnesium and Verapamil After Recanalization in Ischemia of the Cerebrum: a Clinical and Translational Study (MAVARIC) is a Phase 2 clinical trial investigating the safety and feasibility of superselective intraarterial administration of verapamil and magnesium immediately after mechanical thrombectomy (registration no. NCT02912663); 10 mg verapamil/10 ml normal saline and 1000 mg magnesium sulfate/20 ml normal saline are administered over 20 minutes using a microcatheter into vessels that were previously obstructed by thrombus. Outcome measures include symptomatic intracranial hemorrhage and systemic side effects.

Stem cells have been delivered via intraarterial platforms in many clinical stroke trials.⁸⁰ Although stem cells are neuroregenerative, rather than neuroprotective, their intraarterial delivery is worth considering in this discussion. At this time, the optimal mode of stem cell delivery (intracerebral, intraventricular, subarachnoid, intraarterial, intraperitoneal, intravenous, and intranasal) remains unclear. However, the intraarterial route has shown promise.⁶² Battistella et al. first assessed the use of autologous bone marrow mononuclear cells (BM-MNCs) in 6 patients with nonacute middle cerebral artery (MCA) stroke within 90 days of symptom onset.¹³ A large inner diameter microcatheter (SL 1018 Boston Scientific, Target Therapeutics) was used to infuse the stem cells for approximately 10 minutes into the M₁ portion of the MCA. As the trial did not include a control group, efficacy could not be ascer-

tained. However, the study did demonstrate feasibility and safety. Another Phase 1–2 clinical trial aimed to assess the safety, feasibility, and effect of BM-MNC transplantation in subacute MCA stroke.⁶³ BM-MNCs were injected into the M₁ segment of the affected MCA region at low pressure 5–9 days after stroke. Once again, the authors found that intraarterial transplantation of BM-MNCs in subacute MCA stroke is feasible and safe. Using similar delivery methods, another BM-MNC trial demonstrated a 40% rate of good clinical outcome (mRS score ≤ 2) and 30% satisfactory clinical improvement (mRS score of 0 in patients with NIHSS score < 8 , mRS score of 0–1 in patients with NIHSS scores of 8–14, or mRS scores of 0–2 in patients with NIHSS score > 14) in their study population.³⁰

Alternative Endovascular Delivery Methods

We previously described the potential benefits of intravenous cooling during AIS. This strategy has been extended to a direct endovascular approach (Table 4). The Cooling for Acute Ischemic Brain Damage (COOL AID) feasibility trial was the first trial to use triple-looped, helically wound, heat-exchange balloon catheters that were placed in the inferior vena cava via femoral vein access. The investigators found that moderate hypothermia is feasible in the setting of AIS with the aid of an endovascular cooling device.²⁰ The Intravascular Cooling in the Treatment of Stroke (ICTuS) trial expanded on this principle. The study demonstrated that endovascular cooling with a proactive antishivering regimen can be accomplished in awake stroke patients.⁵⁸ This study employed the use of a heparin-coated flexible metal catheter with a metallic heat transfer surface that facilitates extraction of heat from the blood as it flows by the catheter. Later, the ICTuS–Longer window (ICTuS-L) trial was developed to determine if endovascular catheterization and cooling could be performed safely in patients treated with thrombolytic therapy. The investigators found no bleeding complications in patients who underwent catheterization. However, the ICTuS-L trial demonstrated an increase in risk of pneumonia in patients receiving endovascular cooling.^{36,39} The Phase 2 ICTuS trial confirmed the safety and feasibility of intravascular therapeutic hypothermia in patients undergoing

TABLE 5. Neuroprotective delivery following mechanical thrombectomy

Study	Study Name	Study Type	Neuroprotectant/ Neuroprotective Mode	Treatment Method	Primary Outcome	Results
NCT01794182	Glyburide Advantage in Malignant Edema and Stroke - Remedy Pharmaceuticals (GAMES-RP)	RCT	Glyburide	Glyburide via injection	mRS score at Day 90 $\leq$ 4 w/o decompressive craniectomy	Ongoing
NCT02831088	The Efficacy and Safety of Neu2000KWL in Treating Acute Ischemic Stroke Receiving Endovascular Therapy (ENIS I) trial	RCT	Neu2000KWL	Neu2000KWL administered before endovascular therapy w/in 8 hrs of symptom onset w/ 9 consecutive doses	mRS at 5 days, 4 & 12 wks after 1st Neu2000KWL treatment	Ongoing
NCT01976936	Neuroprotection With Statin Therapy for Acute Recovery Trial Phase 2 (NeuSTART2)	RCT	Statin	Randomization of standard dose lovastatin vs short-term high-dose lovastatin 640 mg/day for 3 days within 24 hrs of symptom onset	Primary safety outcome: major hepatic toxicity or rhabdomyolysis	Ongoing
NCT02549846	Administration of Statin on Acute Ischemic Stroke Patient Trial (ASSORT)	RCT	Statin	Atorvastatin 20 mg or pitavastatin 4 mg or rosuvastatin 5 mg initiated for 1 wk after symptom onset vs no statin	mRS score at 12 wks	Ongoing
NCT01369069	Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial	RCT	Insulin	Treatment of hyperglycemic acute ischemic stroke patients with targeted glucose concentration (80–130 mg/dl)	mRS at 3 mos & severe hypoglycemia (primary safety outcome)	Ongoing
NCT02054429	Intensive Insulin Therapy With Tight Glycemic Control to Improve Outcomes After Endovascular Therapy for Acute Ischemic Stroke	RCT	Insulin	Insulin infusion (minimal rate of 2 U/hr while maintaining blood glucose btwn 90 & 120 mg/dl) immediately after endovascular therapy & continued for 48 hrs	mRS at 30 days	Ongoing

thrombolytic therapy. The protocol changes implemented to reduce pneumonia risk appeared to have failed; however, the sample size was small.⁵⁹

Neuroprotective Delivery Following Mechanical Thrombectomy

Despite efforts to achieve vessel recanalization and reperfusion, there remains a percentage of patients who are recalcitrant to endovascular therapy and go on to suffer ischemic injury. In principle, inhibition of inflammatory pathways, prevention of excitotoxicity, reduction of apoptosis, and mitigation of the development of vasogenic edema should improve cellular survival in the area of ischemia and surrounding tissue, commonly referred to as secondary brain injury. Unfortunately, many of the pharmacological treatments developed to target these mechanisms have failed to demonstrate reproducible clinical benefit when evaluated in human subjects. Notably, recent trials of erythropoietin⁷⁰ and progesterone,⁹⁰ when used to mitigate secondary brain injury resulting from traumatic mechanisms, did not demonstrate any superiority over placebo medication.

One of the more promising agents aimed at preventing secondary brain injury recently evaluated in a Phase 2 randomized clinical trial is a sulfonylurea receptor 1 antagonist (intravenous delivery) (registration no. NCT01794182).^{51,88} Inhibition of this receptor has the potential to reduce the development of vasogenic edema fol-

lowing ischemic stroke, a key mediator of secondary brain injury.⁹⁴ Its mechanism rests on an understanding of the ionic movement through the SUR1-TRPM4 nonselective cation channel, which is upregulated in the setting of ischemia. In animal studies, it has been demonstrated that this channel can be effectively blocked with glyburide, a medication approved by the FDA for diabetes treatment. Results of this trial demonstrated that the medication Cirara (Remedy Pharmaceuticals) resulted in a 53% mortality reduction when compared with placebo and the amount of brain swelling (measured by midline shift) was also reduced by half when compared with placebo. This evidence, along with an excellent safety profile, suggests that Cirara has the potential to dramatically change the treatment of ischemic stroke, and supports further investigation in a Phase 3 trial (Table 5).

The Efficacy and Safety of Neu2000KWL in Treating Acute Ischemic Stroke Receiving Endovascular Therapy (ENIS I) trial is a study examining the safety and efficacy of Neu2000KWL, a multitarget drug designed to prevent both excitotoxicity mediated by the *N*-methyl-D-aspartic (NMDA) receptor and free-radical toxicity (registration no. NCT02831088). It combines intravenous drug administration just prior to endovascular therapy with 9 consecutive infusions of Neu2000KWL at 12-hour intervals following mechanical thrombectomy.

Although not classically considered neuroprotectants, multiple treatment strategies/agents (glycemic control,

statins) have been used to decrease infarct volume, mitigate cerebral edema, and improve clinical outcome in the setting of acute stroke.⁸⁹ Trials are being designed to specifically assess the efficacy of these therapies in the subset of large vessel occlusions. Most recently, studies have leveraged some of these treatment strategies as adjuncts after mechanical thrombectomy. The use of statin therapy has been established in primary and secondary stroke prevention.^{9,66} Furthermore, statin administration has been shown to improve recovery after AIS. A population-based prospective cohort study found that initiation of new statin therapy (< 72 hours after stroke) was associated with improved 7-day survival, along with good functional outcomes at 7 days and 1 year.⁶⁹ Statin use initiated within 3 days of stroke hospitalization is strongly associated with improved poststroke survival. By contrast, withdrawal of statin therapy in the hospital was associated with worsened survival.²⁶ A more recent meta-analysis of observational studies and randomized trials found that statin therapy at stroke onset was associated with improved outcome.⁶⁸ The sum of these findings has led investigators to develop clinical trials. The Neuroprotection with Statin Therapy for Acute Recovery Trial (NeuSTART) found that doses of lovastatin up to 8 mg/kg daily for 3 days after AIS was tolerable.²² NeuSTART2 is currently studying the safety and efficacy of low dose (80 mg daily) and high dose (640 mg daily) statins administered within 24 hours of symptom onset for 3 days (registration no. NCT01976936). The Administration of Statin On Acute Ischemic Stroke Patient Trial (ASSORT) is a Phase 4 clinical trial examining the effect of statin (atorvastatin 20 mg or pitavastatin 4 mg or rosuvastatin 5 mg) initiated for a week after AIS (registration no. NCT02549846).

Hyperglycemia is a common finding in patients with AIS and is associated with larger infarct volumes, poor clinical outcomes, and increased risk of mortality.^{18,23,55} The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial is a Phase 3 study examining 1400 hyperglycemic patients who receive either sliding-scale subcutaneous insulin or continuous intravenous insulin for up to 72 hours, beginning within 12 hours of stroke onset (registration no. NCT01369069). The study is powered to detect a 7% absolute difference in favorable outcome at 3 months. This trial is currently ongoing and will help elucidate the proper management parameters for hyperglycemic AIS patients.¹⁶ Another study is examining the effects of Exenatide, a GLP-1 analog. A decreased risk of hypoglycemia may afford an advantage over insulin therapy in the acute management of hyperglycemia in the setting of AIS.⁶⁰ Tight glycemic control in AIS is now being leveraged as an adjunct to mechanical thrombectomy in The Intensive Insulin Therapy With Tight Glycemic Control to Improve Outcomes After Endovascular Therapy for Acute Ischemic Stroke clinical trial (registration no. NCT02054429). This study will examine the effects of intensive insulin therapy versus standard glycemic control in nondiabetic patients presenting within 8 hours of ischemic stroke who have undergone mechanical thrombectomy. The primary outcome is the mRS score at 90 days, and secondary outcome is DWI infarct volume.

Conclusions

Acute stroke treatment has undergone a seismic shift over the past 2 years. A period of rapid device development was coupled with expansion in stroke systems of care. Patients with emergent large vessel occlusion are being diverted to endovascular centers more efficiently and undergoing successful mechanical thrombectomy procedures. Functional outcomes are improving. Combination therapies could be the next great advancement: administering neuroprotective agents and mechanical revascularization procedures in series or parallel could potentially increase efficacy and lengthen the treatment window for acute stroke.

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References

1. Abramson DH, Dunkel IJ, Brodie SE, Marr B, Gobin YP: Superselective ophthalmic artery chemotherapy as primary treatment for retinoblastoma (chemosurgery). *Ophthalmology* **117**:1623–1629, 2010
2. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al: Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation* **115**:e478–e534, 2007
3. Ahmed N, Kellert L, Lees KR, Mikulik R, Tatlisumak T, Toni D: Results of intravenous thrombolysis within 4.5 to 6 hours and updated results within 3 to 4.5 hours of onset of acute ischemic stroke recorded in the Safe Implementation of Treatment in Stroke International Stroke Thrombolysis Register (SITS-ISTR): an observational study. *JAMA Neurol* **70**:837–844, 2013
4. Akbik F, Hirsch JA, Cougo-Pinto PT, Chandra RV, Simonsen CZ, Leslie-Mazwi T: The evolution of mechanical thrombectomy for acute stroke. *Curr Treat Options Cardiovasc Med* **18**:32, 2016
5. Amar AP, Zlokovic BV, Apuzzo ML: Endovascular restorative neurosurgery: a novel concept for molecular and cellular therapy of the nervous system. *Neurosurgery* **52**:402–413, 2003
6. Audebert HJ, Saver JL, Starkman S, Lees KR, Endres M: Prehospital stroke care: new prospects for treatment and clinical research. *Neurology* **81**:501–508, 2013
7. Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J, et al: Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis. *JAMA* **314**:1832–1843, 2015
8. Badjatia N, Topcuoglu MA, Pryor JC, Rabinov JD, Ogilvy CS, Carter BS, et al: Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. *AJNR Am J Neuroradiol* **25**:819–826, 2004
9. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* **376**:1670–1681, 2010

10. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N: Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. **Stroke** **37**:1334–1339, 2006
11. Barreto AD, Albright KC, Hallevi H, Grotta JC, Noser EA, Khaja AM, et al: Thrombus burden is associated with clinical outcome after intra-arterial therapy for acute ischemic stroke. **Stroke** **39**:3231–3235, 2008
12. Bashir A, Andresen M, Bartek J Jr, Cortsen M, Eskesen V, Wagner A: Intra-arterial nimodipine for cerebral vasospasm after subarachnoid haemorrhage: Influence on clinical course and predictors of clinical outcome. **Neuroradiol J** **29**:72–81, 2016
13. Battistella V, de Freitas GR, da Fonseca LM, Mercante D, Gutfilen B, Goldenberg RC, et al: Safety of autologous bone marrow mononuclear cell transplantation in patients with nonacute ischemic stroke. **Regen Med** **6**:45–52, 2011
14. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al: A randomized trial of intra-arterial treatment for acute ischemic stroke. **N Engl J Med** **372**:11–20, 2015
15. Bøtker HE, Kharbanda R, Schmidt MR, Böttcher M, Kaltoft AK, Terkelsen CJ, et al: Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. **Lancet** **375**:727–734, 2010
16. Bruno A, Durkalski VL, Hall CE, Juneja R, Barsan WG, Janis S, et al: The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial protocol: a randomized, blinded, efficacy trial of standard vs. intensive hyperglycemia management in acute stroke. **Int J Stroke** **9**:246–251, 2014
17. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al: Endovascular therapy for ischemic stroke with perfusion-imaging selection. **N Engl J Med** **372**:1009–1018, 2015
18. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC: Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. **Stroke** **32**:2426–2432, 2001
19. Chamorro A, Amaro S, Castellanos M, Segura T, Arenillas J, Martí-Fàbregas J, et al: Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomised, double-blind phase 2b/3 trial. **Lancet Neurol** **13**:453–460, 2014
20. De Georgia MA, Krieger DW, Abou-Chebl A, Devlin TG, Jauss M, Davis SM, et al: Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. **Neurology** **63**:312–317, 2004
21. del Zoppo GJ: Stroke and neurovascular protection. **N Engl J Med** **354**:553–555, 2006
22. Elkind MS, Sacco RL, Macarthur RB, Peerschke E, Neils G, Andrews H, et al: High-dose lovastatin for acute ischemic stroke: results of the phase I dose escalation neuroprotection with statin therapy for acute recovery trial (NeuSTART). **Cerebrovasc Dis** **28**:266–275, 2009
23. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Mönting J, Schumacher M, et al: Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. **Cerebrovasc Dis** **13**:89–94, 2002
24. Feng L, Fitzsimmons BF, Young WL, Berman MF, Lin E, Aagaard BD, et al: Intraarterially administered verapamil as adjunct therapy for cerebral vasospasm: safety and 2-year experience. **AJNR Am J Neuroradiol** **23**:1284–1290, 2002
25. Fisher M, Finklestein SP, Furlan AJ, Goldstein LB, Gorelick PG, Kaste M, et al: Recommendations for standards regarding preclinical neuroprotective and restorative drug development. **Stroke** **30**:2752–2758, 1999
26. Flint AC, Kamel H, Navi BB, Rao VA, Faigles BS, Conell C, et al: Statin use during ischemic stroke hospitalization is strongly associated with improved poststroke survival. **Stroke** **43**:147–154, 2012
27. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, et al: Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. **JAMA** **311**:1632–1640, 2014
28. Fordyce CB, Gersh BJ, Stone GW, Granger CB: Novel therapeutics in myocardial infarction: targeting microvascular dysfunction and reperfusion injury. **Trends Pharmacol Sci** **36**:605–616, 2015
29. French JD, West PM, Von Amerongen FK, Magoun HW: Effects of intracarotid administration of nitrogen mustard on normal brain and brain tumors. **J Neurosurg** **9**:378–389, 1952
30. Friedrich MA, Martins MP, Araújo MD, Klamt C, Vedolin L, Garicochea B, et al: Intra-arterial infusion of autologous bone marrow mononuclear cells in patients with moderate to severe middle cerebral artery acute ischemic stroke. **Cell Transplant** **21** (Suppl 1):S13–S21, 2012
31. Ginsberg MD: Expanding the concept of neuroprotection for acute ischemic stroke: The pivotal roles of reperfusion and the collateral circulation. **Prog Neurobiol** **145-146**:46–77, 2016
32. Ginsberg MD: Neuroprotection for ischemic stroke: past, present and future. **Neuropharmacology** **55**:363–389, 2008
33. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al: Randomized assessment of rapid endovascular treatment of ischemic stroke. **N Engl J Med** **372**:1019–1030, 2015
34. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al: Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. **Lancet** **387**:1723–1731, 2016
35. Griffin JH, Zlokovic B, Fernández JA: Activated protein C: potential therapy for severe sepsis, thrombosis, and stroke. **Semin Hematol** **39**:197–205, 2002
36. Guluma KZ, Hemmen TM, Olsen SE, Rapp KS, Lyden PD: A trial of therapeutic hypothermia via endovascular approach in awake patients with acute ischemic stroke: methodology. **Acad Emerg Med** **13**:820–827, 2006
37. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. **N Engl J Med** **359**:1317–1329, 2008
38. Hahn CD, Manliot C, Schmidt MR, Nielsen TT, Redington AN: Remote ischemic per-conditioning: a novel therapy for acute stroke? **Stroke** **42**:2960–2962, 2011
39. Hemmen TM, Raman R, Guluma KZ, Meyer BC, Gomes JA, Cruz-Flores S: Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. **Stroke** **41**:2265–2270, 2010
40. Hill MD, Martin RH, Mikulis D, Wong JH, Silver FL, ter-Brugge KG, et al: Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair (ENACT): a phase 2, randomised, double-blind, placebo-controlled trial. **Lancet Neurol** **11**:942–950, 2012
41. Hockel K, Diedler J, Steiner J, Birkenhauer U, Danz S, Ernemann U, et al: Long-term, continuous intra-arterial nimodipine treatment of severe vasospasm after aneurysmal subarachnoid hemorrhage. **World Neurosurg** **88**:104–112, 2016
42. Holzer M, Cerchiari E, Martens P, Roine R, Sterz F, Eisenburger P, et al: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. **N Engl J Med** **346**:549–556, 2002 (Erratum in **N Engl J Med** **346**:549–556, 2002)

43. Hossmann KA: Viability thresholds and the penumbra of focal ischemia. **Ann Neurol** 36:557–565, 1994
44. Hougaard KD, Hjort N, Zeidler D, Sørensen L, Nørgaard A, Hansen TM, et al: Remote ischemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. **Stroke** 45:159–167, 2014
45. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demmaerschalk BM, et al: Guidelines for the early management of patients with acute ischemic stroke: a guideline for health-care professionals from the American Heart Association/American Stroke Association. **Stroke** 44:870–947, 2013
46. Jayaraman MV, Hussain MS, Abruzzo T, Albani B, Albuquerque FC, Alexander MJ, et al: Embolectomy for stroke with emergent large vessel occlusion (ELVO): report of the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery. **J Neurointerv Surg** 7:316–321, 2015 (Erratum in **J Neurointerv Surg** 7:622, 2015)
47. Jolkkonen J, Kwakkel G: Translational hurdles in stroke recovery studies. **Transl Stroke Res** 7:331–342, 2016
48. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al: Thrombectomy within 8 hours after symptom onset in ischemic stroke. **N Engl J Med** 372:2296–2306, 2015
49. Kaufmann AM, Firlik AD, Fukui MB, Wechsler LR, Jungries CA, Yonas H: Ischemic core and penumbra in human stroke. **Stroke** 30:93–99, 1999
50. Khanna A, Kahle KT, Walcott BP, Gerzanich V, Simard JM: Disruption of ion homeostasis in the neuroglial vascular unit underlies the pathogenesis of ischemic cerebral edema. **Transl Stroke Res** 5:3–16, 2014
51. Khanna A, Walcott BP, Kahle KT, Simard JM: Effect of glibenclamide on the prevention of secondary brain injury following ischemic stroke in humans. **Neurosurg Focus** 36(1):E11, 2014
52. Khatri P, Yeatts SD, Mazighi M, Broderick JP, Liebeskind DS, Demchuk AM, et al: Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. **Lancet Neurol** 13:567–574, 2014
53. Kidwell CS, Saver JL, Schubert GB, Eckstein M, Starkman S: design and retrospective analysis of the Lost Angeles Prehospital Stroke Screen (LAPSS). **Prehosp Emerg Care** 2:267–273, 1998
54. Krieger DW, De Georgia MA, Abou-Chebl A, Andreisky JC, Sila CA, Katzan IL, et al: Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. **Stroke** 32:1847–1854, 2001
55. Krzyt ND, Biessels GJ, Devries JH, Roos YB: Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. **Nat Rev Neurol** 6:145–155, 2010
56. Kwan J, Hand P, Sandercock P: A systematic review of barriers to delivery of thrombolysis for acute stroke. **Age Ageing** 33:116–121, 2004
57. Linfante I, Cipolla MJ: Improving reperfusion therapies in the era of mechanical thrombectomy. **Transl Stroke Res** 7:294–302, 2016
58. Lyden PD, Allgren RL, Ng K, Akins P, Meyer B, Al-Sanani F, et al: Intravascular Cooling in the Treatment of Stroke (IC-TuS): early clinical experience. **J Stroke Cerebrovasc Dis** 14:107–114, 2005
59. Lyden P, Hemmen T, Grotta J, Rapp K, Ernstron K, Rzesiewicz T: Results of the ICTuS 2 trial (Intravascular Cooling in the Treatment of Stroke 2). **Stroke** 47:2888–2895, 2016
60. McGrath RT, Hocking SL, Priglinger M, Day S, Herkes GK, Krause M, et al: Rationale and design of Short-Term Exenatide Therapy in Acute Ischaemic Stroke (STEXAS): a randomised, open-label, parallel-group study. **BMJ Open** 6:e008203, 2016
61. Meng R, Asmaro K, Meng L, Liu Y, Ma C, Xi C, et al: Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. **Neurology** 79:1853–1861, 2012
62. Misra V, Ritchie MM, Stone LL, Low WC, Janardhan V: Stem cell therapy in ischemic stroke: role of IV and intra-arterial therapy. **Neurology** 79 (13 Suppl 1):S207–S212, 2012
63. Moniche F, Gonzalez A, Gonzalez-Marcos JR, Carmona M, Piñero P, Espigado I, et al: Intra-arterial bone marrow mononuclear cells in ischemic stroke: a pilot clinical trial. **Stroke** 43:2242–2244, 2012
64. Mosnier LO, Zlokovic BV, Griffin JH: Cytoprotective-selective activated protein C therapy for ischaemic stroke. **Thromb Haemost** 112:883–892, 2014
65. Musahl C, Henkes H, Vajda Z, Coburger J, Hopf N: Continuous local intra-arterial nimodipine administration in severe symptomatic vasospasm after subarachnoid hemorrhage. **Neurosurgery** 68:1541–1547, 2011
66. Naci H, Bruggs JJ, Fleurence R, Ades AE: Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials. **QJM** 106:299–306, 2013
67. Newton HB: Intra-arterial chemotherapy of primary brain tumors. **Curr Treat Options Oncol** 6:519–530, 2005
68. Ní Chroíín D, Asplund K, Åsberg S, Callaly E, Cuadrado-Godia E, Díez-Tejedor E, et al: Statin therapy and outcome after ischemic stroke: systematic review and meta-analysis of observational studies and randomized trials. **Stroke** 44:448–456, 2013
69. Ní Chroíín D, Callaly EL, Duggan J, Merwick Á, Hannon N, Sheehan Ó, et al: Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: the North Dublin Population Stroke Study. **Stroke** 42:1021–1029, 2011
70. Nichol A, French C, Little L, Haddad S, Presneil J, Arabi Y, et al: Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. **Lancet** 386:2499–2506, 2015
71. Olsen TS, Larsen B, Herning M, Skriver EB, Lassen NA: Blood flow and vascular reactivity in collaterally perfused brain tissue. Evidence of an ischemic penumbra in patients with acute stroke. **Stroke** 14:332–341, 1983
72. Petty MA, Wettstein JG: Elements of cerebral microvascular ischaemia. **Brain Res Brain Res Rev** 36:23–34, 2001
73. Pico F, Rosso C, Meseguer E, Chadenat ML, Cattenoy A, Aegerter P, et al: A multicenter, randomized trial on neuroprotection with remote ischemic pre-conditioning during acute ischemic stroke: the Remote Ischemic Conditioning in Acute Brain Infarction study protocol. **Int J Stroke** 11:938–943, 2016
74. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, et al: 2015 American Heart Association/American Stroke Association focused update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment: a guideline for health-care professionals from the American Heart Association/American Stroke Association. **Stroke** 46:3020–3035, 2015
75. Prabhakaran S, Ruff I, Bernstein RA: Acute stroke intervention: a systematic review. **JAMA** 313:1451–1462, 2015
76. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P: Regional ischemic ‘preconditioning’ protects remote virgin myocardium from subsequent sustained coronary occlusion. **Circulation** 87:893–899, 1993
77. Rha JH, Saver JL: The impact of recanalization on ischemic stroke outcome: a meta-analysis. **Stroke** 38:967–973, 2007
78. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingle R, Deuschl G, Jansen O: The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. **Stroke** 42:1775–1777, 2011
79. Riina HA, Fraser JF, Fralin S, Knopman J, Scheff RJ, Boock-

- var JA: Superselective intraarterial cerebral infusion of bevacizumab: a revival of interventional neuro-oncology for malignant glioma. **J Exp Ther Oncol** 8:145–150, 2009
80. Rosado-de-Castro PH, Pimentel-Coelho PM, da Fonseca LM, de Freitas GR, Mendez-Otero R: The rise of cell therapy trials for stroke: review of published and registered studies. **Stem Cells Dev** 22:2095–2111, 2013
 81. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al: Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. **N Engl J Med** 372:2285–2295, 2015
 82. Saver JL, Kidwell C, Eckstein M, Starkman S: Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) pilot trial. **Stroke** 35:e106–e108, 2004
 83. Saver JL, Starkman S, Eckstein M, Stratton S, Pratt F, Hamilton S, et al: Methodology of the Field Administration of Stroke Therapy—Magnesium (FAST-MAG) phase 3 trial: part 1—rationale and general methods. **Int J Stroke** 9:215–219, 2014
 84. Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, et al: Prehospital use of magnesium sulfate as neuroprotection in acute stroke. **N Engl J Med** 372:528–536, 2015
 85. Sheth KN, Elm JJ, Molyneaux BJ, Hinson H, Beslow LA, Sze GK, et al: Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial. **Lancet Neurol** 15:1160–1169, 2016
 86. Shields CL, Shields JA: Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. **Curr Opin Ophthalmol** 21:203–212, 2010
 87. Shuaib A, Butcher K, Mohammad AA, Saqqur M, Liebeskind DS: Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. **Lancet Neurol** 10:909–921, 2011
 88. Simard JM, Chen M, Tarasov KV, Bhatta S, Ivanova S, Melnitchenko L, et al: Newly expressed SUR1-regulated NC(Ca-ATP) channel mediates cerebral edema after ischemic stroke. **Nat Med** 12:433–440, 2006
 89. Simard JM, Sahuquillo J, Sheth KN, Kahle KT, Walcott BP: Managing malignant cerebral infarction. **Curr Treat Options Neurol** 13:217–229, 2011
 90. Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, Ward JD, et al: A clinical trial of progesterone for severe traumatic brain injury. **N Engl J Med** 371:2467–2476, 2014
 91. van der Worp HB, Macleod MR, Bath PM, Demotes J, Durand-Zaleski I, Gebhardt B, et al: EuroHYP-1: European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke. **Int J Stroke** 9:642–645, 2014
 92. Walcott BP, Boehm KM, Stapleton CJ, Mehta BP, Nahed BV, Ogilvy CS: Retrievable stent thrombectomy in the treatment of acute ischemic stroke: analysis of a revolutionizing treatment technique. **J Clin Neurosci** 20:1346–1349, 2013
 93. Walcott BP, Kahle KT, Simard JM: Novel treatment targets for cerebral edema. **Neurotherapeutics** 9:65–72, 2012
 94. Walcott BP, Miller JC, Kwon CS, Sheth SA, Hiller M, Cronin CA, et al: Outcomes in severe middle cerebral artery ischemic stroke. **Neurocrit Care** 21:20–26, 2014
 95. Wheeler HM, Mlynash M, Inoue M, Tipirnini A, Liggins J, Bammer R, et al: The growth rate of early DWI lesions is highly variable and associated with penumbral salvage and clinical outcomes following endovascular reperfusion. **Int J Stroke** 10:723–729, 2015
 96. Willeit J, Geley T, Schöch J, Rinner H, Tür A, Kreuzer H, et al: Thrombolysis and clinical outcome in patients with stroke after implementation of the Tyrol Stroke Pathway: a retrospective observational study. **Lancet Neurol** 14:48–56, 2015
 97. Wu TC, Grotta JC: Hypothermia for acute ischaemic stroke. **Lancet Neurol** 12:275–284, 2013
 98. Yilmaz G, Granger DN: Leukocyte recruitment and ischemic brain injury. **Neuromolecular Med** 12:193–204, 2010
 99. Zlokovic BV, Griffin JH: Cytoprotective protein C pathways and implications for stroke and neurological disorders. **Trends Neurosci** 34:198–209, 2011

Disclosures

Dr. Amar reports that he has received time-based compensation for research in clinical trials.

Author Contributions

Conception and design: Mack. Drafting the article: Mack, Babadjouni, Walcott. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mack.

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