Curr Treat Options Neurol (2016) 18: 38
DOI 10.1007/s11940-016-0421-6

Critical Care Neurology (K Sheth, Section Editor)

Novel Treatments in Neuroprotection for Aneurysmal Subarachnoid Hemorrhage

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Published online: 20 June 2016

This article is part of the Topical Collection on *Critical Care Neurology*

Keywords Aneurysmal subarachnoid hemorrhage · SAH · Unfractionated heparin · Glyburide · Ibuprofen · Cilostazol · Omega 3 fatty acid · Molsidomine · Cortical spreading depolarization · Ischemic preconditioning · Partial aortic occlusion

Opinion statement

New neuroprotective treatments aimed at preventing or minimizing "delayed brain injury" are attractive areas of investigation and hold the potential to have substantial beneficial effects on aneurysmal subarachnoid hemorrhage (aSAH) survivors. The

underlying mechanisms for this "delayed brain injury" are multi-factorial and not fully understood. The most ideal treatment strategies would have the potential for a pleotropic effect positively modulating multiple implicated pathophysiological mechanisms at once. My personal management (RFJ) of patients with aneurysmal subarachnoid hemorrhage closely follows those treatment recommendations contained in modern published guidelines. However, over the last 5 years, I have also utilized a novel treatment strategy, originally developed at the University of Maryland, which consists of a 14-day continuous low-dose intravenous heparin infusion (LDIVH) beginning 12 h after securing the ruptured aneurysm. In addition to its well-known anti-coagulant properties, unfractionated heparin has potent anti-inflammatory effects and through multiple mechanisms may favorably modulate the neurotoxic and neuroinflammatory processes prominent in aneurysmal subarachnoid hemorrhage. In my personal series of patients treated with LDIVH, I have found significant preservation of neurocognitive function as measured by the Montreal Cognitive Assessment (MoCA) compared to a control cohort of my patients treated without LDIVH (RFJ unpublished data presented at the 2015 AHA/ASA International Stroke Conference symposium on neuroinflammation in aSAH and in abstract format at the 2015 AANS/CNS Joint Cerebrovascular Section Annual Meeting). It is important for academic physicians involved in the management of these complex patients to continue to explore new treatment options that may be protective against the potentially devastating "delayed brain injury" following cerebral aneurysm rupture. Several of the treatment options included in this review show promise and could be carefully adopted as the level of evidence for each improves. Other proposed neuroprotective treatments like statins and magnesium sulfate were previously thought to be very promising and to varying degrees were adopted at numerous institutions based on somewhat limited human evidence. Recent clinical trials and meta-analysis have shown no benefit for these treatments, and I currently no longer utilize either treatment as prophylaxis in my practice.

Introduction

The modern treatment of aneurysmal subarachnoid hemorrhage has resulted in a decline in the rate of physical disability and case fatality over the last 20 years [1]. These improvements have correlated with early treatment of the aneurysm to prevent re-bleeding, along with improved critical care management of cerebral vasospasm and other derangements by neurointensivists in dedicated neurocritical care units [2]. Unfortunately, in spite of these advances, those fortunate patients with minimal "early brain injury" are still at significant risk for other types of "delayed brain injury" often attributable to the direct neurotoxic and neuroinflammatory processes secondary to breakdown products from the initial hemorrhage burden. This direct hemorrhage toxicity to the surrounding brain can result in global brain atrophy, which is commonly manifested as new cognitive disability including difficulties with memory, executive function and language [3•, 4–7]. These problems can lead to serious difficulty for patients to re-integrate into their previous lives including the inability to return to work, school, or previous productivity [8]. New neuroprotective treatments aimed at preventing or minimizing various types of "delayed brain injury" are attractive areas of investigation and hold the potential to have substantial beneficial effects on aneurysmal subarachnoid hemorrhage survivors.

Novel treatments

- Here, we will review promising treatment options for aneurysmal subarachnoid hemorrhage that have yet to be widely accepted or adopted.
- Some treatments may not meet a minimum threshold of evidence to currently support their use in patients outside of clinical trials.

Pharmacological neuroprotectants

Modulation of neuroinflammation

Unfractionated heparin

Unfractionated heparin (UFH) is a well-known anti-coagulant and most commonly utilized to treat deep venous thrombosis, pulmonary embolism, and other conditions requiring anti-coagulation. UFH has other biological effects that are much less appreciated and it has recently been proposed as a prophylactic neuroprotection treatment for aSAH patients [9, 10]. UFH is a highly sulfated glycosaminoglycan polymer of varying chain lengths and carries the highest negative charge of any endogenously produced biological molecule. This allows it to bind to many positively charged biological molecules [11, 12]. These interactions can result in a wide range of physiological effects, of which many can be linked to the multiple pathophysiological mechanisms implicated as potential contributors to "delayed brain injury" in aSAH patients [10, 13–15]. UFH can exert a potent anti-inflammatory effect. It binds and deactivates several positively charged inflammatory mediators e.g. (cytokines, chemokines, and other endothelial and platelet-related proteins) [10, 16–18]. Heparin interacts with free hemoglobin and forms a complex that neutralizes the irritative effects of oxyhemoglobin [10, 19]. It can also act as a scavenger for deleterious oxygen free radicals [10, 20]. UFH has also been shown to counteract the effects of endothelin which is a potent vasoconstrictor implicated in aSAH-induced cerebral vasospasm by inhibiting endothelin receptor transactivation and additionally reducing endothelin transcription [10, 21–26].

The neuroprotective effects of heparin in SAH have been investigated with animal and human studies. In one study, adult male rats underwent bilateral stereotactic injections of autologous blood (50 μL) into the subarachnoid space of the entorhinal cortex. The rats received either vehicle or unfractionated heparin (10 u/kg/h IV) 12 h after SAH through mini-osmotic pumps. In controls assessed at 48 h, SAH was associated with

robust neuroinflammation in the adjacent cortex and neurodegeneration. In the hippocampus, a neuroinflammatory response was indicated by Iba1-positive, ED1-negative microglia exhibiting an activated morphology. The perforant pathway showed Fluoro-Jade C staining and demyelination, and granule cells of the dentate gyrus showed upregulation of cleaved caspase-3, consistent with transsynaptic apoptosis. The study showed that the administration of heparin significantly reduced neuroinflammation, demyelination, and transsynaptic apoptosis [27].

Enoxaparin (low-molecular weight fractionated heparin) has been investigated in aSAH patients. A group of 57 patients received 20 mg of enoxaparin (treatment). A second group of 60 patients received isotonic saline (placebo). There was a statistically significant reduction in the rate of delayed ischemic deficit and vasospasm-related cerebral infarctions between the heparin group and the control group (8.8 vs. 66.7 % and 3.5 vs. 28.3 %, respectively; $p < 0.001$). They also reported better overall outcomes at 1-year follow-up among the heparin group [28]. However, another randomized clinical trial reported conflicting results [29].

A recent human retrospective cohort study at the University of Maryland compared patients with Fisher grade 3 aSAH due to a ruptured supratentorial aneurysm that presented within 36 h and were treated by surgical clipping within 48 h of their ictus. Forty-three patients were managed postoperatively with a low-dose intravenous heparin (LDIVH) infusion (8 u/kg/h progressing over 36 h to 10–12 U/kg/h) starting 12 h after surgery and continuing until day 14 after the ictus. Forty-three control patients received conventional subcutaneous heparin (5000 U) twice daily as deep vein thrombosis prophylaxis. In the LDIVH group, there were no clinically significant hemorrhages, instances of heparin-induced thrombocytopenia, or deep vein thrombosis encountered. Results showed that the frequency of clinical vasospasm was 47 % in the control group and only 9 % in the LDIVH group ($p = 0.0002$). Likewise, vasospasm-related infarction on CT was higher in the control group compared to the heparin group (21 vs. 0 %, $p = 0.003$). Additionally, the rate of patients discharged to home vs. to rehabilitation facility was higher in the heparin group compared to the control group (62.8 vs. 39.5 % ($n = 43$) and 40.4 vs. 59.5 %, respectively ($n = 42$), $p = 0.05$) [30••].

Heparin may also help prevent potentially devastating neurocognitive dysfunction after subarachnoid hemorrhage. In a retrospective cohort study, cognition was studied using the Montreal Cognitive Assessment (MoCA) at the 90-day follow-up or later. The MoCA was previously validated in aSAH, and scores can range from 0 to 30 with "normal" designated as a score of 26 or greater [31•, 32]. Twenty-two SAH control patients had a mean MoCA score of 22.7 ± 7.0 compared to 25 patients treated with the LDIVH protocol (up to 12 U/kg/h) over 14 days resulting in a mean MoCA score of 26.4 ± 2.3 ($p = 0.013$;one-tailed unequal variance independent t test). Importantly, univariate and multivariate linear regressions confirmed that LDIVH treatment significantly influenced MoCA scores in a favorable manner while simultaneously controlling for factors which can negatively influence cognition such as fever and aneurysm location (RFJ unpublished data, presented at a 2015 AHA/ASA International Stroke Conference symposium session and in abstract form at the 2015 AANS/CNS

Cerebrovascular Section Annual Meeting).
So far, studies that investigated the role of heparin as a neuroprotective agent in SAH have shown encouraging results in preventing the undesirable sequelae of cognitive impairment and focal neurological deficits. Further study of heparin in aSAH is ongoing. A multi-center randomized phase II clinical trial, comparing LDIVH-treated patients to controls, the Aneurysmal Subarachnoid hemorrhage Trial RandOmizing Heparin (ASTROH) is actively enrolling with plans to enroll 88 patients. Enrollment is estimated to be complete by March 2018 with the 90-day primary outcomes available soon thereafter (NCT02501434).

Standard dosage	Continuous intravenous infusion (no bolus) starting 12 h after securing aneurysm at 8 u/kg/h and increasing every 12 h up to approximately 12 u/kg/h for a duration of 14 days
Contraindications	History of heparin-induced thrombocytopenia (HIT) or other heparin insensitivity, incompletely secured aneurysm, any known and significant risk of bleeding complications
Main side effects	Risk of bleeding and HIT
Special points	No study has yet shown any serious safety concerns. Nevertheless, cerebrovascular specialists may be concerned about administering heparin to patients with a recently ruptured aneurysm. Non-anti-coagulating heparins are being designed which may retain the anti-inflammatory and other salutary effects of heparin, offering the potential for even safer therapies.

Glyburide/(aka Glibenclamide)

Glyburide, a well-known oral anti-diabetic medication, recently has been studied for a possible neuroprotective effect. The theorized mechanism for this effect is through selective inhibition of SUR1, which is a membrane protein that co-associates with heterologous pore-forming subunits to form ion channels. Following injury in neurons and endothelium, SUR1 binds with an ATP- and Ca2+-sensitive nonselective cat-ion-channel, known as transient receptor potential melastatin 4 (Trpm4), to form Sur1-Trpm4 channels. Opening of SUR1-Trpm4 channels is associated with excess influx of Na+, which is accompanied by influx of Cl– and H2O, resulting in oncotic cell swelling (cytotoxic edema) and necrotic cell death [33•, 34]. Sur1–Trpm4 channels are upregulated in neurons, astrocytes, oligodendrocytes, and microvascular endothelial cells after hemorrhagic CNS insult [35–37]. Depletion of ATP, as occurs in ischemia and hemorrhage, can result in persistent activation of Sur1–Trpm4 channels leading to excessive influx of Na+, Cl–, and water, ensuing cytotoxic edema and necrotic (oncotic) cell death in the CNS [37].
SUR1 blockade by glibenclamide is associated with a significant reduction in several markers of neuroinflammation in a SAH rat model and human tissue. Förster resonance energy transfer (FRET) was used to detect co-associated Sur1 and Trpm4 in human autopsy brains with SAH and rat models of SAH involving entorhinal cortex. Sur1-Trpm4 channels were upregulated in humans and rats with SAH. In rats, inhibiting Sur1 using the selective Sur1 inhibitor glibenclamide reduced SAH-induced immunoglobulin G extravasation and TNFα overexpression. In models with entorhinal SAH, rats treated with glibenclamide for 7 days after SAH exhibited

better platform search strategies and better performance on incremental and rapid spatial learning than control animals [38••].

Simard et al. demonstrated in animal studies and in in vitro experiments that SUR1 which is encoded by Abcc8 gene is upregulated in cortex adjacent to SAH. This upregulation was attributed to prominent TNFa and (NF)kB signaling in areas of SAH. In vitro experiments showed that TNFa/(NF)kB resulted in increased transcription of Abcc8 gene. They studied the effects of SUR1 inhibitor (glibenclamide) on blood brain barrier permeability, inflammation, and cell death. They found that inhibiting SUR1 using low-dose glibenclamide after SAH resulted in a significant attenuation in the SAH-induced alteration in barrier permeability. They also demonstrated that in rats treated with glibenclamide after SAH, local inflammation reflected by levels of TNFa/(NF)kB and reactive astrocytosis were significantly reduced. Additionally, in animals treated with glibenclamide, caspase-3 activation was absent in four of five rats and was minimal in the fifth [39].

Patients with type 2 diabetes taking a sulfonylurea drug for glycemic control and patients with type 2 diabetes who are not taking a sulfonylurea were studied to determine whether sulfonylureas are protective against ischemic edema and its associated sequelae. Kunte et al. conducted a retrospective study to determine whether sulfonylurea therapy conferred protection against symptomatic hemorrhagic transformation in patients with type 2 diabetes. The authors compared 43 patients taking a sulfonylurea drug before and during hospital admission for ischemic stroke with 177 controls not taking a sulfonylurea drug. They found that the patients receiving sulfonylureas had significantly fewer deaths (0 vs 10 % of controls) and a significantly lower rate of symptomatic hemorrhagic transformation (0 vs 11 % of controls) [40].

A recent pilot study [41], and a multicenter, randomized, double-blind, phase II trial examined the efficacy of RP-1127 (Glyburide for injection/Cirara; Remedy Pharmaceuticals, Inc) in the prevention of malignant edema in severe anterior circulation ischemic stroke (Glyburide Advantage in Malignant Edema and Stroke–Remedy Pharmaceuticals [GAMES-RP], NCT01794182, ClinicalTrials.gov) [42]. Preliminary results were presented in abstract form at the 2016 American Heart Association, International Stroke Conference in Los Angeles, CA. While there were no safety concerns, the study did not show significance of the primary endpoint, avoidance of decompressive craniectomy, and 0–4 mRS. However, the study did demonstrate strong trends towards decreased mortality in the glyburide group and highly significant reduction in midline shift and MMP-9 levels. A phase III study for ischemic stroke is actively being planned. While direct correlation to aSAH patients is not possible, animal models support consideration of future studies in aSAH and we expect that human trials of intravenous glyburide in aSAH may be planned shortly.

Standard dosage	Glyburide for Injection (Cirara): 24 ml bolus (5.4 ug/ml) given over 2 min followed by a daily infusion at a rate of 31 mL/h for the first 6 h and then 21 mL/h for 66 h for a total of 72 h (GAMES-RP Protocol).
Contraindications	No insulin when blood glucose <120 mg/dL; no "Tight" blood glucose control (80–110 mg/dL) during infusion

Main side effects	Hypoglycemia
Special points	Not FDA approved, available only through investigational use (IND held by Remedy Pharmaceuticals, Inc.)

Ibuprofen

The anti-inflammatory effect of ibuprofen is well known and specific to fever. The application of ibuprofen to in vitro models of thermal stress has been shown to be a potent inhibitor of ICAM expression for a sustained period of up to 36 h [43]. ICAM-1 is located on the vascular endothelium and binds the CD18 complex on circulating leukocytes [44, 45]. Studies in animal models of cerebral infarction and SAH have implicated ICAM expression in the development of postischemic microvascular failure, delayed tissue injury, and delayed arterial spasm following SAH [44–49]. In addition, ICAM-1 expression is elevated in human stroke and aneurysmal SAH [50, 51]. In a clinical study, serial serum assessments of soluble ICAM levels were performed in aneurysmal SAH ($N = 80$) compared with levels in patients without SAH, to determine whether degree of elevation was predictive of outcome independent of the initial clinical grade [52, 53]. The timeline for ICAM elevation closely corresponded with that observed for fever after SAH. When compared with non-SAH controls, early soluble ICAM levels were elevated in the entire SAH cohort. Further analysis across Hunt Hess grades found a linear relationship with higher levels in patients with Hunt Hess grade 5 as compared to grade 1 and ICAM mean levels in the acute setting to be significantly associated with vasospasm ($p < 0.01$) and outcome ($p < 0.05$) after SAH.

In experimental SAH, the use of ibuprofen has been studied in multiple species, including primates. The first studies to establish the central biologic impact of systemic intravenous ibuprofen infusion after SAH was conducted in a double hemorrhage dog model. Ibuprofen was injected 12.5 mg/kg and every 8 h during the study at a dose of 12.5 mg/kg and compared to controls as well as animals that did not receive any treatment after injury for 8 days after hemorrhage. The animals treated with ibuprofen demonstrated marked reduction in inflammation and angiographic evidence of arterial vasoconstriction [54, 55]. This dose of ibuprofen was not associated with any adverse bleeding complications in the brain or systemically. Further validation of the biologic effect of ibuprofen has been demonstrated utilizing a locally implanted ibuprofen loaded polymer. The first studies were performed in a rat model of SAH, found an inhibition of cerebral vasospasm associated with a decreased concentration of extravasated macrophages and granulocytes in the periadventitial space of ibuprofen-treated vessels [56]. A subsequent study with sham controls conducted in New Zealand White rabbits, the intracranial controlled release of ibuprofen resulted in a significant inhibition of vasospasm when treatment was initiated acutely [57]. A third study was conducted in cynomolgus monkeys and found that animals implanted with ibuprofen polymers showed no signs of local or systemic toxicity. Further, those treated with ibuprofen polymers significantly higher patency of the middle cerebral artery, compared with animals treated with blank polymers [58].

These experimental studies demonstrate a reliable and reproducible specific

anti-inflammatory impact of ibuprofen in wide range of experimental models of SAH, including primate models, and not a single study reported any intracranial bleeding associated with the administration of ibuprofen. The administration of intracranial implanted polymers is not feasible in subjects who have their ruptured aneurysm secured by endovascular coiling. However, with the availability of an intravenous preparation, a continuous infusion of ibuprofen is an approach that may allow for more widespread use [59].

Standard dosage 2.0 to 2.8 g/day continuous infusion for 7 days

Contraindications Patients with significant bleeding risk

Main side effects Acute kidney injury; Bleeding

Special points In 2009, the FDA-approved Calador (first injectable dosage form of ibuprofen) manufactured by Cumberland Pharmaceuticals, Inc. Nashville, TN

Cilostazol

Cilostazol, a phosphodiesterase (PDE) 3 inhibitor, has been evaluated for treatment of SAH after success as a treatment for cardiac complications [60]. Mechanistically, PDE inhibition increases the cellular concentration of 3′,5′-cyclic adenosine monophosphate (cAMP) which has been linked to decreased platelet aggregation, increased smooth muscle relaxation, reduced inflammation, prevention of endothelial damage, and alteration in the phenotypic changes observed in vessels following SAH [60–62].

After success in animal studies, a preliminary randomized controlled trial was conducted in aSAH patients. The treatment group received 100 mg of cilostazol twice daily for 14 days. Although no difference was found in the incidence of symptomatic vasospasm (37.3 % control vs. 22.4 % treatment, $p = 0.18$) and infarct (27.5 % control vs. 10.2 % treatment, $p = 0.09$), mRS scores were significantly decreased (2.6 control vs. 1.5 treatment, $p = 0.04$) with an OR of 5.52 (95 % CI = 1.61–18.9) seen for improved outcome [62]. Further randomized or quasi-randomized controlled trials were done with multiple exhibiting positive effects on symptomatic vasospasm, severe vasospasm, infarction, and poor outcome [62, 63•, 64, 65•, 66]. Given the small size of the trials, a meta-analysis was conducted involving four controlled trials with similar protocols, resulting in a total of 340 patients. With 2 weeks of treatment of cilostazol, significant improvement was seen in symptomatic vasospasm (RR = 0.47; 95 % CI 0.31–0.72; $p < 0.01$), severe vasospasm (RR = 0.48; 95 % CI 0.28–0.82; $p < 0.01$), and vasospasm-related infarct (RR = 0.38; 95 % CI 0.22–0.67; $p < 0.01$). Most impressively, cilostazol also showed a reduction in poor outcome (RR = 0.57; 95 % CI 0.37–0.88; $p = 0.011$), providing a remarkably low number needed to treat (5.4), making it one of the few agents that effectively alters clinical outcome. Importantly, it did not show a benefit in mortality ($p = 0.552$) [67••].

Standard dosage 100 mg twice daily or 200 mg daily, enterally for 14 days total

Main side effects 11 % adverse events (one GI bleed, two intracerebral hemorrhage, three non-life threatening arrhythmias); No difference in adverse events between groups.

Special points In non-SAH trials, cilostazol has been shown to be safer than aspirin.

Other pharmacological neuroprotectants

Free fatty acids

The role of lipid peroxidation after SAH has been recognized in both laboratory and clinical settings [68, 69]. This process directly stimulates smooth muscle contraction by exerting cytotoxic effects on the vessel wall and by generating an inflammatory response involving omega 6 fatty acid metabolites. These metabolites may be the trigger for a cascade of deleterious events that follows SAH by causing the destruction of the electrochemical potential in mitochondria and resultant mitochondrial dysfunction, contributing to cellular edema, inhibiting transmitter and amino acid uptake and/or ion channel activity, releasing intracellular calcium from the endoplasmic reticulum, and/or by acting as detergents and/or ionophores [69, 70]. Specifically, linoleic acid metabolites decrease nitric oxide synthase activity through a PKC-dependent mechanism in endothelial cells and increase endothelin binding and constriction in vascular smooth muscle cells [69]. Tirilazad, a non-glucocorticoid 21 amino-steroid free radical scavenger with a mechanism of action, believed to be an inhibition of iron-dependent lipid peroxidation was studied in several controlled trials [71] following promising results in primate vasospasm models [72]. While it had an inconsistent effect on overall outcome, possibly related to gender differences in drug metabolism and an adverse effects profile related to its steroid properties, a consistent reduction in symptomatic vasospasm was observed in a recent meta-analysis of five randomized controlled trials involving 3821 SAH patients [71, 73].

Much of the secondary injury in SAH that occurs in relation to vasospasm may be related to the accumulation of omega 6 fatty acids. In a prospective cohort study, the omega 6: omega 3 fatty acid ratio was elevated in those patients who developed DCI [74]. Omega 3 fatty acids have been shown to be anti-inflammatory, and commercially available formulations with omega 3 fatty acids have already been shown to modulate the inflammatory response and improve physiologic profiles in ARDS and septic patients [75, 76]. In SAH, the evidence is limited to a singular pilot randomized clinical trial where eicosapentaenoic acid, a n-3 fatty acid, was orally administered at a daily dose of 1800 mg between day 4 and day 14 and compared with placebo in terms of the frequency of symptomatic vasospasm and cerebral infarction [77]. Serum levels of eicosapentaenoic acid increased significantly and were associated with a decreased frequency of symptomatic vasospasm-related deterioration and infarcts. Findings of this pilot study need further confirmation with additional data regarding systemic oxygen consumption (VO_2) [78] as well as eicosapentaenoic acid levels and n-6 FFA levels to better understand the mechanism by which n-3 FFAs may reduce the occurrence of DCI and improve outcome after SAH. The administration of omega 3 fatty acids may help establish a causal link in SAH patients by modulating of both responses given their competition for lipoxygenase and cyclooxygenase and resultant reduction and opposing effect on the inflammatory modulators which are the metabolic products of arachidonic acid (omega 6 fatty acid) when acted on by these enzymes [79, 80].

Standard dosage	1800 mg of n-3 fatty acid, orally administered between day 4 and 14.

Molsidomine

The role of NO in vasospasm and DCI has been well documented making it a principal therapeutic target [81–85]. Molsidomine is an NO donating agent with a well-tolerated side effect profile and success in the cardiac literature. Recently, molsidomine was used as a rescue therapy in patients with known vasospasm following SAH. Twenty-nine patients with aSAH-associated vasospasm received moslidomine and compared to controls of 25 aSAH patients with vasospasm and 20 patients with aSAH and no vasospasm. Dosing was 20–40 mg/24 h IV and was titrated to mean arterial pressure goals [86•].

In the treatment group, there was significantly less vasospasm-related cerebral infarcts vs. the control group (13.8 vs 48 %, $p < 0.01$) and the modified National Institute of Health Stroke Scale (mNIHSS) scores and modified Rankin Scale (mRS) scores were also significantly less (mNIHSS 3.0, mRS 2.5 vs. 11.5, 5.0, $p < 0.001$). Mortality also differed between the groups with one death in the treatment group and 12 deaths in the standard group ($p < 0.01$). Although these results are promising, this study was observational in nature. Additionally, the 25 patients with vasospasm used as controls had refused molsidomine therapy, and patients that died of causes not related to vasospasm were excluded (nine patients). All three groups were well matched except for age, where the treatment group was significantly younger [86•]. Still, these results warrant further investigation with a randomized controlled, prospective trial.

Standard dosage	20–40 mg every 24 h intravenously, titrated to mean arterial pressure goals of >65 mm Hg; weaned slowly after resolution of hypotension. Transitioned to 8 mg slow release oral tablets four times a day for 14–28 days.
Contraindications	Hypotension
Main side effects	Hypotension, some requiring low-dose norepinephrine

Inhibition of cortical spreading depolarization/cortical spreading ischemia

Cortical spreading depolarization (CSD) describes the phenomenon of complete loss of ion homeostasis in neurons, and subsequent spreading to nearby areas, resulting in loss of neurocommunication and depression of electric activity [87–89]. After an inciting neurotoxic event (e.g. blunt trauma, seizure, sah), neurons are exposed to an altered microenvironment (likely from blood brain barrier disruption), which leads to an opening of N-methyl-D-aspartate (NMDA) receptors and other cation channels resulting in a disorganized depolarization and swelling of the neuron [89, 90]. The depolarization spreads at a slow rate of around 2–6 mm per minute [89, 91].

To restore homeostasis, the neurons require increased blood flow. In healthy tissue, a characteristic vascular pattern is seen on the arteriolar level. First, oligemia is noted with vasoconstriction. Subsequently, over the course of minutes, this changes to a hyperemic response with vasodilation, likely mediated by increased nitric oxide (NO) [89, 92, 93]. The tissue then restores hyperpolarization and recovers. In damaged tissue, the hyperemic

response does not occur and the tissue is left with a high energy demand and no substrate to help recover. A state of ischemia develops, referred to as cortical spreading ischemia (CSI), which can lead to infarcts when severe [89, 94–99].

Aneurysmal SAH is a particularly potent environment for CSD and CSI [94, 96, 98]. It has been proposed that the presence of SAH and breakdown of blood products result in release of arachidonic acid metabolites and NO scavengers leading to a paucity of vasodilatory substances [89]. Evidence supports the role of CSD in DCI in a number of ways. (1) Both CSD and CSI have both been described in humans following aSAH as measured by cortical electrodes [100]. (2) In rats, CSD-induced oligemic response and subsequent ischemia in a SAH model were reduced with the addition of both nimodipine, and increased fluids, indicating that the mechanism of protection may be similar [101]. (3) The concordance of DCI with angiographic vasospasm is poor, around 50 %[102], and CSD-directed vasospasm occurs on the angiographically occult arteriolar level [92]. Humans implanted with cortical electrodes following aSAH showed a correlation between CSD events and DCI, which was not correlated with angiographic vasospasm [100], indicating an independent association. (4) The microenvironments conducive to CSD, decreased NO and increased extracellular potassium, are also seen in non-CSD-induced DCI [103–106]. (5) Endothelin-1, a powerful vasoconstrictive peptide seen in aSAH-induced vasospasm, was shown to result in CSD and ischemia, without SAH in animal models [107–110].

Taken in aggregate, the strength of evidence indicating that CSD plays a role in DCI is high. This presents a novel target for DCI treatment. Although few treatments have been attempted direct reduction of CSD-induced DCI, many treatments used for aSAH-induced vasospasm have an affect on CSD. Following stroke in rat cortex, reduction of CSD and cortical infarct size (which may be the correlate to DCI in stroke) was seen with NMDA-receptor antagonists [106, 111, 112]. Sodium channel blockade has also been effective at reducing CSD; tetrodotoxin, a voltage-gated sodium channel inhibitor, and topiramate, an anti-epileptic that has at least moderate sodium channel inhibitory action, both reduced CSD in rats [90]. Calcitonin gene-related peptide, seen in CSD-induced migraine, showed dose-dependent reduction in CSD with inhibition [90]. Reduction of Endothelin-1 receptor activation also exhibited reduction in CSD [109, 110]. Papaverine and a NO donor have been tried to directly reduce CSD-induced ischemia, both with some success in rat cortex [95].

Non-Pharmacological neuroprotectants

Ischemic preconditioning

Ischemic conditioning is the application of transient sublethal ischemia to induce endogenous defense mechanisms to protect the tissue from further insult [113]. Varieties of ischemic conditioning include classic (tissue of interest is conditioned) and remote in which periods of mild ischemia in the extremities convey similar defense mechanisms to organs far from the initial ischemia [114–116]. Both classic and remote conditioning can be

done before (preconditioning) [117] or after (postconditioning) [118] the concerning event occurs.

Transient ischemia and reperfusion causes substantial change in genomic expression. The effect of ischemic conditioning on tissue is multifactorial and involves a complex interaction of signaling mechanisms [114, 119, 120, 121••]. An important mediator of the effects is the protein hypoxia-inducible factor (HIF). Under normal oxygenation, the HIFα subunit is hydroxylated and tagged for proteosomal degradation. When a tissue is hypoxic, hydroxylation does not occur and HIF rapidly accumulates, signaling activation of genes related to adaptive cell survival, including pH regulation, angiogenesis, oxygen transport, and vasomotor control. In addition to this increase in protective factors, conditioning also causes suppression of inflammation and cell activity. Microarray analysis of mice undergoing middle cerebral artery preconditioning and subsequent MCA occlusion showed downregulation of expression of some genes, resulting in decreased activity of metabolic pathways, ion channel activity, coagulation factors, and immune responses [122, 123]. The net effect of the change in genomic expression is to increase substrate delivery while simultaneously improving the cell's ability to function with decreased substrate.

Both classic and remote ischemic conditioning were first described in myocardium [115, 124] and continue to be studied in cardiac surgery [125]. The principles have since been validated in the brain, with the first in vivo demonstration of neuroprotection after ischemic conditioning by Kitagawa et al. in 1990 [126]. Several investigators have demonstrated the feasibility of ischemic conditioning in the brain and have used animal models to elucidate the mechanism of the induced neuroprotection [118, 122, 127–131]. In humans, evidence of ischemic tolerance in the brain is suggested by studies that show that stroke patients with previous transient ischemic attacks fare better than patients without previous insult [132, 133], although one large retrospective study had contradictory results [134].

Subarachnoid hemorrhage presents a clinical scenario ideal for application of ischemic conditioning [135, 136], as patients often suffer delayed cerebral infarction due to vasospasm after their initial bleeds. This is a major cause of morbidity and mortality in SAH patients [137]. Remote ischemic preconditioning has the advantage of being noninvasive and practical, simply requiring the application of a blood pressure cuff to an extremity [135]. Recent studies of patients with aneurysmal SAH tested remote limb preconditioning to determine safety of the protocol. All studies found the method safe and tolerable with some preliminary evidence of efficacy [138••, 139, 140•]. Another study in patients with recent SAH examined gene expression and methylation changes after remote ischemic conditioning, with results suggesting that methylation alters gene expression in humans, playing some role in subsequent neuroprotection [141]. Because of these promising preliminary reports, teams continue to investigate the efficacy of RIPC in SAH [142]. Currently, two large-scale prospective trials on remote ischemic preconditioning in patients with SAH are underway (NCT02411266, NCT02381522).

Standard procedure

In one study [138••], four sessions of remote ischemic conditioning with each session having 4 cycles of ischemia/reperfusion were performed. The leg that did not receive catheter treatments (angiography/coiling) had the dorsalis pedis

	artery identified and marked using a pulsed Doppler. A large blood pressure cuff was inflated to 20 mm Hg above systolic pressure and inflated further if needed to have cessation of flow in the dorsalis pedis by Doppler. This was maintained for 5 min. Then, the cuff was deflated and 5 min of reperfusion was allowed. This was repeated three more times (four total cycles or ischemia/reperfusion) to complete a session. Sessions were performed on non-consecutive days.
Contraindications	Current or history of deep venous thrombosis (DVT); History of peripheral vascular disease; Lower-extremity bypass; History of peripheral neuropathy
Complications	Risk of new DVT or bruising
Special points	Promising treatment that would be very cost-effective and take advantage of the body's endogenous ischemic neuroprotection machinery. Limited data on clinical effectiveness in aSAH patients at this time.

Partial aortic occlusion (NeuroFlo™)

	The CoAxia NeuroFlo™ system is approved by the FDA under the Humanitarian Device Exemption (HDE) pathway and is authorized for use in the treatment of cerebral ischemia resulting from symptomatic vasospasm following aneurysmal subarachnoid hemorrhage for patients who have failed maximal medical management [143]. While the exact mechanism of action is unclear and likely to be multifactorial [144], it has been shown to enhance cerebral blood flow even after removal of the device [145]. It is theorized that much of the effect is mediated by increased collateral blood flow through leptomeningeal vessels [146•]. There are reports of significant clinical improvement after use in aSAH patients [147]. In a study sponsored by the company for FDA submission, 50 % of treated patients had a 3-point or greater decrease in NIH Stroke Scale scores upon completion of treatment with that improvement being sustained for at least 24 h [143]. In another study, it was shown to increase middle cerebral artery mean velocities in 20 of 24 patients [145]. Additionally, it has been studied for use in ischemic stroke in patients not eligible for tPA or who are non-responders [148, 149]. Safety has been demonstrated most robustly through the SENTIS trial funded by the manufacturer [149]. Utilization of the device has no requirements for ongoing anti-coagulation.
Standard procedure	The device is deployed through a 9F femoral artery access typically with the aid of fluoroscopy, but bedside introduction with ultrasound guidance has also been described [150]. The device is then advanced retrograde into the descending aorta. The device is a multilumen device with two independent balloons, which are positioned so that one is proximal and the other is distal to the renal arteries. The infrarenal balloon is inflated first to a diameter sufficient to occlude 70 % of the aortic cross sectional area for 5 min. Next, the suprarenal balloon is inflated in the same manner and this configuration is left to partially occlude the descending aorta and renal arteries for an additional 40 min for a total of 45 min [143, 145]. This partial aortic occlusion is sufficient to create the recommended 10–20 mm Hg decrease in mean arterial pressure between the upper abdominal aorta and the iliac artery. The balloons are then deflated. The device allows for pressure monitoring at both the supra and infrarenal locations. The central lumen is large enough to allow for contemporaneous intraarterial thrombolysis or thrombectomy treatments although this procedural combination has not been studied in depth.

Contraindications	Patients with significant left ventricular dysfunction Patients with aortic aneurysm including those which have been treated with endovascular grafts Patients with a history of bleeding disorders Pregnant women
Complications	Standard femoral arterial access complications, potential for increased intracranial pressure, renal dysfunction secondary to hypoperfusion, or IV contrast

Limited efficacy of previously promising treatments

- The summed evidence for these treatments no longer supports their clinical efficacy in aneurysmal SAH, and we no longer recommend them as prophylactic neuroprotective treatment options.

Magnesium sulfate

Magnesium sulfate is a voltage-gated calcium channel antagonist and decreases NMDA-receptor activity through co-binding [151]. It also may act as a neuroprotective and vasodilatory agent [151]. Although most studies have been small, a RCT of 327 patients was conducted and showed no difference in long-term outcomes (OR 1.0, 95 % CI 0.7–1.6) [152]. A meta-analysis was recently conducted and showed a reduction in DCI (RR 0.54, 95 % CI 0.38–0.75). However, no difference was seen in delayed ischemic neurologic deficit (RR 0.93, 95 % CI 0.62–1.39) outcome as measured by the Glasgow Outcome Scale and mRS (RR 0.93, 95 % CI 0.82–1.06) or mortality (RR 0.95, 95 % CI 0.76–1.17) [153••]. Thus far, no benefit has been shown from administration of magnesium sulfate.

Special points	It is reasonable to infuse magnesium sulfate to maintain normal serum magnesium levels, however prophylactic administration of magnesium sulfate is no longer recommended.

Statins

>Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and are used primarily in the reduction of cholesterol, however they have also been implicated in upregulating endothelial NO production, inhibiting vascular smooth muscle proliferation, altering platelet function, and reducing vascular inflammation [154, 155]. Statins have thus been used in several studies for the treatment of aSAH and DCI, with mixed results [154, 156, 157]. An early RCT with 39 patients showed a trend towards reduction in ischemic deficits (RR 0.44, 95 % CI 0.19 to 1.01, $p = 0.05$). More recently, the Simvastatin in Aneurysmal Subrachnoid Hemorrhage (STASH) trial was undertaken. A multicenter effort included 803 patients with aSAH and administered simvastatin 40 mg or placebo for 21 days; outcome was mRS at 6 months. No difference in outcome at 6 months was noted (OR 0.97, 95 % CI 0.75–1.25, $p = 0.803$). Mortality and adverse events were similar in the two groups [158••]. Although statins carry a low risk, no benefit has been established in any RCT.

Special points It is reasonable to continue statin therapy on patients who take a statin as a home medicine prior to admission for their SAH. We do not recommend starting new statin therapy as a neuroprotectant for aneurysmal SAH.

Compliance with Ethical Standards

Conflict of Interest

Robert F. James, MD and J. Marc Simard, MD, PhD, are national co-principal investigators for the ASTROH study (A phase II, multi-center randomized trial evaluating a continuous low-dose IV heparin infusion for aneurysmal SAH). Neither has any personal financial gain at stake for this therapeutic option. NCT02501434 Robert F. James, MD and J. Marc Simard, MD, PhD, own private stock in Remedy Pharmaceuticals, which manufactures and develops therapeutic indications for intravenous glyburide (Cirara/RP1127). Dr. Simard is a company board member for Remedy Pharmaceuticals, Inc. and has received royalty payments.

Neeraj Badjatia, MD is the national study chair for the NASH trial (Normothermia after Aneurysmal Subarachnoid Hemorrhage) which is a double-blinded, placebo-controlled study evaluating continuous intravenous ibuprofen in aSAH. Dr. Badjatia has no personal financial gain at stake for this therapeutic option.

Daniel R. Kramer, Zaid S. Aljuboori, Gunjan Parikh, Shawn W. Adams, Jessica C. Eaton, Hussam Abou Al-Shaar, and William J. Mack declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol. 2009;8:635–42.
2. Samuels O, Webb A, Culler S, Martin K, Barrow D. Impact of a dedicated neurocritical care team in treating patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;14:334–40.
3. • Tam AK, Kapadia A, Ilodigwe D, Li Z, Schweizer TA, Macdonald RL. Impact of global cerebral atrophy on clinical outcome after subarachnoid hemorrhage. J Neurosurg. 2013;119:198–206.

An excellent article demonstrating that aSAH can cause global cerebral atrophy leading to poor cognitive function.

4. Tam AK, Ilodigwe D, Li Z, Schweizer TA, Macdonald RL. Global cerebral atrophy after subarachnoid hemorrhage: a possible marker of acute brain injury and assessment of its impact on outcome. Acta Neurochir Suppl. 2013;115:17–21.
5. Bendel P, Koivisto T, Niskanen E, Kononen M, Aikia M, Hanninen T, et al. Brain atrophy and neuropsychological outcome after treatment of ruptured anterior cerebral artery aneurysms: a voxel-based morphometric study. Neuroradiology. 2009;51:711–22.
6. Kwon MS, Woo SK, Kurland DB, Yoon SH, Palmer AF, Banerjee U, et al. Methemoglobin is an endogenous toll-like receptor 4 ligand-relevance to subarachnoid hemorrhage. Int J Mol Sci. 2015;16:5028–46.
7. Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. Stroke. 2010;41:e519–36.
8. Passier PE, Visser-Meily JM, Rinkel GJ, Lindeman E, Post MW. Life satisfaction and return to work after aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis. 2011;20:324–9.

9. Lindahl U, Lidholt K, Spillmann D, Kjellen L. More to "heparin" than anticoagulation. Thromb Res. 1994;75:1–32.
10. Simard JM, Schreibman D, Aldrich EF, Stallmeyer B, Le B, James RF, et al. Unfractionated heparin: multitargeted therapy for delayed neurological deficits induced by subarachnoid hemorrhage. Neurocrit Care. 2010;13:439–49.
11. Gandhi NS, Mancera RL. The structure of glycosaminoglycans and their interactions with proteins. Chem Biol Drug Des. 2008;72:455–82.
12. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of action and pharmacology of unfractionated heparin. Arterioscler Thromb Vasc Biol. 2001;21:1094–6.
13. Young E. The anti-inflammatory effects of heparin and related compounds. Thromb Res. 2008;122:743–52.
14. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 1992;22:359–74.
15. Casu B. Structure of heparin and heparin fragments. Ann N Y Acad Sci. 1989;556:1–17.
16. Coombe DR. Biological implications of glycosaminoglycan interactions with haemopoietic cytokines. Immunol Cell Biol. 2008;86:598–607.
17. Elsayed E, Becker RC. The impact of heparin compounds on cellular inflammatory responses: a construct for future investigation and pharmaceutical development. J Thromb Thrombolysis. 2003;15:11–8.
18. Tyrrell DJ, Horne AP, Holme KR, Preuss JM, Page CP. Heparin in inflammation: potential therapeutic applications beyond anticoagulation. Adv Pharmacol. 1999;46:151–208.
19. Amiconi G, Zolla L, Vecchini P, Brunori M, Antonini E. The effect of macromolecular polyanions on the functional properties of human hemoglobin. Eur J Biochem. 1977;76:339–43.
20. Engelberg H. Actions of heparin that may affect the malignant process. Cancer. 1999;85:257–72.
21. Chansel D, Ciroldi M, Vandermeersch S, Jackson LF, Gomez AM, Henrion D, et al. Heparin binding EGF is necessary for vasospastic response to endothelin. FASEB J. 2006;20:1936–8.
22. Kuwahara-Watanabe K, Hidai C, Ikeda H, Aoka Y, Ichikawa K, Iguchi N, et al. Heparin regulates transcription of endothelin-1 gene in endothelial cells. J Vasc Res. 2005;42:183–9.
23. Yokokawa K, Mandal AK, Kohno M, Horio T, Murakawa K, Yasunari K, et al. Heparin suppresses endothelin-1 action and production in spontaneously hypertensive rats. Am J Physiol. 1992;263:R1035–41.
24. Rider CC. Heparin/heparan sulphate binding in the TGF-beta cytokine superfamily. Biochem Soc Trans. 2006;34:458–60.
25. Kalmes A, Daum G, Clowes AW. EGFR transactivation in the regulation of SMC function. Ann N Y Acad Sci. 2001;947:42–54. discussion 54–45.
26. Higashiyama S, Iwabuki H, Morimoto C, Hieda M, Inoue H, Matsushita N. Membrane-anchored growth factors, the epidermal growth factor family: beyond receptor ligands. Cancer Sci. 2008;99:214–20.
27. Simard JM, Tosun C, Ivanova S, Kurland DB, Hong C, Radecki L, et al. Heparin reduces neuroinflammation and transsynaptic neuronal apoptosis in a model of subarachnoid hemorrhage. Transl Stroke Res. 2012;3:155–65.
28. Wurm G, Tomancok B, Nussbaumer K, Adelwohrer C, Holl K. Reduction of ischemic sequelae following spontaneous subarachnoid hemorrhage: a double-blind, randomized comparison of enoxaparin versus placebo. Clin Neurol Neurosurg. 2004;106:97–103.
29. Siironen J, Juvela S, Varis J, Porras M, Poussa K, Ilveskero S, et al. No effect of enoxaparin on outcome of aneurysmal subarachnoid hemorrhage: a randomized, double-blind, placebo-controlled clinical trial. J Neurosurg. 2003;99:953–9.
30.•• Simard JM, Aldrich EF, Schreibman D, James RF, Polifka A, Beaty N. Low-dose intravenous heparin infusion in patients with aneurysmal subarachnoid hemorrhage: a preliminary assessment. J Neurosurg. 2013;119:1611–9.

This human study demonstrates impressive protection against vasospasm related infarction in the heparin treated group.

31.• Wong GK, Lam SW, Wong A, Ngai K, Poon WS, Mok V. Comparison of montreal cognitive assessment and mini-mental state examination in evaluating cognitive domain deficit following aneurysmal subarachnoid haemorrhage. PLoS One. 2013;8, e59946.

Validation of the Montreal Cognitive Assessment in aneurysmal SAH patients.

32. Schweizer TA, Al-Khindi T, Macdonald RL. Mini-Mental State Examination versus Montreal Cognitive Assessment: rapid assessment tools for cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. J Neurol Sci. 2012;316:137–40.
33.• Woo SK, Kwon MS, Ivanov A, Gerzanich V, Simard JM. The sulfonylurea receptor 1 (Sur1)-transient receptor potential melastatin 4 (Trpm4) channel. J Biol Chem. 2013;288:3655–67.

Detailed information on the SUR1-Trpm4 channel.

34. 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. 2006;12:433–40.
35. Urday S, Kimberly WT, Beslow LA, Vortmeyer AO, Selim MH, Rosand J, et al. Targeting secondary injury in intracerebral haemorrhage—perihaematomal oedema. Nat Rev Neurol. 2015;11:111–22.
36. Mehta RI, Tosun C, Ivanova S, Tsymbalyuk N, Famakin BM, Kwon MS, et al. Sur1-Trpm4 cation channel expression in human cerebral infarcts. J Neuropathol Exp Neurol. 2015;74:835–49.
37. Caffes N, Kurland DB, Gerzanich V, Simard JM. Glibenclamide for the treatment of ischemic and hemorrhagic stroke. Int J Mol Sci. 2015;16:4973–84.
38.•• Tosun C, Kurland DB, Mehta R, Castellani RJ, de Jong JL, Kwon MS, et al. Inhibition of the Sur1-Trpm4 channel reduces neuroinflammation and cognitive impairment in subarachnoid hemorrhage. Stroke. 2013;44:3522–8.

This study demonstrates glibenclamide inhibition of SAH induced neuroinflammation and cognitive impairment in the rat.

39. Simard JM, Geng Z, Woo SK, Ivanova S, Tosun C, Melnichenko L, et al. Glibenclamide reduces inflammation, vasogenic edema, and caspase-3 activation after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2009;29:317–30.
40. Kunte H, Busch MA, Trostdorf K, Vollnberg B, Harms L, Mehta RI, et al. Hemorrhagic transformation of ischemic stroke in diabetics on sulfonylureas. Ann Neurol. 2012;72:799–806.
41. Sheth KN, Kimberly WT, Elm JJ, Kent TA, Mandava P, Yoo AJ, et al. Pilot study of intravenous glyburide in patients with a large ischemic stroke. Stroke. 2014;45:281–3.
42. Sheth KN, Elm J, Hinson H, Molyneaux B, Beslow L, Sze G, et al. GAMES (Glyburide Advantage in Malignant Edema and Stroke) RP: a phase II study toward preventing edema after ischemia (S7.004). Neurology. 2016;86:1526–1632X.
43. Kapiotis S, Sengoelge G, Sperr WR, Baghestanian M, Quehenberger P, Bevec D, et al. Ibuprofen inhibits pyrogen-dependent expression of VCAM-1 and ICAM-1 on human endothelial cells. Life Sci. 1996;58:2167–81.
44. Bavbek M, Polin R, Kwan AL, Arthur AS, Kassell NF, Lee KS. Monoclonal antibodies against ICAM-1 and CD18 attenuate cerebral vasospasm after experimental subarachnoid hemorrhage in rabbits. Stroke. 1998;29:1930–5.
45. Polin RS, Bavbek M, Shaffrey ME, Billups K, Bogaev CA, Kassell NF, et al. Detection of soluble E-selectin, ICAM-1, VCAM-1, and L-selectin in the cerebrospinal fluid of patients after subarachnoid hemorrhage. J Neurosurg. 1998;89:559–67.
46. Aihara Y, Kasuya H, Onda H, Hori T, Takeda J. Quantitative analysis of gene expressions related to inflammation in canine spastic artery after subarachnoid hemorrhage. Stroke. 2001;32:212–7.
47. Nissen JJ, Mantle D, Gregson B, Mendelow AD. Serum concentration of adhesion molecules in patients with delayed ischaemic neurological deficit after aneurysmal subarachnoid haemorrhage: the immunoglobulin and selectin superfamilies. J Neurol Neurosurg Psychiatry. 2001;71:329–33.
48. Oshiro EM, Hoffman PA, Dietsch GN, Watts MC, Pardoll DM, Tamargo RJ. Inhibition of experimental vasospasm with anti-intercellular adhesion molecule-1 monoclonal antibody in rats. Stroke. 1997;28:2031–7. discussion 2037–2038.
49. Sills Jr AK, Clatterbuck RE, Thompson RC, Cohen PL, Tamargo RJ. Endothelial cell expression of intercellular adhesion molecule 1 in experimental posthemorrhagic vasospasm. Neurosurgery. 1997;41:453–60. discussion 460–451.
50. Gallia GL, Tamargo RJ. Leukocyte-endothelial cell interactions in chronic vasospasm after subarachnoid hemorrhage. Neurol Res. 2006;28:750–8.
51. Lin CL, Shih HC, Lieu AS, Lee KS, Dumont AS, Kassell NF, et al. Attenuation of experimental subarachnoid hemorrhage-induced cerebral vasospasm by the adenosine A(2A) receptor agonist CGS 21680. J Neurosurg. 2007;106:436–41.
52. Mack WJ, Mocco J, Hoh DJ, Huang J, Choudhri TF, Kreiter KT, et al. Outcome prediction with serum intercellular adhesion molecule-1 levels after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002;96:71–5.
53. Mocco J, Mack WJ, Kim GH, Lozier AP, Laufer I, Kreiter KT, et al. Rise in serum soluble intercellular adhesion molecule-1 levels with vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg. 2002;97:537–41.
54. Chyatte D. Prevention of chronic cerebral vasospasm in dogs with ibuprofen and high-dose methylprednisolone. Stroke. 1989;20:1021–6.
55. Chyatte D, Fode NC, Nichols DA, Sundt TM. Preliminary-report - effects of high-dose methylprednisolone on delayed cerebral-ischemia in patients at high-risk for vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurgery. 1987;21:157–60.
56. Thai QA, Oshiro EM, Tamargo RJ. Inhibition of experimental vasospasm in rats with the periadventitial administration of ibuprofen using controlled-release polymers. Stroke. 1999;30:140–7.
57. Frazier JL, Pradilla G, Wang PP, Tamargo RJ. Inhibition of cerebral vasospasm by intracranial delivery of ibuprofen from a controlled-release polymer in a rabbit model of subarachnoid hemorrhage. J Neurosurg. 2004;101:93–8.
58. Pradilla G, Thai QA, Legnani FG, Clatterbuck RE, Gailloud P, Murphy KP, et al. Local delivery of ibuprofen via controlled-release polymers prevents angiographic vasospasm in a monkey model of subarachnoid hemorrhage. Neurosurgery. 2005;57:184–90. discussion 184–190.
59. Smith HS, Voss B. Pharmacokinetics of intravenous ibuprofen: implications of time of infusion in the treatment of pain and fever. Drugs. 2012;72:327–37.
60. Kamal AK, Naqvi I, Husain MR, Khealani BA: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. Cochrane Database Syst Rev 2011:CD008076.
61. Yamaguchi-Okada M, Nishizawa S, Mizutani A, Namba H. Multifaceted effects of selective inhibitor of phosphodiesterase III, cilostazol, for cerebral vasospasm after subarachnoid hemorrhage in a dog model. Cerebrovasc Dis. 2009;28:135–42.
62. Suzuki S, Sayama T, Nakamura T, Nishimura H, Ohta M, Inoue T, et al. Cilostazol improves outcome after subarachnoid hemorrhage: a preliminary report. Cerebrovasc Dis. 2011;32:89–93.
63.• Kimura H, Okamura Y, Chiba Y, Shigeru M, Ishii T, Hori T, et al. Cilostazol administration with combination enteral and parenteral nutrition therapy remarkably improves outcome after subarachnoid hemorrhage. Acta Neurochir Suppl. 2015;120:147–52.

Cilastazol demonstrates improved outcomes in aSAH.
64. Murahashi T, Kamiyama K, Hara K, Ozaki M, Mikamoto M, Nakagaki Y, et al. The efficiency of cilostazol for cerebral vasospasm following subarachnoid hemorrhage. No Shinkei Geka. 2013;41:393–400.
65.• Senbokuya N, Kinouchi H, Kanemaru K, Ohashi Y, Fukamachi A, Yagi S, et al. Effects of cilostazol on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a multicenter prospective, randomized, open-label blinded end point trial. J Neurosurg. 2013;118:121–30.
Inhibition of cerebral vasospasm by cilostazol.
66. Yoshimoto T, Shirasaka T, Fujimoto S, Yoshidumi T, Yamauchi T, Tokuda K, et al. Cilostazol may prevent cerebral vasospasm following subarachnoid hemorrhage. Neurol Med Chir (Tokyo). 2009;49:235–40. discussion 240–231.
67.•• Niu PP, Yang G, Xing YQ, Guo ZN, Yang Y. Effect of cilostazol in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Neurol Sci. 2014;336:146–51.
Pooled results from four controlled studies with 340 patients.
68. Pilitsis JG, Coplin WM, O'Regan MH, Wellwood JM, Diaz FG, Fairfax MR, et al. Measurement of free fatty acids in cerebrospinal fluid from patients with hemorrhagic and ischemic stroke. Brain Res. 2003;985:198–201.
69. Pilitsis JG, Coplin WM, O'Regan MH, Wellwood JM, Diaz FG, Fairfax MR, et al. Free fatty acids in human cerebrospinal fluid following subarachnoid hemorrhage and their potential role in vasospasm: a preliminary observation. J Neurosurg. 2002;97:272–9.
70. Bazan NG, Birkle DL, Tang W, Reddy TS. The accumulation of free arachidonic acid, diacylglycerols, prostaglandins, and lipoxygenase reaction products in the brain during experimental epilepsy. Adv Neurol. 1986;44:879–902.
71. Jang YG, Ilodigwe D, Macdonald RL. Metaanalysis of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2009;10:141–7.
72. Suzuki H, Kanamaru K, Kuroki M, Sun H, Waga S, Miyazawa T. Effects of tirilazad mesylate on vasospasm and phospholipid hydroperoxides in a primate model of subarachnoid hemorrhage. Stroke. 1999;30:450–5. discussion 455–456.
73. Zhang S, Wang L, Liu M, Wu B: Tirilazad for aneurysmal subarachnoid haemorrhage. Cochrane Database of Syst Rev:CD006778.
74. Badjatia N, Seres D, Carpenter A, Schmidt JM, Lee K, Mayer SA, et al. Free Fatty acids and delayed cerebral ischemia after subarachnoid hemorrhage. Stroke. 2012;43:691–6.
75. Singer P, Shapiro H, Theilla M, Anbar R, Singer J, Cohen J. Anti-inflammatory properties of omega-3 fatty acids in critical illness: novel mechanisms and an integrative perspective. Intensive Care Med. 2008;34:1580–92.
76. Pontes-Arruda A, Demichele S, Seth A, Singer P. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data.[see comment]. JPEN J Parenter Enteral Nutr. 2008;32:596–605.
77. Yoneda H, Shirao S, Nakagawara J, Ogasawara K, Tominaga T, Suzuki M. A prospective, multicenter, randomized study of the efficacy of eicosapentaenoic acid for cerebral vasospasm: the EVAS study. World Neurosurg. 2014;81:309–15.
78. Badjatia N, Carpenter A, Fernandez L, Schmidt JM, Mayer SA, Claassen J, et al. Relationship between C-reactive protein, systemic oxygen consumption, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Stroke. 2011;42:2436–42.
79. Shirao S, Fujisawa H, Kudo A, Kurokawa T, Yoneda H, Kunitsugu I, et al. Inhibitory effects of eicosapentaenoic acid on chronic cerebral vasospasm after subarachnoid hemorrhage: possible involvement of a sphingosylphosphorylcholine-rho-kinase pathway. Cerebrovasc Dis. 2008;26:30–7.
80. Yoneda H, Shirao S, Kurokawa T, Fujisawa H, Kato S, Suzuki M. Does eicosapentaenoic acid (EPA) inhibit cerebral vasospasm in patients after aneurysmal subarachnoid hemorrhage? Acta Neurol Scand. 2008;118:54–9.
81. Adamczyk P, He S, Amar AP, Mack WJ. Medical management of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: a review of current and emerging therapeutic interventions. Neurol Res Int. 2013;2013:462491.
82. Crowley RW, Medel R, Kassell NF, Dumont AS. New insights into the causes and therapy of cerebral vasospasm following subarachnoid hemorrhage. Drug Discov Today. 2008;13:254–60.
83. Gabikian P, Clatterbuck RE, Eberhart CG, Tyler BM, Tierney TS, Tamargo RJ. Prevention of experimental cerebral vasospasm by intracranial delivery of a nitric oxide donor from a controlled-release polymer: toxicity and efficacy studies in rabbits and rats. Stroke. 2002;33:2681–6.
84. Lee TJ. Nitric oxide and the cerebral vascular function. J Biomed Sci. 2000;7:16–26.
85. Momin EN, Schwab KE, Chaichana KL, Miller-Lotan R, Levy AP, Tamargo RJ. Controlled delivery of nitric oxide inhibits leukocyte migration and prevents vasospasm in haptoglobin 2–2 mice after subarachnoid hemorrhage. Neurosurgery. 2009;65:937–45. discussion 945.
86.• Ehlert A, Schmidt C, Wölfer J, Manthei G, Jacobs AH, Brüning R, Heindel W, Ringelstein EB, Stummer W, Pluta RM, et al. Molsidomine for the prevention of vasospasm-related delayed ischemic neurological deficits and delayed brain infarction and the improvement of clinical outcome after subarachnoid hemorrhage: a single-center clinical observational study. J Neurosurg. 2016;124(1):51–8.
Single-center clinical observational study of 29 SAH patients with proven cerebral vasospasm (CVS) receiving molsidomine

plus nimodipine, 25 SAH patients with proven CVS receiving only nimodipine, and 20 SAH patients without CVS treated with nimodipine alone. Results were 4 of 29 patients in the first group had vasospasm-associated infarcts on MRI compared to 22 of 45 of the patients receiving nimodipine alone (groups 2 and 3 combined; $P < 0.01$). NIHSS and mRS in the molsidomine group were 3.0 and 2.5 respectively while the CVS group with nimodipine alone had NIHSS and mRS of 11.5 and 5.0 respectively ($P < 0.001$). This post-hoc analysis shows promise for molsidomine treatment in SAH patients with cerebral vasospasm.

87. Takano K, Latour LL, Formato JE, Carano RA, Helmer KG, Hasegawa Y, et al. The role of spreading depression in focal ischemia evaluated by diffusion mapping. Ann Neurol. 1996;39:308–18.
88. Kraig RP, Nicholson C. Extracellular ionic variations during spreading depression. Neuroscience. 1978;3:1045–59.
89. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med. 2011;17:439–47.
90. Tozzi A, de Iure A, Di Filippo M, Costa C, Caproni S, Pisani A, et al. Critical role of calcitonin gene-related peptide receptors in cortical spreading depression. Proc Natl Acad Sci U S A. 2012;109:18985–90.
91. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. Brain. 1994;117(Pt 1):199–210.
92. Dreier JP, Korner K, Ebert N, Gorner A, Rubin I, Back T, et al. Nitric oxide scavenging by hemoglobin or nitric oxide synthase inhibition by N-nitro-L-arginine induces cortical spreading ischemia when K+ is increased in the subarachnoid space. J Cereb Blood Flow Metab. 1998;18:978–90.
93. Dreier JP, Victorov IV, Petzold GC, Major S, Windmuller O, Fernandez-Klett F, et al. Electrochemical failure of the brain cortex is more deleterious when it is accompanied by low perfusion. Stroke. 2013;44:490–6.
94. Bosche B, Graf R, Ernestus RI, Dohmen C, Reithmeier T, Brinker G, et al. Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. Ann Neurol. 2010;67:607–17.
95. Dreier JP, Petzold G, Tille K, Lindauer U, Arnold G, Heinemann U, et al. Ischaemia triggered by spreading neuronal activation is inhibited by vasodilators in rats. J Physiol. 2001;531:515–26.
96. Dreier JP, Woitzik J, Fabricius M, Bhatia R, Major S, Drenckhahn C, et al. Delayed ischaemic neurological deficits after subarachnoid haemorrhage are associated with clusters of spreading depolarizations. Brain. 2006;129:3224–37.
97. Dreier JP, Major S, Manning A, Woitzik J, Drenckhahn C, Steinbrink J, et al. Cortical spreading ischaemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid haemorrhage. Brain. 2009;132:1866–81.
98. Dreier JP, Drenckhahn C, Woitzik J, Major S, Offenhauser N, Weber-Carstens S, et al. Spreading ischemia after aneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl. 2013;115:125–9.
99. Hartings JA, Strong AJ, Fabricius M, Manning A, Bhatia R, Dreier JP, et al. Spreading depolarizations and late secondary insults after traumatic brain injury. J Neurotrauma. 2009;26:1857–66.
100. Woitzik J, Dreier JP, Hecht N, Fiss I, Sandow N, Major S, et al. Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2012;32:203–12.
101. Dreier JP, Windmuller O, Petzold G, Lindauer U, Einhaupl KM, Dirnagl U. Ischemia triggered by red blood cell products in the subarachnoid space is inhibited by nimodipine administration or moderate volume expansion/hemodilution in rats. Neurosurgery. 2002;51:1457–65. discussion 1465–1457.
102. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. In Stroke. Edited by; 2012:1711–1737. vol 43.
103. Busch E, Gyngell ML, Eis M, Hoehn-Berlage M, Hossmann KA. Potassium-induced cortical spreading depressions during focal cerebral ischemia in rats: contribution to lesion growth assessed by diffusion-weighted NMR and biochemical imaging. J Cereb Blood Flow Metab. 1996;16:1090–9.
104. Mies G, Iijima T, Hossmann KA. Correlation between peri-infarct DC shifts and ischaemic neuronal damage in rat. Neuroreport. 1993;4:709–11.
105. Back T, Ginsberg MD, Dietrich WD, Watson BD. Induction of spreading depression in the ischemic hemisphere following experimental middle cerebral artery occlusion: effect on infarct morphology. J Cereb Blood Flow Metab. 1996;16:202–13.
106. Gill R, Andine P, Hillered L, Persson L, Hagberg H. The effect of MK-801 on cortical spreading depression in the penumbral zone following focal ischaemia in the rat. J Cereb Blood Flow Metab. 1992;12:371–9.
107. Dreier JP, Kleeberg J, Petzold G, Priller J, Windmuller O, Orzechowski HD, et al. Endothelin-1 potently induces Leao's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura? Brain. 2002;125:102–12.
108. Dreier JP, Kleeberg J, Alam M, Major S, Kohl-Bareis M, Petzold GC, et al. Endothelin-1-induced spreading depression in rats is associated with a microarea of selective neuronal necrosis. Exp Biol Med (Maywood). 2007;232:204–13.
109. Jorks D, Major S, Oliveira-Ferreira AI, Kleeberg J, Dreier JP. Endothelin-1(1–31) induces spreading depolarization in rats. Acta Neurochir Suppl. 2011;110:111–7.

110. Kleeberg J, Petzold GC, Major S, Dirnagl U, Dreier JP. ET-1 induces cortical spreading depression via activation of the ETA receptor/phospholipase C pathway in vivo. Am J Physiol Heart Circ Physiol. 2004;286:H1339–46.
111. Lauritzen M, Hansen AJ. The effect of glutamate receptor blockade on anoxic depolarization and cortical spreading depression. J Cereb Blood Flow Metab. 1992;12:223–9.
112. Lu XC, Williams AJ, Wagstaff JD, Tortella FC, Hartings JA. Effects of delayed intrathecal infusion of an NMDA receptor antagonist on ischemic injury and peri-infarct depolarizations. Brain Res. 2005;1056:200–8.
113. Dirnagl U, Simon RP, Hallenbeck JM. Ischemic tolerance and endogenous neuroprotection. Trends Neurosci. 2003;26:248–54.
114. Mergenthaler P, Dirnagl U. Protective conditioning of the brain: expressway or roadblock? J Physiol. 2011;589:4147–55.
115. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation. 1993;87:893–9.
116. Hausenloy DJ, Yellon DM. Preconditioning and postconditioning: underlying mechanisms and clinical application. Atherosclerosis. 2009;204:334–41.
117. TV N, Sangwan A, Sharma B, Majid A, Gk R. Cerebral ischemic preconditioning: the road so far. Mol Neurobiol. 2016;53:2579–93.
118. Zhao H. Ischemic postconditioning as a novel avenue to protect against brain injury after stroke. J Cereb Blood Flow Metab. 2009;29:873–85.
119. Kitagawa K. Ischemic tolerance in the brain: endogenous adaptive machinery against ischemic stress. J Neurosci Res. 2012;90:1043–54.
120. Kirino T. Ischemic tolerance. J Cereb Blood Flow Metab. 2002;22:1283–96.
121.•• Wang Y, Reis C, Applegate II R, Stier G, Martin R, Zhang JH. Ischemic conditioning-induced endogenous brain protection: applications pre-, per- or post-stroke. Exp Neurol. 2015;272:26–40.

This study is a good review of the concept of ischemic conditioning.

122. Jones NM, Bergeron M. Hypoxic preconditioning induces changes in HIF-1 target genes in neonatal rat brain. J Cereb Blood Flow Metab. 2001;21:1105–14.
123. Stenzel-Poore MP, Stevens SL, Xiong Z, Lessov NS, Harrington CA, Mori M, et al. Effect of ischaemic preconditioning on genomic response to cerebral ischaemia: similarity to neuroprotective strategies in hibernation and hypoxia-tolerant states. Lancet. 2003;362:1028–37.
124. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation. 1986;74:1124–36.
125. Haji Mohd Yasin NA, Herbison P, Saxena P, Praporski S, Konstantinov IE. The role of remote ischemic preconditioning in organ protection after cardiac surgery: a meta-analysis. J Surg Res. 2014;186:207–16.
126. Kitagawa K, Matsumoto M, Tagaya M, Hata R, Ueda H, Niinobe M, et al. 'Ischemic tolerance' phenomenon found in the brain. Brain Res. 1990;528:21–4.
127. Malhotra S, Naggar I, Stewart M, Rosenbaum DM. Neurogenic pathway mediated remote preconditioning protects the brain from transient focal ischemic injury. Brain Res. 2011;1386:184–90.
128. Dave KR, Saul I, Busto R, Ginsberg MD, Sick TJ, Perez-Pinzon MA. Ischemic preconditioning preserves mitochondrial function after global cerebral ischemia in rat hippocampus. J Cereb Blood Flow Metab. 2001;21:1401–10.
129. Zhan RZ, Fujihara H, Baba H, Yamakura T, Shimoji K. Ischemic preconditioning is capable of inducing mitochondrial tolerance in the rat brain. Anesthesiology. 2002;97:896–901.
130. Ren C, Gao X, Niu G, Yan Z, Chen X, Zhao H. Delayed postconditioning protects against focal ischemic brain injury in rats. PLoS One. 2008;3, e3851.
131. Perez-Pinzon MA, Xu GP, Dietrich WD, Rosenthal M, Sick TJ. Rapid preconditioning protects rats against ischemic neuronal damage after 3 but not 7 days of reperfusion following global cerebral ischemia. J Cereb Blood Flow Metab. 1997;17:175–82.
132. Weih M, Kallenberg K, Bergk A, Dirnagl U, Harms L, Wernecke KD, et al. Attenuated stroke severity after prodromal TIA: a role for ischemic tolerance in the brain? Stroke. 1999;30:1851–4.
133. Moncayo J, de Freitas GR, Bogousslavsky J, Altieri M, van Melle G. Do transient ischemic attacks have a neuroprotective effect? Neurology. 2000;54:2089–94.
134. Johnston SC. Ischemic preconditioning from transient ischemic attacks? Data from the Northern California TIA Study. Stroke. 2004;35:2680–2.
135. Dirnagl U, Becker K, Meisel A. Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. Lancet Neurol. 2009;8:398–412.
136. Koch S, Gonzalez N. Preconditioning the human brain: proving the principle in subarachnoid hemorrhage. Stroke. 2013;44:1748–53.
137. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, et al. Defining vasospasm after subarachnoid hemorrhage: what is the most clinically relevant definition? Stroke. 2009;40:1963–8.
138.•• Gonzalez NR, Connolly M, Dusick JR, Bhakta H, Vespa P. Phase I clinical trial for the feasibility and safety of remote ischemic conditioning for aneurysmal subarachnoid hemorrhage. Neurosurgery. 2014;75:590–8.

discussion 598. This study is an initial feasbility study and demonstrated promising results encouraging further study.

139. Koch S, Katsnelson M, Dong C, Perez-Pinzon M. Remote ischemic limb preconditioning after subarachnoid hemorrhage: a phase Ib study of safety and feasibility. Stroke. 2011;42:1387–91.

140.• Mayor F, Bilgin-Freiert A, Connolly M, Katsnelson M, Dusick JR, Vespa P, et al. Effects of remote ischemic preconditioning on the coagulation profile of patients with aneurysmal subarachnoid hemorrhage: a case–control study. Neurosurgery. 2013;73:808–15. discussion 815.

A good study detailing positive effects of remote ischemic preconditioning in aSAH.

141. Nikkola E, Laiwalla A, Ko A, Alvarez M, Connolly M, Ooi YC, et al. Remote ischemic conditioning alters methylation and expression of cell cycle genes in aneurysmal subarachnoid hemorrhage. Stroke. 2015;46:2445–51.

142. Keep RF, Wang MM, Xiang J, Hua Y, Xi G. Full steam ahead with remote ischemic conditioning for stroke. Transl Stroke Res. 2014;5:535–7.

143. CoAxia: NeuroFlo perfusion augmentation: Instructions for use. Edited by; 2005. vol 2016.

144. Liebeskind DS. Aortic occlusion for cerebral ischemia: from theory to practice. Curr Cardiol Rep. 2008;10:31–6.

145. Lylyk P, Vila JF, Miranda C, Ferrario A, Romero R, Cohen JE. Partial aortic obstruction improves cerebral perfusion and clinical symptoms in patients with symptomatic vasospasm. Neurol Res. 2005;27 Suppl 1:S129–35.

146.• Ramakrishnan G, Dong B, Todd KG, Shuaib A, Winship IR. Transient aortic occlusion augments collateral blood flow and reduces mortality during severe ischemia due to proximal middle cerebral artery occlusion. Transl Stroke Res. 2016;7:149–55.

Evidence supporting the use of partial aortic occlusion.

147. Alnaami I, Saqqur M, Chow M. A novel treatment of distal cerebral vasospasm. A case report. Interv Neuroradiol. 2009;15:417–20.

148. Emery DJ, Schellinger PD, Selchen D, Douen AG, Chan R, Shuaib A, et al. Safety and feasibility of collateral blood flow augmentation after intravenous thrombolysis. Stroke. 2011;42:1135–7.

149. Shuaib A, Bornstein NM, Diener HC, Dillon W, Fisher M, Hammer MD, et al. Partial aortic occlusion for cerebral perfusion augmentation: safety and efficacy of NeuroFlo in Acute Ischemic Stroke trial. Stroke. 2011;42:1680–90.

150. Appelboom G, Strozyk D, Hwang BY, Prowda J, Badjatia N, Helbok R, et al. Bedside use of a dual aortic balloon occlusion for the treatment of cerebral vasospasm. Neurocrit Care. 2010;13:385–8.

151. van den Bergh WM, Dijkhuizen RM, Rinkel GJ. Potentials of magnesium treatment in subarachnoid haemorrhage. Magnes Res. 2004;17:301–13.

152. Wong GK, Poon WS, Chan MT, Boet R, Gin T, Ng SC, et al. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized, double-blinded, placebo-controlled, multicenter phase III trial. Stroke. 2010;41:921–6.

153.•• Reddy D, Fallah A, Petropoulos JA, Farrokhyar F, Macdonald RL, Jichici D. Prophylactic magnesium sulfate for aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. Neurocrit Care. 2014;13:356–64.

This study pools results of prophylactic magnesium treatment for subarachnoid hemorrhage and demonstrates no positive treatment effect.

154. Vergouwen MD, Meijers JC, Geskus RB, Coert BA, Horn J, Stroes ES, et al. Biologic effects of simvastatin in patients with aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled randomized trial. J Cereb Blood Flow Metab. 2009;29:1444–53.

155. Liu Z, Liu L, Zhang Z, Chen Z, Zhao B. Cholesterol-reducing agents for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2013;4, Cd008184.

156. Tseng MY, Hutchinson PJ, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute pravastatin treatment on intensity of rescue therapy, length of inpatient stay, and 6-month outcome in patients after aneurysmal subarachnoid hemorrhage. Stroke. 2007;38:1545–50.

157. Kramer AH, Gurka MJ, Nathan B, Dumont AS, Kassell NF, Bleck TP. Statin use was not associated with less vasospasm or improved outcome after subarachnoid hemorrhage. Neurosurgery. 2008;62:422–7. discussion 427–430.

158.•• Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol. 2014;13:666–75.

This study is a multi-center randomized trial of 803 patients evaluating 40 mg of simvastatin versus placebo for 21 days with primary outcomes at 6 months. There was no benefit of simvastatin at 6 month outcomes and similar morbidity and mortality between groups.